The epidemiology of inflammatory bowel disease in the United Kingdom: early environmental associations

By

Dr Danielle L Morris MBBS BSc MSc MRCP (UK)

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Royal Free Hospital and University College Hospital School of Medicine
University of London

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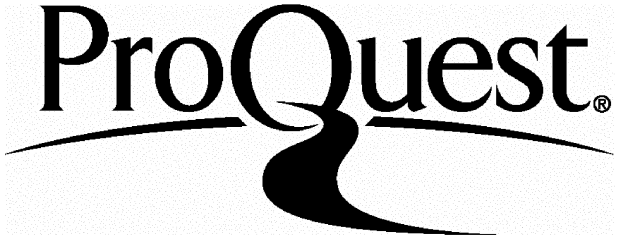


Abstract

Aims: To examine associations between childhood environmental factors and inflammatory bowel disease.

Introduction: Recent rises in incidence support environmental factors in the aetiology of inflammatory bowel disease. Studies examining environmental exposures have varying conclusions. Childhood infectious exposures have been proposed. Infections studied including measles have highly controversial conclusions. Atypical infectious patterns such as early or delayed exposure and improved hygiene are hypothesised.

Methods: This study used data from the 1970 British Cohort Study, a longitudinal population based birth cohort study of 18,000 children in Great Britain, born in 1970. Data were collected prospectively aged 5, 10 and 16 years. At 26 years, cohort members were questioned about inflammatory bowel disease. Physicians confirmed diagnoses where possible and histology was independently analysed. Factors examined included demographic and perinatal factors, family history, material and cultural circumstances and specific infectious exposures (including measles, other viral infections and vaccinations).

Results: The prevalence of inflammatory bowel disease aged 26 years was 49.2 per 10,000 population. 30 subjects reported Crohn's disease and 22 ulcerative colitis. Asian ethnic origins, family history of inflammatory bowel disease and childhood eczema were independent risk factors for inflammatory bowel disease. Passive smoke exposure by age 16 was associated with reduced odds for Crohn's disease. Older siblings and increased maternal parity were associated with increased odds for ulcerative colitis and reduced odds for Crohn's disease. There was no association between measles infection or measles vaccination and inflammatory bowel disease.

Conclusions: The study supports the role of childhood environmental factors in inflammatory bowel disease. Measles infection and vaccination in isolation were not risk factors. Additional evidence is required to support the hypothesis that abnormal patterns of infectious exposures in childhood are risks for inflammatory bowel disease. This research should be repeated when more members have developed disease and the study power improved.

List of Figures **Page**

List of Tables **Page**

List of Appendices **Page**

Aims and Hypotheses

A nationally representative population-based cohort study was used:

- To examine the importance of early environmental factors in the aetiology of inflammatory bowel disease with respect to previously suggested risk factors.

- To examine the hypothesis that atypical patterns of infectious or antigenic exposures may be a risk for later inflammatory bowel disease. To assess surrogate markers of material and cultural circumstances that are thought to influence such exposures.

- To examine the similarities and differences between ulcerative colitis and Crohn's disease with respect to specific environmental exposures.

- To examine the hypotheses by Wakefield (2) that measles infection, measles vaccination and atypical measles exposures increase risk of inflammatory bowel disease.

Introduction

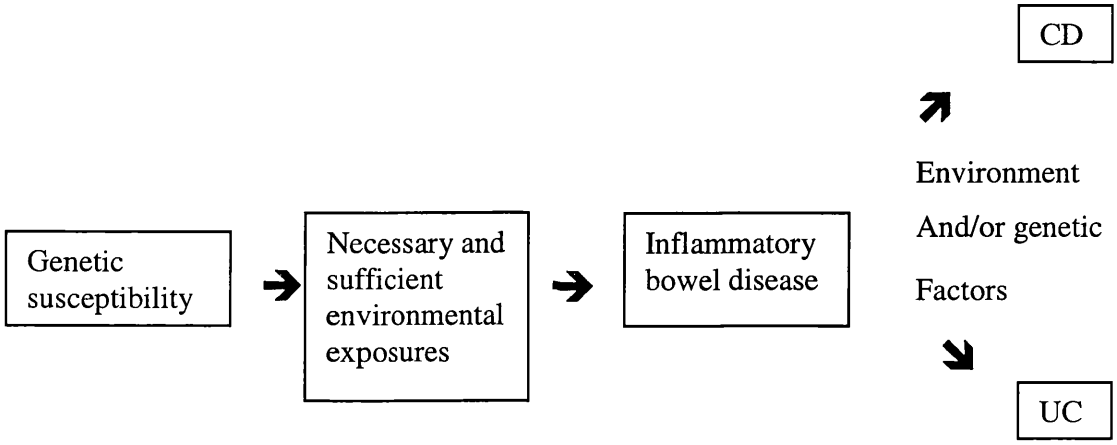
Crohn's disease (CD) and ulcerative colitis (UC) are chronic relapsing inflammatory conditions predominantly affecting the colon (UC) and/or the small bowel (CD). Collectively they are termed inflammatory bowel disease (IBD), although they may show quite different clinical and epidemiological features. Differential diagnosis is based on a combination of clinical, radiological and histological findings, but may be difficult.

Crohn's disease was possibly first described in the 16th century,(3) but not until the mid 19th century were more consistent case-reports of fistulous and stricturing Crohn's disease recorded.(3) In 1913, Dalziel described extensive ileocolitis, where tuberculosis had been excluded and histological granulomas now recognised in Crohn's were first identified. The eponymous name came from a case series described by Crohn in America in 1932, but Crohn's colitis was not generally accepted as a diagnostic entity until the 1960's, when Lockhart-Mummary and Morson described a series of 25 cases from St. Mark's hospital in London. (3)

Descriptions consistent with ulcerative colitis are found in ancient medicine, but are difficult to distinguish from dysenteric diseases. Case reports of repeated bouts of 'bloody flux' in Europe in the 18th century, along with post-mortem pathology suggests that ulcerative colitis was present with increasing recognition.(3) Between 1883 and 1908 more than 300 cases were described in London, and the complications and mortality associated with the diseases were becoming apparent in Europe and America. In 1964 a study by Edwards and Truelove in Oxford reported on 624 patients seen between 1938 and 1962, where both local and systemic complications of the disease were described in detail.(3)

IBD has become an important cause of morbidity in industrialised countries. In contrast to many other non-communicable diseases such as cardiovascular diseases, they are increasing in incidence. Their contribution to the burden of health care is substantial (4), and the lifetime risk for IBD in developed countries is estimated at greater than 0.5%.(5)There is still much to learn about their aetiology. Detailed descriptive epidemiology of inflammatory bowel diseases can generate valuable hypotheses and provide useful estimates of ongoing trends.

Fig 1 A proposed model of causation for inflammatory bowel disease



Disease Definitions

Both CD and UC may present with similar features of diarrhoea, abdominal pain, weight loss and anaemia, depending on the disease extent, as well as extra-intestinal manifestations such as arthritis and sclerosing cholangitis. In UC, inflammation is confined to the mucosa and submucosa of the colon alone and is usually continuous. By comparison, any part of the gastrointestinal tract may be involved in CD, often with transmural patchy inflammation and granuloma formation.

In spite of these differences, the distinction between CD and UC is often equivocal, as there may be marked overlap in their clinical and histopathological features. This is particularly a problem with Crohn's colitis and ulcerative colitis, which may be often indistinguishable. About 10%-15% of patients with colonic disease cannot be classified(6),(7), and a third category termed indeterminate colitis (IC) is sometimes used to describe this group. Distinction from other infectious and non-infectious colonic diseases may also be hard.

A considerable overlap in the spectrum of inflammatory bowel disease is likely, but it may important to distinguish between the two conditions both for future clinical management and for epidemiological research. Whilst they have many epidemiological similarities, such as age of onset and geographic distribution, and familial clustering (with both diseases seen within the same families) they also show many important differences such as sex distribution,

association with cigarette smoke, and measures of childhood hygiene. Epidemiological studies where CD and UC are combined can therefore be misleading. Unfortunately many existing studies have insufficient statistical power to separate the two diseases, and so require cautious interpretation. Larger studies or meta-analyses may help our understanding in the future.

As there is no 'gold standard' for diagnosis, a variety of diagnostic criteria have been evaluated for distinguishing IBD phenotype.(8),(9), (10)These are based on clinical, endoscopic, radiological and histopathological findings. In this thesis, the criteria described by Riis (9) have been used in order to be consistent with previous studies.(11) (See Table 1)

Table 1 **Riis Criteria for the Diagnosis of Crohn's disease and ulcerative colitis (9)**

Criteria for UC	Ulcerative colitis*	Criteria for CD	Crohn's disease**
Clinical History	Blood in stools or mucus	**Clinical History**	Abdominal pain
	Urgency of defaecation or diarrhoea		Malaise
Proctoscopy or colonoscopy	Friable granular mucosa		Diarrhoea or rectal bleeding
	Pseudopolyps		Weight loss
	Ulceration	**Colonoscopy**	Discontinuous ulceration
	Luminal mucopus		Cobblestone mucosa
Radiology	Spiculation		Ulceration
	Ulcers		Strictures or fistulae
	Pseudopolyps		Severe perianal disease
Histology	Ulceration	**Radiology**	Cobblestone mucosa or aphthous ulceration
	Crypt abscesses	**Evidence of enteric fistulae or abscess**	Radiological or colonoscopic
	Chronic inflammatory cell infiltrate	**Histology**	Transmural inflammatory cell infiltrate
			Giant cell granulomas
			Other infectious agents not identified

*At least 3 Criteria required for diagnosis of UC

**At least 2 Criteria required for diagnosis of CD

All criteria carry equal weight

Age Distribution

Both UC and CD onset is most common in the third decade of life, with the incidence twice that for other ages. A second peak between around 70 years is recognised in some studies. (6),(12)A 'trimodal' age distribution is described in one study, with a third peak in the 50-59 age group. (13) It has been suggested that this older group is becoming more prominent in recent years(14), (15). It is notable that both UC and CD have a similar age-specific incidence pattern, suggesting that they may be part of the same disease entity.

The presence of a second (and possibly third) peak in age–specific incidence of IBD is similar to that found in other diseases such as multiple sclerosis, Hodgkin's disease and aplastic anaemia (16). This pattern may suggest that there are different aetiological risks or triggering factors acting at different ages in susceptible people or possible cohort effects. It is unlikely that these groups represent different disease entities as they show similar clinical patterns. (6)Alternatively it may be an artefact of the smaller studies where older patients are more likely to be investigated. Different populations also vary in age-specific incidence over time. Ekbom suggests that countries with a high incidence of IBD show a more pronounced peak in the 20-40 year group, compared with lower incidence areas.(5;15). In periods when IBD incidence increases over time, the increase is most predominant in the 20-40 year group. (5)

Paediatric inflammatory bowel disease

Both CD and UC were previously thought to be rare in children under 10 years.(16) More recently an increase in paediatric cases has been reported.(17), (18),(19) Whilst this may partly reflect earlier case ascertainment, a true rise in childhood IBD seems likely as these studies have been replicated in different countries where diagnostic practices differ. Prospective studies in Sweden have found an increase in childhood IBD from 4.6 to 7 per 100,000 between 1984 and 1995, mainly due to an increase in ulcerative colitis. (20) In contrast, a retrospective study in the United Kingdom reported a threefold rise in incidence of paediatric CD from 1.3 to 3.11 per 100,000 between 1983 and 1993. (19) The prevalence of paediatric UC is reported as higher than that of CD in Italy and Scandinavia, but not in the UK, France, the Netherlands and possibly America. These data are hard to interpret as cases of indeterminate colitis, more often diagnosed in childhood, are often later reclassified as CD or UC and are not always included. (21)

There may be differences in the aetiology and phenotype of paediatric IBD compared with adult onset. It has been suggested that younger age at diagnosis of CD may be associated with a more aggressive course and a greater degree of genetic predisposition. (21)

Sex differences

The male to female ratio for IBD varies with time and phenotype (UC or CD) (6). Females (especially older women) outweigh males with CD, with a 20-30% excess risk than men. This is most marked in areas of high overall CD incidence, and during time periods when a large increase in CD incidence is seen.(15), (22) In contrast, for UC a male predominance is found. Again, this is most pronounced during time periods and regions of high UC incidence, especially in older age groups.

Such consistent differences in sex-specific incidence of IBD suggest that hormonal or lifestyle factors (for example different childhood behaviour patterns between sexes) may be important in disease aetiology.

Geographic Variation

There are striking geographic differences in the distribution of Crohn's disease. Annual incidence risks of between 0.9/100,000 (Greece) and 9.2 /100,000 (Netherlands) are reported in Europe from 1991-3.(23) (Appendix 1) In contrast with Argentina and Panama where the disease is almost unrecognised (Appendix 2). (24)Prevalence studies show similar diversity. (25),(26) A North-South divide, with higher incidence of CD in the North has been suggested by the EC-IBD study .(23) A similar difference has been found between North and South in USA. (22)

There is considerable variation in the reporting of incidence figures for ulcerative colitis. Recent annual incidence risks vary between 0.68 per 100,000 in Korea and 24.3 per 100,000 in Iceland (27), (23) (Appendix 1-3). This is partly due to the variable inclusion of ulcerative proctitis in different series. As proctitis may often be asymptomatic, it is frequently under-reported. (28)Recent improvements in diagnosis are probably partly responsible for the rising incidence of proctitis in recent years, although a change in disease phenotype or aetiological factors may be an additional explanation. (29) In general, geographic variations in ulcerative colitis incidence are similar to those of Crohn's disease.

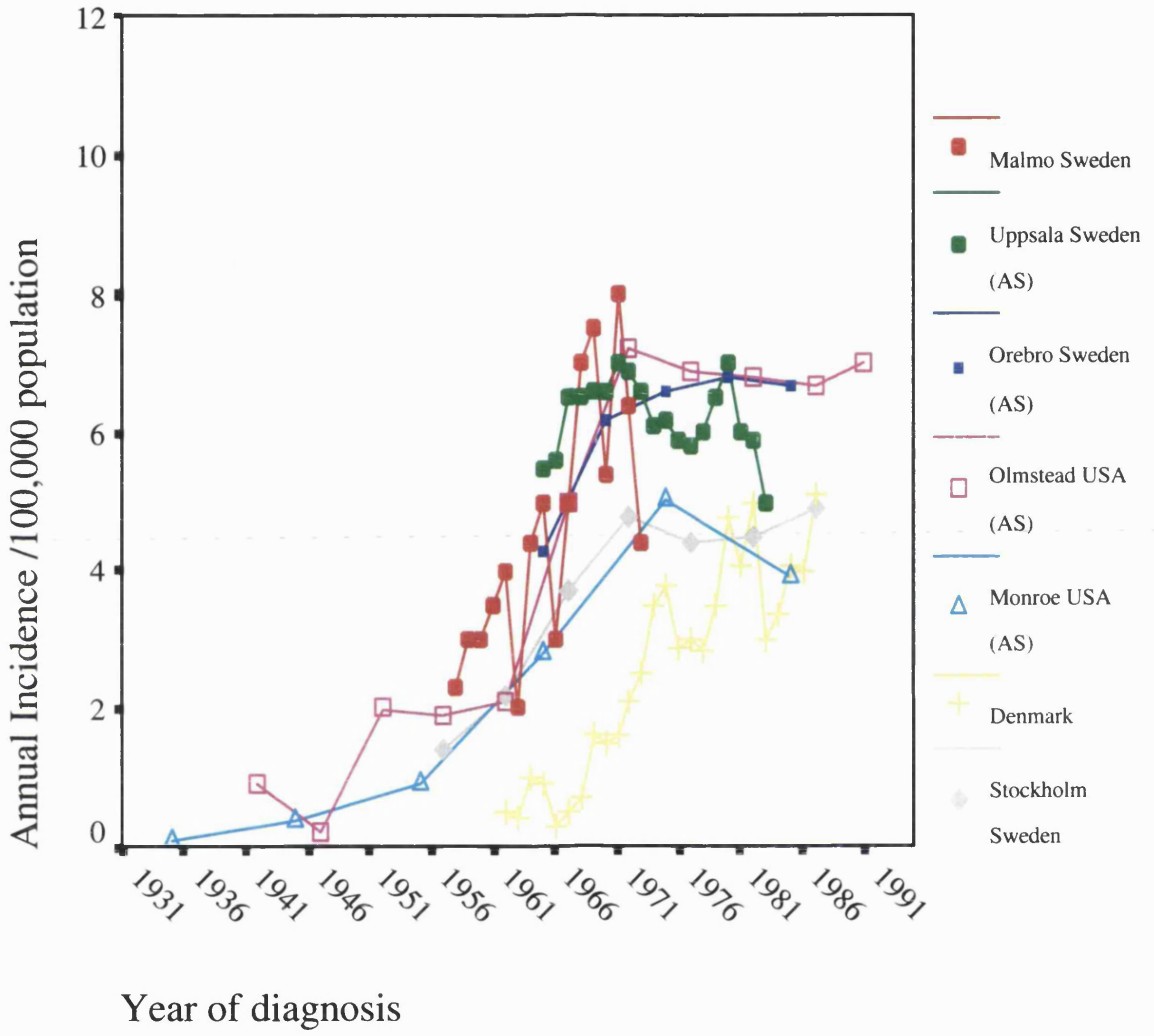
Within the United Kingdom recent CD incidence estimates vary between 3.8 per 100,000 (Leicester) and 9.8 per 100,000 (Northeast Scotland). (23;30). For UC, comparable figures lie between 5.3 per 100,000 (Leicester) and 22.1 per 100,000 (North Tees).(31), (32) Nation-wide, prevalence of IBD has been estimated in two British national birth cohort studies. An overall national prevalence of 254 cases of IBD per 100,000 at age 33 years was reported from the National Child Development Study (NCDS) in 1991(11) As part of the1970 British Cohort Study (BCS70) used in this thesis, the prevalence of UC and CD at age 26-years was 194 and 298 per 100,000 population respectively.(33). These last two studies showed a much greater prevalence than other earlier studies. This may represent a true temporal increase in prevalence as well as better case ascertainment. Although some of the increase may be due to selection bias, this is unlikely to be greater than in other studies.

Temporal Variation-Trends Over Time

A sharp rise in the incidence of IBD, and particularly CD is documented in several countries since World War II. A temporal trend from ulcerative colitis to Crohn's disease is apparent, with the rise in UC preceding that of CD by 15-20 years (5). This pattern is seen in countries at different stages of industrialisation, with CD now predominating in some. (3)

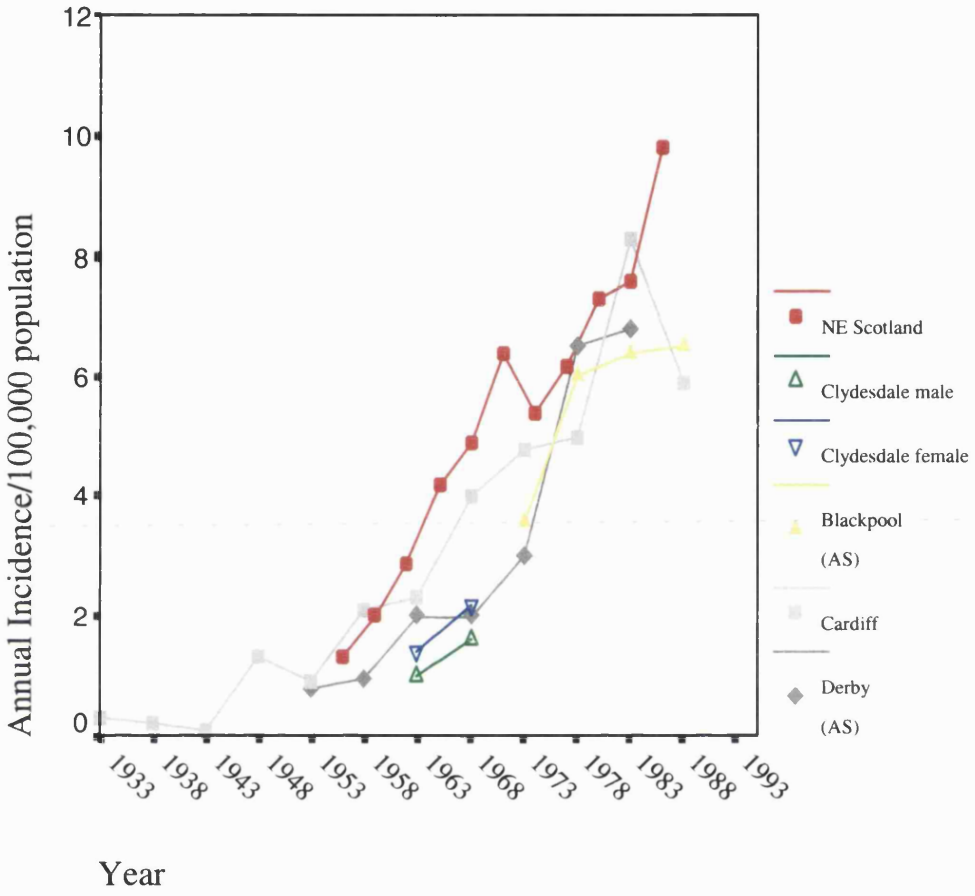
A few centres in the United Kingdom, Europe and USA have monitored CD incidence over time. (30) (34;35) (12;14;15;26;36-38) (Figure 2 and 3). These have provided the most useful assessment of trends in disease incidence. Although they are inconsistent in the methods of case ascertainment and age standardisation, they consistently support a rise in the incidence of CD since 1960, although it is unclear if this is continuing into the next century. UC incidence patterns have shown less consistent changes with time (Figure 4). The great variation in geographic incidence demonstrated in these graphs at any point in time may reflect both population and diagnostic differences as well as differences in distribution of risk factors.

Fig 2 Time trends in Crohn's disease incidence- Europe and USA



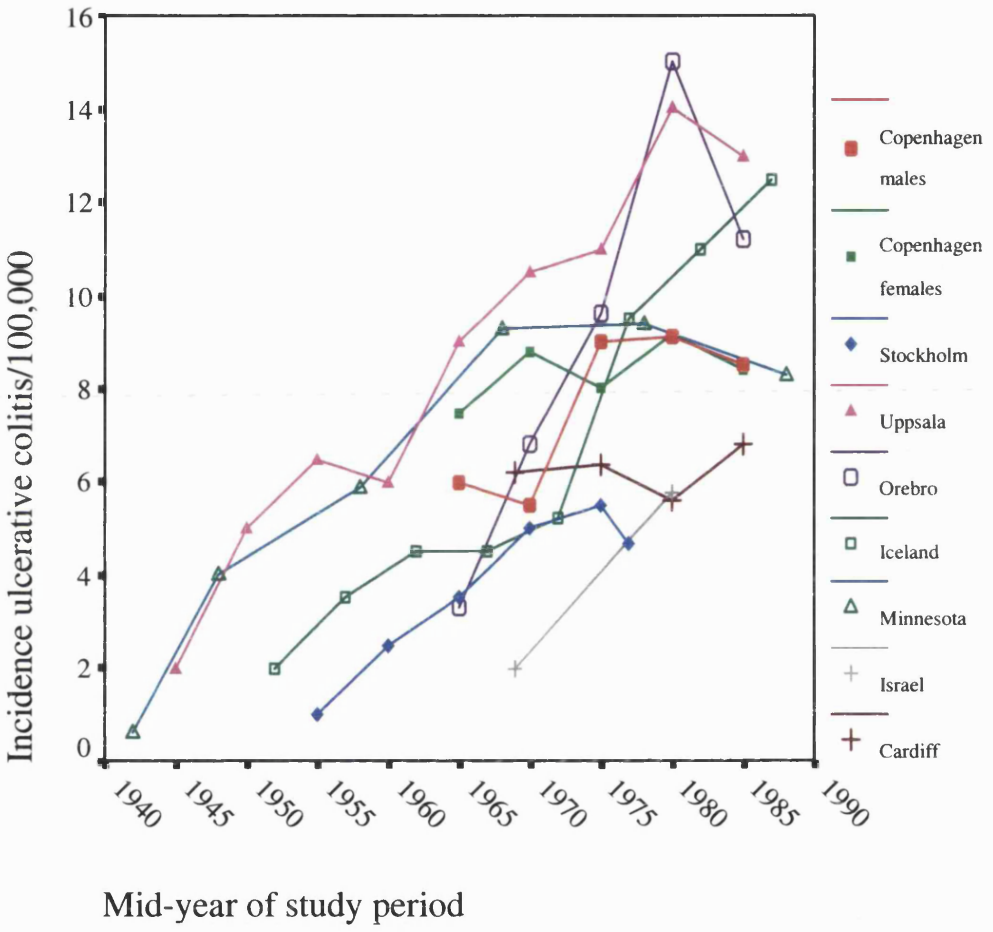
AS=Age-standardised

Fig 3 Time trends in Crohn's disease incidence- United Kingdom



AS=Age-standardised

Fig 4 Time trends in ulcerative colitis incidence- UK, Europe and USA



Temporal Variation- Birth Cohort Effects

Time trends in some chronic diseases may follow patterns that are predictable (at least in part) by year of birth, independent of age or calendar time of observation. Such effects are known as birth cohort or generation effects. They may reflect exposure of the cohort to common environmental factors early in life before disease onset (although the exact window of exposure is uncertain). When studying diseases of unknown aetiology, birth cohort analysis can help identify early determinants of disease that may vary over time.(39)This may be especially useful if exposure to suspected risk factors early in life affect the risk of developing subsequent disease or if adult habits are taken up by subsequent generations.

Such principles have been applied to the analysis of time trends in inflammatory bowel disease mortality and incidence. One study has looked for specific birth cohorts at risk of mortality from IBD in the United Kingdom. A peak in mortality from UC in those born around 1900 was reported in England. This was not found for CD, but combining UC and CD together (mortality data prior to 1950 included both diseases together), suggested a combination of both period and cohort effects. A similar pattern was shown for IBD combined using Scottish data.(40) Another study found similar birth cohort effects for UC mortality in Switzerland.(41) Analysis of mortality data, whilst widely available, may be problematic, for several reasons. The data is usually obtained from death certificates, which are subject to misclassification and may vary by country. Mortality from IBD is low and may not be a good reflection of incidence: deaths are usually from associated carcinomas that may occur many years after disease onset. (42)

Some centres have looked for birth cohort effects using CD incidence data. Two Swedish studies found those born from 1945-1954 had higher age specific rates of IBD combined than other birth cohorts. (37;43) Another study using 8 decades of birth found no increase in incidence in any birth cohort.(14) Two other studies also failed to find a birth cohort effect. (26;44)

As the quality of the data varied considerably between these studies and diagnostic practice also showed considerable variation between countries it is difficult to

reach a conclusion as to whether birth cohort effects are important in the aetiology of IBD. No large studies using age-period –cohort modelling have been reported yet.

Seasonality of birth

Infectious exposures in early childhood are implicated in the aetiology of IBD, although no single specific infectious agent has been implicated. (45), (46), (47),(48),(49),(50) Clustering of cases in time and space has been reported and evidence for seasonal differences in birth found by some, supporting an infectious aetiology. (6)

A large population based study in Sweden, found clustering of CD (but not UC) cases by birth date and season, peaking in spring. This was particularly for those born in spring after 1944. (43)A multinational study found seasonal differences for UC only. (47)A third study in Leicester also found an excess of births in late spring. (51) Other centres have not found a seasonal birth effect. (45)

Genetic Predisposition and Family History of IBD

Evidence for the role of genetics in the pathogenesis of IBD comes from several sources. Genetic epidemiology using twin studies and studies of familial IBD, and more recently the availability of genome wide scanning and candidate gene analysis have rapidly improved our understanding of the genetic component of these diseases.

Genetic epidemiology

There are several recent twin studies that have strongly supported the role of genetic factors in the pathogenesis of IBD. (52-54) A recent review combining these data suggested concordance rates for CD of 37% for monozygotic twins (who have 100% genes in common) and 7% for dizygotic twins (who have 50% genes in common). For UC the genetic influence was less marked, with 10% monozygotic and 3% dizygotic twins showing concordance. (55)

Further follow-up of the UK twin registry of 249 twin pairs (120 UC, 129 CD), found an increased Crohn's disease concordance of 42.2% in monozygotic twins compared with 12% of dizygotic twins. However, concordance in non-identical twins (12%) was twice that for siblings (6%) suggesting the additional importance of a shared early environment. For UC the genetic influence was less marked, with 16.5% monozygotic, 5.3% dizygotic and 6.8% sibling concordance respectively. (56) Heritability studies assessing the magnitude of the genetic effect using the analysis of concordant and discordant twin pairs may further quantify this.

Recently monozygotic twins discordant for IBD phenotypes (one with CD, one with UC) have been described,(57). This suggests that environmental factors must be important in determining disease type in those who are genetically susceptible to IBD.

Family History

Familial clustering is described with 4% to 40% of first-degree relatives reporting IBD. (50)Such first-degree relatives have a 10-15 fold increased risk of developing the

same disease as their family member. (58) A recent Danish study found a risk for UC and CD amongst children of patients with IBD of 2 to 13 times that of the general population. This risk was greatest for those with Crohn's disease that had a parent with CD. (59)Although other studies have found greatest risk associated with affected siblings.(55) Phenotype tends to remain consistent within families, which may partly relate to common environmental exposures.

This is supported by studies that have found increased disease concordance between siblings rather than between generations, and the occurrence of CD in married couples (6) (50)i However up to 26% discordance in disease phenotype was described in one study. (60)Another recent study of 339 sibling pairs found 21/23 sib pairs discordant for smoking behaviour and IBD type, with CD occurring in the smoker and UC in the non-smoker. This provides suggestive evidence for the interaction between genes and environment, with smoking acting on the genetic predisposition and shifting the phenotype from UC to CD.

High concordance rates for disease type, site, disease behaviour and extra-intestinal manifestations have also been reported within affected families. Familial IBD also seems more prevalent amongst Ashkenazi Jews. (55)

Genome–wide scanning and susceptibility loci

The availability of genome screening led to the discovery of the IBD1 gene localised to chromosome 16 being linked with Crohn's disease in several studies. (61) (62). The more recently identified NOD2 gene, located in the peak region of IBD1, may have a role in the immune response to the enteric flora via NF kappa beta activation in response to bacterial lipopolysaccharides. Mutated forms of the NOD2 gene may alter such responsiveness, allowing an abnormal response to bacteria in Crohn's disease. (63) (64)The NOD2 genotype may also determine the clinical course of CD.(65;66)

Three other gene loci have also been repeatedly documented. The IBD2 loci on chromosome 12q13 has been associated with UC and possibly CD.(67) The IBD3 loci on the major histocompatability complex on chromosome 6p23 (associated with CD and

UC) and the IBD4 loci on chromosome 14q11-12 (associated with CD) have also been identified although the candidate genes have not yet been established.

Such rapid development in the understanding of the genetic component of IBD may have important influences on specific therapies in the future.

Environmental associations

The rapid rise in incidence of inflammatory bowel disease this century is not compatible with a solely genetic aetiology. The consistency of the descriptive epidemiology between centres, in spite of the differences in diagnostic criteria and case ascertainment, suggest the trends are real. Current understanding is that both CD and UC are likely to be polygenic disorders that are related to each other, by sharing some susceptibility genes. Phenotype is probably determined by interaction between environmental factors and different alleles.(55) The pattern of age, sex, phenotype, migrant studies and possible birth cohort effects described above support the essential role of the environment, especially infections, in the aetiology of these diseases. Early environmental factors are hard to measure, but proxy indicators of hygiene and infections, such as socio-economic class, infant mortality, and birth order can been used as guides.

Whilst a complex genetic predisposition is apparent for inflammatory bowel disease, in particular CD, environmental causes are most likely to explain the trends in incidence seen this century, with UC predominating in the first half and CD emerging in the latter half. Common environmental factors seem likely for both phenotypes although changing patterns of exposure to these may explain the incidence pattern observed.

One of the most likely early environmental factors to account for the changing pattern of IBD may be early childhood infection. Clustering of cases by date and place of birth supports this. (15),(43) A high risk of IBD has also been described in one study in offspring of mothers who experienced viral infections in the third trimester of pregnancy. (46)

However, early studies of IBD found association between higher socio-economic class and risk of CD. This and the finding that CD was more common in those whose first house had hot water, led to the hypothesis that exposure to poor standards of hygiene in early life, and greater infectious exposure, may be protective against developing CD, and that improved hygiene may be a risk.(68) It has been suggested that this may be due to delayed exposure to enteric infection, which results in later abnormal immune response to

gut pathogens. A more recent study has replicated these findings.(69) Similar hypotheses have been suggested for acute appendicitis and atopic diseases.(70)

Another study found a protective effect of being a prisoner of war (used as a proxy for poor hygiene) and later development of CD, but not UC.(71) The authors also suggest that the time period for exposure risk may extend outside early childhood. However, selection bias and survival factors as well as the effects of such severe stress on immune functioning make this study hard to interpret.

Overall, these studies imply that it may be the *pattern* of infectious exposure that is important in IBD aetiology. Material and cultural circumstances influence such exposure patterns in childhood, as these affect the risk of infectious exposure and the outcome and severity of infections.(48)

Measurement of such infectious or antigenic exposures may be problematic. Proxy measures using indicators of material and cultural circumstances that influence such exposures are often used. These include measures of socio-economic class, infant mortality, family size and composition, and hygienic measures such as crowding, and presence of hot water in the home

Material and cultural circumstances in childhood as proxy measures of pattern of infectious exposure

Socio-economic status

Some of the early studies of IBD found association between higher socio-economic status (when measured by the subjects educational level and occupation) and risk of inflammatory bowel disease, especially CD. (72),(73),(74),(75) More recent studies do not show this gradient. Some have found the reverse, with lower social class groups being associated with increased risk of IBD. (47), (46) Two recent British studies, including one national cohort study using the data from this thesis (33;45) do not find differences in social class (as measured by parental occupation at time of cohort members' birth). This is similar to time trends in paralytic poliomyelitis, for which

initially the most affluent were at risk, but as living conditions improved affected all social classes.

To further confuse these conflicting findings, three studies using availability of a hot water tap as a measure of childhood hygiene found this to be protective against developing CD, but not UC. Traditional measures of parental socio-economic status in infancy and parental education did not vary between IBD cases and controls in these studies. (68;69) (76)

Overall, this suggests that socio-economic status *in isolation*, as conventionally measured by current or parental occupation, is not relevant in explaining the trends in IBD, but that they become important only when there are substantial differences in conditions between social groups.(5) If improved early environmental influences are important, those from higher socio-economic strata will therefore show an increased incidence of IBD first, but only in countries where a social gradient is still marked. This may explain why some studies have shown an association between Jewish ethnicity and risk of IBD in Israel, as they are more affluent than native Arabs, but the incidence figures for both groups remain lower than those in Europe.

Infant and perinatal mortality

Infant and perinatal mortality rates are surrogate markers of early environment. They particularly reflect mortality associated with infections, and have decreased dramatically, although at varying rates, throughout the world during the last century. There is a strong inverse relationship between infant and perinatal mortality rates and IBD incidence in both longitudinal (a single country over time) and geographical (several countries at a point in time) ecological studies IBD is almost unknown in countries with a higher mortality in childhood. (77;78) In addition, an increased risk of IBD in Asian children born in the UK has been reported although none of their parents, born in Asia, had the diseases. (See subsequent section on ethnicity and race) (79)

If early childhood infection is important in the pathogenesis of IBD, one hypothesis suggested by Montgomery is that susceptible children would not survive into adulthood during periods of high infant mortality and so IBD incidence rates would be

low in cohorts surviving during this time. Alternatively, those more vulnerable (perhaps genetically susceptible) to developing IBD may be more likely to survive in improved conditions. However infant mortality rates have declined much faster than the rise in incidence of IBD. A more plausible explanation is that essential environmental factors (possibly atypical exposure to infections) may have increased in prevalence as social circumstances improve with time. (77;78)

Birth order and family size

Birth order and family size give surrogate measures of the level of infectious exposures an individual may be exposed to during their childhood. The number of older or younger siblings may affect the type and severity of early childhood infections experienced: earlier, more intensive infections occur in those with older siblings, whilst later less severe disease occurs in those without older children in the family setting. (80) (81)Some disease risks also vary with sex of the siblings. (80) Similar distinctions have been found with IBD, and vary with disease phenotype.

A case-control study found that having no siblings was a significant risk factor for CD (OR 1.8 95% CI 1.0-3.4), and associated with increased relative odds for UC (OR 1.8, 95% CI 0.9-3.3). (82)

A study combining two birth cohorts by Montgomery (one, the BCS70, which is used in this thesis) found having two or more than two older siblings was associated with statistically significant increased risk of UC (relative odds of 2.6, 95% CI 1.06 to 6.36, p=0.037) when compared with those who had no siblings. In contrast, a significant protective effect was shown for CD (relative odds 0.24, 95% CI 0.07-0.79, p=0.011). Having younger siblings was not associated with risk of IBD (83) A German study has also described increasing relative odds of IBD with increasing birth order. (76)

Families have become smaller over this century, and this may partly explain the shift in disease incidence from UC to CD. If early infections are important, these may now be experienced at an older age in lower dose, severity and number than previously and therefore increase the risk of CD. This atypical pattern of infectious exposure, if real,

may be one of several environmental risk factors for IBD. Family structure may be less important in countries where there is a greater socio-economic gradient between social groups and the outcome of childhood infectious exposure patterns are different as suggested by infant mortality studies previously. Close or wide spacing of subsequent siblings may also be relevant.

Urban childhood environment

Several studies have found a lower incidence of Crohn's disease in rural populations when compared with urban areas, although not for UC. (10;15;84;85) This may reflect differing environmental exposures and crowding although this may be partly confounded by differential patterns of referral and diagnosis of IBD.

Smoking

The relationship between smoking and IBD is now well established and has led to research into its mechanism of action and potential therapeutic roles. Smoking has a positive association with Crohn's disease and a negative relationship with ulcerative colitis.

Subjects who smoke are approximately 2 to 2.4 times increased risk of developing CD than one who has never smoked. (86;87) This risk appears greater in women than men, and a dose-response effect has been noted in some cohort studies.(88) Ex-smokers have a lower risk of CD than current smokers and patients with Crohn's disease who continue to smoke have a greater risk of relapse, hospital admissions and repeat surgery than non-smokers.(88)

In contrast, subjects who smoke seem to have about half the risk of developing ulcerative colitis than those who don't smoke. (86) (87) This protective effect appears similar in both sexes, and a dose-response effect has again been noted in some cohort studies. Studies also suggest that ex-smokers have an increased risk of developing UC, and that stopping smoking increases disease activity. In patients with UC who have had a

restorative proctocolectomy, smokers are also less likely to develop pouchitis than non-smokers.(88) In view of these findings, two randomised trials of transdermal nicotine have been undertaken. One found nicotine patches significantly improved remission rates and rectal histology, whilst the second found no differences between active drug and placebo in maintenance therapy. (89) (36) Betel nut use in Asian population has also been found to be protective against UC. (90)

Of note smoking is also a risk for appendicitis and appendicectomy has been found to be protective against UC (see next section), suggesting associated protective mechanisms. It has been suggested that smoking disables the exaggerated immune response in UC but renders the appendix more susceptible to acute infection. (91) Cigarette smoke has also been found to increase anaerobic bacteria and alter bacterial flora in the intestines. (92) Recurrent respiratory infections and other infections have been proposed as risk factors for IBD in some studies. (47) (93) The mechanisms by which smoking effects the development and course of IBD are not well established but there may be different mechanisms in action for CD and UC. These include changes in immunoglobulins, and T-cell populations in smokers, procoagulant effects, changes in colonic mucus and intestinal permeability as well as the potential effects of nicotine on eicosanoid production (88)

Studies have also been performed to assess the role of passive smoking on development of IBD although the findings are less clear than those studies of active smoking (See Table 2). One study has found passive smoke exposure in non-smoking adults to be protective against CD. Two studies have found passive smoking (one at birth and one in childhood) to be a statistically significant risk factor for Crohn's disease. (94;95) For UC the studies are in conflict with those for active smoking –except for one study (93) most have not found passive smoking to be protective against UC and one study found passive smoking to be a statistically significant risk for UC. (94) A metaanalysis of these studies has not yet been reported. Animal studies have found passive smoking to potentiate the colonic damage in the trinitrobenzene rat model of inflammatory bowel disease. (96)

Table 2 **Studies investigating the role of passive smoking in inflammatory bowel disease**

Author and reference	Study question	Study design	Disease	Relative Odds of disease (95% CI)
Eliakem 2000(97)	Passive exposure as adult non-smoker	Case-control	CD UC	P<0.05 protective No significant association
Gruber 1996(98)	Maternal smoking in pregnancy	Case-control	CD	No significant association
Thompson 1995(45)	Passive exposure in childhood	Case-control	CD UC	1.04 (0.88-1.23) 1.10 (0.86-1.41)
Lashner 1993(94)	Any exposure at birth Maternal smoking at birth	Matched case-control	IBD CD UC IBD	3.02 (1.28-7.06) 5.32 2.19 2.09 (1.02-4.29)
Rigas 1993(99)	Maternal smoking in childhood		CD UC	0.8 (0.3-2.5) 1.4 (0.4-5.1)
Sandler 1992(100)	Active smoking as adult Passive parental smoking in childhood	Case-control Case-control	UC UC	0.53 (0.24-1.14) 0.50 (0.25-1.00)
Persson 1990(95)	Passive exposure in childhood	Case-control	CD UC	1.5 (1.2-2.3) 0.98 (0.6-1.5)

Appendicectomy and Tonsillectomy

There have been several epidemiological studies to examine the role of appendicectomy in IBD. A statistically significant negative association has been reported between appendicectomy and UC in some, but not all, studies. A recent review and metaanalysis of 17 published case-control studies showed a pooled odds ratio of 0.31 (95% CI 0.26-0.37, p=<0.0001) in favour of appendicectomy. This represents a 69% reduction in UC in those who have undergone appendicectomy. Potential confounding factors, especially smoking, are unlikely to account for these findings and smoking was adjusted or matched for in 7 out of 17 of these studies. The strength and consistency of this association suggests that appendicectomy may be a protective factor against the development of UC. (101).

It is unclear whether actual inflammation of the appendix and subsequent primary appendicectomy are requisite for the protective effect against UC or whether surgical removals for other causes have the same protective effect. Similarly the response of UC to appendicectomy after disease onset is unknown. (102)

Several theories have been developed to explain the association between UC and appendicectomy. (101)

Animal studies support the theory that appendicectomy is a true protective factor for UC. Appendicectomy in young mice models of colitis (TCR-$\alpha^{-/-}$ model) reduced mesenteric lymph node mass and suppressed development of IBD. (103) Other studies have shown a delayed onset and decreased disease activity in a dextran sulphate sodium mice model of UC undergoing appendicectomy.(104) It has been suggested that removal of the appendix, as part of the gut-associated lymphoid tissue may alter the balance between T helper and suppresser cells in the intestine in a manner that is protective against UC. (105) However appendicitis is declining in incidence in developed countries, whilst the incidence of UC is stabilising. (101)

A second theory suggests that infectious agents or antigens responsible for UC in predisposed individuals, is present in the appendix. No common pathogen has yet been identified. (106)

Other groups have suggested that the pattern of mucosal immune response seen in acute appendicitis (a type 1 immune response) and ulcerative colitis (a type 2 immune mediated response) are incompatible with each other. Such that 'bystander immune suppression' occurs in colonic mucosa after appendicitis that prevents the development of later UC in those genetically predisposed. (101;107)

Alternatively, the association between UC and appendicectomy could be because those who are predisposed to UC are less likely to develop appendicitis, perhaps due to changes in motility and intestinal mucin. (108)

A less consistent positive association has been noted between appendicectomy and CD, although this may reflect subclinical CD at the time of surgery. (109) (47;68;110;111)

There have been several case-control studies to examine whether removal of the tonsils, another gut-associated lymphoid tissue, might also be protective against UC. Most studies have not found any significant association between tonsillectomy and UC or CD. (69;112) (109;113;114) However, Wurzelmann did find a significant increase in tonsillectomy and childhood infections in Crohn's disease patients when compared with neighbour controls. Subjects with UC also reported more childhood infections but there was no increase in tonsillectomy rates. (111)

Ethnicity, race and immigration

All of the patients in Crohn's original description of regional ileitis in 1932 were of Jewish descent. (5) Since then ethnic differences have been sought in the distribution IBD. The excess incidence of IBD in Jews of Ashkenazi descent may be partially confounded by access to health care facilities and this is a major problem when examining disease trends in ethnic groups that differ in socio-economic status. (100) It is unclear whether Jews are at excess overall risk of IBD; incidence patterns in Israel remain lower than most European countries overall, although immigrant studies in Sweden and the UK suggest an increased risk in Ashkenazi Jews. (115), (116) An American study showed a significantly increased number of first degree relatives with IBD, of Jewish subjects with CD or UC compared with non-Jewish patients. The lifetime

risk of IBD was 7.8% for Jews and 5.2% for non-Jews in those who had a first degree relative with CD. For UC the comparable figures were 4.5% for Jews and 1.6% for non-Jews, suggesting an important ethnic predisposition. (117)

In the USA, UK and South Africa, IBD appears more common in whites than blacks and least common in Hispanics. With increasing westernisation, and homogenisation of socio-economic circumstances in childhood, rates of non-whites match those of whites and may exceed them, especially in Southern Asians. (6), (118), (79), (119) Some studies of second generation south Asian immigrants in Leicester have shown them to be at greater risk of extensive UC than their parents and further studies will allow investigation of the relative importance of early environmental and genetic risks. (119)

For UC, the risk associated with a family history of UC in first-degree relatives is small in South Asians in Leicestershire (relative odds 3.5) when compared with Europeans (relative odds 15). No confidence intervals were stated in this paper. However, the prevalence of UC amongst siblings was similar in both groups. For CD, the association with family history is less clear, suggesting environmental factors may be more important. (120) Risk of IBD in Southern Asian groups varies with cultural and religious groups. Sikhs were found to have a greater incidence of both UC and CD than Hindus and Muslims. Part of this excess risk in Sikhs may reflect diet, greater assimilation into a Western lifestyle and increased smoking (and possibly betel nut) habits. Of note Sikhs in this study now have a higher incidence of UC than indigenous Europeans. This may reflect a greater genetic risk than Europeans that is being revealed by Westernisation. Whilst CD incidence does not show this pattern, risks of CD in immigrants are still greater than those in the originating countries, suggesting that Western environmental factors are still important. (120)

Previous analysis of the BCS70 cohort used in this thesis has found a significantly increased risk of IBD in young Asians (Indian and Pakistani) with relative odds of 7.02, (95% CI 2.39 to 20.65), compared with those who reported 'British' origin. This was independent of family history, sex and crowding. (79) As the incidence of IBD in Asian countries is very low, this suggests that early environmental risks acquired in this country may be responsible.

Perinatal and other events

Breastfeeding

Breastfeeding has been proposed as a protective factor against chronic immune disorders such as asthma and eczema, and has been investigated as a risk factor for inflammatory bowel disease. The published studies are summarised in Table 3. Two studies have found a duration-dependant protective effect of breastfeeding on the development of CD, but not UC. (99) (121) Another study found the protective effect of breastfeeding in UC was confined to those who were breast fed in the first two weeks of life only.(122) This suggests that protective factors associated with early breastfeeding or risk factors associated with bottle-feeding are important in the neonatal period. The studies are hard to compare as they were heterogeneous in their control groups and were undertaken in various countries where breastfeeding practice and material circumstances in childhood showed great variability.

Table 3

Breast feeding as a risk for inflammatory bowel disease-published studies

Author and reference	Study question	Study design	Disease	P value	Relative Odds of disease (95% CI)
Acheson (75)	Not breastfed		UC	p<0.05	Risk increased
Whorwell (122)	Frequency and duration of breast-feeding	Case-control	UC CD	p = 0.005 in first 2 weeks of life NS	Breast feeding protective
Bergstrand (121)	Frequency and duration	Case-control	CD	p < 0.01	Breast feeding and increased duration protective
Koletzko (123;124)	**Not** breast fed	Case-control	CD	p = 0.005	3.8 (1.5-9.5)
Koletzko (123)	**Not** breast fed	Case-control	UC	p= 0.19	1.7 (0.77-3.65)
Gilat (47)	Frequency and duration	Case-control	UC CD	p>0.05	Not stated
Ekbom (46)	Breastfed only at hospital discharge	Case-control	CD UC IBD	p>0.05 p>0.05 p>0.05	1.0 (0.5-2.2) 0.8 (0.5-1.4) 0.9 (0.5-1.4)
Persson (82)	**Not** Breastfed and <2 mths	Case-control	CD UC	p>0.05 p>0.05	1.0 1.0
Rigas (99)	Duration of breast-feeding	Case-control	CD 5 mths 6-11 mths >12 mths UC 5 mths 6-11 mths >12 mths	p for trend 0.04 p for trend 0.07	0.7 (0.3-1.5) 0.6 (0.2-1.5) 0.1 (0.01-1.1) 0.7 (0.3-1.6) 0.5 (0.2-1.5) 0.2 (0.03-2.2)
Wurzelmann (111)	Breast fed	Case-control	UC CD	p>0.05 p>0.05	Not stated
Kono (125)	?	Case-control	UC	p>0.05	Not stated

Table 3 (continued) Breast feeding as a risk for inflammatory bowel disease published studies

Author and reference	Study question	Study design	Disease	P value	Relative Odds of disease (95%CI)
Thompson (45)	Breast fed	Case-control	CD UC	p>0.05 p>0.05	1.04 (0.88-1.25) 1.16 (0.90-1.50)
Corrao G (126)	**Not** breast fed	Case-control	CD UC	Not stated	1.9 (1.1-3.3) 1.5 (1.1-2.1)
Klein I (127)	?	Case-control	IBD	p>0.05	Not stated
Thompson (128)	Ever breast-fed	Nested case-control in 2 Birth cohorts	CD UC	P=0.07 P=0.20	0.40 (0.15-1.03) 2.76 (0.86-9.81)

Oral Contraceptives

The pathogenesis in Crohn's disease has been found to result in multifocal gastrointestinal infarction, probably secondary to a mesenteric vasculitis. In view of this both smoking and the oral contraceptive pill may aggravate focal thrombosis (129) Several studies have examined the contraceptive pill as a potential risk factor for IBD.

An increased risk of both CD and UC of about 50% has been found in current contraceptive pill users compared with those that have never used the contraceptive pill. (88) A meta-analysis up to 1993 found a risk ratio of 1.44 (95% CI 1.12-1.86) for CD and 1.29 (95% CI 0.94-1.77) for UC in pill users, after adjusting for smoking. (130) More recent studies and those that have stratified by duration of use are shown in Table 4.

Several studies have also investigated Crohn's disease activity in oral contraceptive pill users. One study found hazard ratio of 3 (95% CI 1.5-5.9) for CD relapse in 'ever users' compared with those who had never used the contraceptive pill, that was independent of smoking. (131) This contrasts with a cohort study that did not find significant differences in Crohn's disease activity in contraceptive pill users and non-users over an 18-month period. (132)

Overall it would seem that any association between contraceptive pill use and IBD is likely to be modest, and the possibility of residual confounding in these studies, particularly by smoking cannot be excluded.

Table 4

Oral contraceptive use as a risk for inflammatory bowel disease-published studies that stratify by duration of use.

Author and reference	Study design	Adjustment for smoking	Disease	Relative Odds of disease (95% CI)
Lesko 1985(133)	Case-control		CD <1 yr use 1-5 yrs use >5 yrs use	1.2 1.7 7.2
Vessey 1986(134)	Cohort		CD <2yrs use >2yrs use	0.7 2.3
Katschinski 1993(135)	Case-control	Adjusted for smoking	CD 1-3 yrs use >3 yrs use	 2.5 (1.0-6.6) 4.3 (1.3-14.4)
Boyko 1994(136)	Case-control	Adjusted for smoking	CD Used OCP < 6 mths onset UC Used OCP < 6 mths onset	2.6 (1.2-5.5) 2.0 (1.2-3.3)
Corrao 1998(126)	Case-control		CD Used OCP > 1 mth onset UC Used OCP >1 mth onset	3.4 (1.0-11.9) NS

Diet

A variety of dietary factors have been investigated in association with the development of IBD, including cow's milk, refined sugar, fruit, vegetables, cereals, fibre, fast food, coffee, food additives and alcohol. Apart from a high consumption of refined sugar, associated with increased CD risk, (137) and low dietary fruit and vegetable consumption associated with both CD and UC, (138) (139) the studies are inconsistent and inconclusive. Epidemiological studies of diet are notoriously difficult to undertake, as there is often differential recall of food intake in subjects that may have modified their diet as a result of their disease, due to symptoms.

Handedness

Left-handedness has been associated with various diseases, many of which are thought to have an autoimmune origin. These include asthma and other atopic conditions, migraine, thyroid disease, type I diabetes mellitus, autism, developmental learning disorders and AIDS. (140) (141) (142) (143) (144)

The inflammatory bowel diseases, Crohn's disease and ulcerative colitis, have also been linked with left-handedness in some, but not all studies. Geschwind originally described an association in 1982 based on self-reporting of immune disorders in customers using a specialised shop for left-handers. (143) A case-control study later found a significant increased odds ratio for left-handedness in those with Crohn's disease (OR 2.5, 95% CI 1.5-4.2), ulcerative colitis (OR 2.9, 95% CI 1.4-5.9) and inflammatory bowel diseases overall (OR 2.7, 95% CI 1.7-4.4), after adjusting for sex. (145) However a hospital-based case control study of 83 subjects with Crohn's diseases or ulcerative colitis failed to find such an association. (146) A meta-analysis of these studies supported a significant association between left-handedness and inflammatory bowel disease overall (OR 2.01, 95% CI 1.35-2.98). (147) Other studies have included both Crohn's disease and ulcerative colitis with other diseases of "immune disorders", but have had insufficient number of cases to analyse them separately (148) (149)

Other Putative Factors

A variety of other factors ranging from toothpaste, soft toys and fizzy drinks to dietary microparticles have also been studied without conclusive support.

Evidence supporting an infectious aetiology

Non-specific infections

As indicated above, there is much evidence to suggest an infectious role in the aetiology for both CD and UC. Both infections in the perinatal and childhood period have been implicated as well as infections acting as triggering events at the onset of symptoms of disease many years later.

The clustering of IBD in by birth date and place as well as the surrogate measures of early environment (infant mortality, birth order and family composition) described above suggest infections early in life are important in the aetiology of IBD. (15) Some studies have found birth cohorts at specific risk of IBD. (See previous section on birth cohort effects).

Several studies of childhood risk factors in IBD have suggested increased infections in childhood may be important. A multicentre study in the 1980's reported significantly increased number of respiratory infections in childhood in patients with CD and UC. (47) This was confirmed by another retrospective study suggesting an increase in frequency of childhood infections in general for both UC and CD, and an increase in pharyngitis reported for CD. (150) Further studies report increased diarrhoeal illness in infancy and childhood in subjects who develop subsequent CD and UC. (82;122;123)

One criticism of these studies is that their retrospective nature makes them subject to recall bias that may have affected the results. The findings of improved childhood hygiene and lower *H.Pylori* seropositivity in CD subjects is in opposition to these studies, and suggests that perhaps pattern of infection (such as age or dose) may be more important. (68),(69),(151)

Geographic clustering of cases of CD has been reported (152;153), as has the development of CD in married couples, (154-156) both of which support a role for infections in IBD.

Non-specific perinatal infections

Infections in the perinatal period have been implicated in the aetiology of IBD. Clustering of cases at birth and birth cohort phenomena, and infant mortality studies

described above support this concept. A Swedish study found an adjusted odds ratio of 3.8 (95% CI 2.6-5.8) for the development of inflammatory bowel disease in those who had evidence of pre or postnatal infection. For viral infections, this odds ratio increased to 18 (95% CI 4.2-77.6). (46) This was not repeated in two other studies. (47;128)

Bowel Flora

Luminal pathogens have been implicated in the pathogenesis of IBD, and are a necessary cofactor for animal models of IBD. Inflammation of the colon is exacerbated by bacterial faecal flow and may respond to antibiotics, especially in CD. Whilst a role of bowel flora in exacerbating intestinal inflammation is evident, tolerance to such flora can be altered with improved symptoms but this effect may not be due to the bacteria themselves. Specific luminal pathogens have not been found and it is questionable whether specific organisms are directly pathogenic or are mediators of the disease in subjects who have increased intestinal permeability and genetic predisposition. (21)

M.Paratuberculosis

Crohn's disease has similar histopathological findings to Johne's disease, a disease found in cattle, sheep and goats due to early infection with *M Paratuberculosis*. It has been proposed that this infection may be spread from animals via infected milk (it survives pasteurisation), and cause CD in humans. (50) However, immunohistochemical and polymerase chain reaction attempts to isolate mycobacterium antigens and genomic evidence have failed. Trials of anti-tuberculous therapy have not proved efficacious, and animal models have not shown transmission of infection. Additionally, in Sweden, *M Paratuberculosis* was eradicated from dairy herds 25 years ago, yet CD continues to increase in this country. (156)

Measles infection and monovalent measles vaccination

Measles infection, both wild type and vaccine strains have been implicated in the aetiology of inflammatory bowel disease, predominantly Crohn's disease. The evidence for and against the measles hypothesis is highly controversial and a summary of the published data will be overviewed here.

Wakefield's Hypothesis

Wakefield has proposed that measles maybe causally related to Crohn's disease and possibly ulcerative colitis. His hypothesis has been published in a review (2) In summary he suggests that:

- Crohn's disease is associated with a granulomatous vasculitis, multifocal gastrointestinal infarction and a hypercoagulable state. Measles virus infection or a response to measles infection may be responsible for these pathological changes. (129)
- The relationship between measles virus and inflammatory bowel disease is unlikely to be simple: Measles exposure was inevitable prior to mass immunisation, yet Crohn's disease has emerged only recently. Any association is therefore likely to reflect an *atypical* exposure to measles virus.
- Wild measles is an infection that previously was associated with a high infant mortality, which has declined over this century. Children continue to be exposed to measles epidemics, but since the 1920's they were increasingly likely to survive these. The reduction in case-fatality is a direct consequence of socio-economic change and improved nutrition, with smaller family size and less overcrowding. Infants experiencing measles infection may be more likely to have been exposed to a lower dose at an early age (possibly with vaccine strains) and with improved survival. It is hypothesised that this may result in an increased risk of later CD.
- The temporal change in infant mortality from measles coincides with the emergence of Crohn's disease 20 to 30 years later (the peak age of onset of CD). Crohn's disease has emerged since 1940's in developed countries. In countries where measles

mortality is still high, CD is extremely rare. Survivors of measles epidemics are now emerging who are at increased risk of CD, perhaps due to experiencing atypical patterns of measles infection in childhood.

- The outcome of measles infection may be determined by many factors such as genotype, age and sex as well as dose and route of infection. Other cofactors such as concurrent infections with other viruses may also be important.
- Measles virus has immunomodulatory effects, which are consistent with the immune activation found on the background of impaired cellular immunity in CD. (157) Wakefield suggests that persistence of measles virus in the gut may occur due to initial immune tolerance. Persistence of measles virus on a background of genetic risk may then itself cause altered immune programming in early life. Later loss of immune tolerance due to an unknown triggering event may lead to the pathological immune response seen in clinical Crohn's disease. Subsequent loss of tolerance to enteric flora secondary to immunodysregulation from persistent measles virus is also possible.
- As part of his hypothesis, Wakefield has proposed that measles vaccination and more recently the MMR vaccination may be important in the pathogenesis of CD and possibly UC. Vaccination changes the nature of wild measles exposure in a complex way. It will improve survival from acute wild measles, in vaccinated individuals as well as reduce the dose of exposure to wild measles in those who are unvaccinated, due to a reduction in the number of index cases with measles infection in the population. If such low-dose exposure to wild measles infection is associated with increased risk of CD, both vaccinated and unvaccinated subjects may have a higher risk of CD at least at the inception of a measles vaccination programme. (48) This is in keeping with the continued rise in incidence of CD in the UK, and a notable increase in paediatric Crohn's disease for which measles vaccination has been their only known exposure to measles.
- Wakefield suggests a speculative mechanism for the role of measles vaccination following wild infection has been as a triggering event for loss of immune tolerance to persistent wild measles infection that leads to a pathological immune response, and disease onset. Other studies of CD and UC suggest that intercurrent infections are often precipitants of disease onset. (158)

A flow diagram of Wakefield's proposed role of measles virus in the aetiopathogenesis of inflammatory bowel disease is shown in Figure 5.
Evidence for and against the above hypothesis is outlined below.

Comparison with Subacute Sclerosing pan encephalitis (SSPE)

Wakefield makes a comparison with subacute sclerosing pan-encephalitis (SSPE), a disease known to result from *atypical* exposure to measles virus in childhood. In this disease children were most at risk if infected with wild measles at an unusually young age (<2 years). (80;159)The disease is most often seen in boys, rural populations, developing countries, overcrowded environment and lower birth-order. (160),(161), (162), (163) Close temporal relationship of measles infection with another viral infection has also been found to be a risk for SSPE. (163),(164) These features are thought to be associated with a 'high-zone model' of immune tolerance and reflect intensive exposure to measles virus.

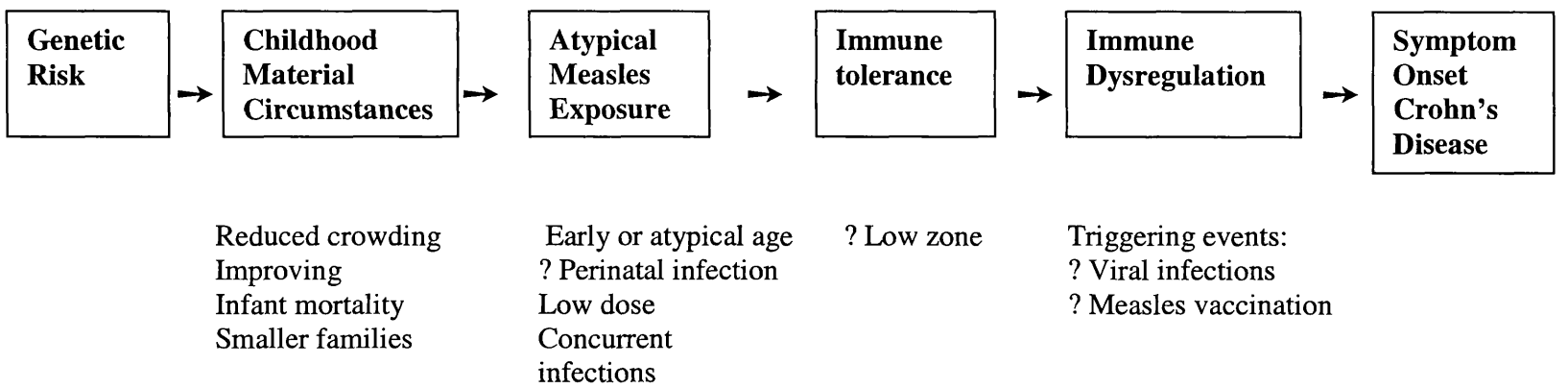
These features of SSPE contrast with Crohn's disease, where female sex, urban populations, developed countries, high birth order, are found. Here a model of 'low-zone' tolerance has been proposed, where initial atypical measles infection due to early or atypical age at low-dose measles virus exposure may result in later CD. This may require further triggering events such as infections to produce disease. (165), (2), (66)

The introduction of measles vaccination has greatly reduced the overall risk of SSPE. However, some studies suggest that vaccination may have acted as a co-factor in hastening the onset of SSPE, in those who experienced previous natural measles. (163) (166) This was at a time when wild measles was prevalent. The overall effect of single dose monovalent measles has been to protect against SSPE, with the disease becoming extremely rare in the UK since 1980's. (160) Since the number of those experiencing wild measles and measles vaccination together will have steadily dropped with time, Wakefield suggests that the 'at risk' population will have been removed, giving protection against SSPE. If the same were true for IBD, more recent studies of measles

vaccination in those who were unlikely to have been exposed to wild measles may also show a protective effect. (2)

This does not explain why Crohn's disease, especially in younger children, continues to increase in incidence. The possible association of IBD with the introduction of MMR in 1988 is also unknown, under current investigation and beyond the aims of this thesis.

Fig 5 Flow diagram of Wakefield's proposed role of measles virus in the aetiopathogenesis of Crohn's disease.



Epidemiological studies-perinatal and in utero exposure to measles

Perinatal and *in utero* exposure to measles virus has been identified as a risk factor for Crohn's disease in some studies (167),(168), but not others (169),(170) (11;171) A Swedish group found a significant excess of patients with CD in those born in the 3-month period following a measles epidemic. (167)The study was restricted to those born between 1945-1954, for whom a birth cohort effect has also been described. (43) This pattern has not been replicated in other countries or in other years (11;172). However, as measles followed an approximately 2-yearly epidemic pattern in Europe prior to mass vaccination (although less frequent earlier in the century), a cohort pattern for SSPE or IBD is unlikely to be found (2) (11)

The same Swedish investigators reported in detail on four of the offspring of mothers who experienced measles infection in the third trimester or puerperium. Three out of four had developed extensive Crohn's disease by the age of 30 years. All three had preceding antibiotic resistant, presumably viral, pneumonia. The one case that did not report CD had reported typical measles infection age 6 years. Examination of intestinal tissue from all three patients showed positive immunostaining with measles-virus primary antibody, and immunogold electron microscopy also supported the finding of measles–virus like nucleoprotein antigen in granulomata and lymphoid aggregates, suggesting possible persistent measles infection of the gut. (168)

There have been four other studies that have not found any association between *in utero* exposure to measles and subsequent IBD. A Danish register study traced the offspring of 25 women who had been exposed to measles in pregnancy. None of the 26 offspring identified had a diagnosis of IBD recorded in the national hospital discharge register or in the regional IBD register, although case ascertainment may have been incomplete. (170) A prospective controlled British study of 47 people exposed to measles in utero found no cases of IBD from GP questionnaires in the exposed group. (169) An American study followed up 6 offspring whose mothers had documented measles infection in pregnancy, and again none had developed IBD after a mean of 38 years follow-up. (171) Another national British study examined specific childhood and in utero

infections: measles, mumps and whooping cough, in two longitudinal birth cohorts and failed to find any association with CD or UC. (128)

Whilst all these studies are based on small numbers of cases, and some may have had incomplete case ascertainment, they contradict the findings by Ekbom that in-utero measles is a significant risk for Crohn's disease in the offspring. (168) It is possible that the original findings were due to chance. Alternatively, the association may have reflected other additional risk factors that were peculiar to those born in Sweden in 1940's and 1950's, such as concurrent infections, specific wild measles virus strains, or childhood material circumstances. (2)

Epidemiological studies-childhood infection with measles virus

If measles infection in childhood is a risk for subsequent IBD, an age window of susceptibility may be apparent. This is found for SSPE, where early infection (before 5 years) is a recognised risk factor for persistent measles infection and subsequent SSPE. However, as measles followed an approximately 2-yearly epidemic pattern in Europe prior to mass vaccination, a cohort pattern for SSPE or IBD is unlikely to be found (2;11)

Several studies have looked at specific viral infections in childhood and subsequent IBD, although only one has found a significant association between measles infection and IBD. (171) (11;45;47;111;128)

A multi-centre international retrospective case-control study of 498 cases and 998 age and sex matched hospital controls found no differences in reported measles, mumps, German measles, gastro-enteritis or scarlet fever between cases and controls by age 10 years. Chickenpox was significantly less frequent in UC cases. There was also a significant excess of recurrent respiratory infections in IBD cases overall. The main criticisms of this study are the problems of recall bias and the combination of data from disparate sources and countries that may have masked individual differences between them. (47) An American case-control study found increased but non-significant relative odds for CD and UC in those reporting measles infection (OR 1.32, 95% CI 0.77-2.26 and OR 2.14, 95% CI 0.97-4.75 respectively).(111)

A British national case-control study utilising cases from a national IBD patient support group found no association between CD and exposure to a measles epidemic around birth or measles infection in childhood. The validity of these findings is hampered by a low response rate (21%\) and the possibility of recall and selection biases. (11;45)

A second study by the same authors used two prospective birth cohort studies in a nested case-control design. Specific data on childhood infection with measles, mumps and whooping cough was obtained prospectively by age 7 years, reducing recall bias. No significant association was found between CD, UC and any of the childhood infections. The lack of association with any previously identified risk factors for IBD may reflect limited power of the study, as only 55 IBD cases were found. The prevalence of IBD by age 43 years was 5.12/1000 and 2.54/1000 by age 33 years: amongst the highest reported in Europe.

A twin study, that used a same-sex unaffected twin as a control did not find a significant increase in childhood measles, mumps or chickenpox infection in twins with IBD. This is unsurprising, as in early childhood twins are likely to be simultaneously or sequentially exposed to the same infections, even though one twin may have had subclinical disease. (173)

The most recent study (from the Mayo clinic) to look for specific risk of IBD associated with childhood measles infection, examined measles infection before 5 years (based on the SSPE model, where infection under 5 years is a risk for SSPE). Subjects with prospectively documented clinical measles infection before age 5 years, diagnosed at least 30 years previously, were identified from the Rochester Epidemiology Project register. Standardised incidence ratios (SIR) were calculated using recent age-specific incidence rates of IBD in the same population base to calculate the expected number of cases of UC and CD. 12 confirmed cases of IBD were identified out of 662 who responded to questionnaires. The standardised incidence ratios (SIR) for CD and UC in those with documented measles infection before age 5 years respectively were 3.1 (95% CI 1.1-6.8) and 3.9 (95% CI 1.1-6.5). Measles infection before age 2 years (an extremely atypical age) had a greater risk (SIR 4.4, 95% CI 1.9-8.7). A response rate of 57% may have biased the results, although non-responders did not differ in sex or age from

responders. Another problem was the lack of adjustment for potential confounding factors such as childhood material circumstances.

The authors suggest that timing of measles infection may be important in determining possible persistence of measles infection, perhaps due to the lack of immune competence at an early age. It may also reflect an atypical immune response to measles when experienced at an early age, which may coincide with a window of vulnerability for subsequent immune regulation. This immune programming, on a background of genetic predisposition may increase the risk for later IBD (most children **prior** to vaccination would develop measles infection between 5 and 9 years). (171)Measles virus infection may have a prolonged effect on immune function, for some years after wild infection. (174;175)

This could be one explanation why most of the retrospective studies of childhood measles infection have not found any association with IBD, as studies would have to look at potentially subtle differences in childhood infectious exposures (see below) which are nearly impossible to examine retrospectively.

Wakefield suggests that additional factors must be important and necessary to produce IBD, as most subjects whom reported early measles did not develop IBD. These factors could be a combination of genetic susceptibility and as suggested by some studies, atypical exposures such as age or concurrent viral infections (See below). (176)

Epidemiological studies-atypical measles exposure: concurrent infections and animal exposures

From the above studies it appears that factors other than age of exposure to measles virus alone must be important if the measles hypothesis holds true. For SSPE, these other characteristics have been studied in some detail. A close temporal relationship between chickenpox infection (163) and encephalitogenic enterovirus (164) within six months of encountering wild measles infection was found to be a significant risk for SSPE. This has led to two studies investigating the role of concurrent infections as potential risks for IBD, a hypothesis suggested by Montgomery. (48)

The first study used prospectively collected data from the BCS70 study, but this work was not part of my hypotheses. Measles and mumps in the same year of life were significantly associated with both UC (relative odds 7.47, 95% CI 2.42- 23.06) and CD (relative odds 4.27, 95% CI 11.24-14.46). A second study using population data from Iceland examined exposure to measles and mumps and chickenpox epidemics occurring within a year of each other and subsequent risk of IBD. Concurrent measles and mumps epidemics before age 6 years were significantly associated with both UC and CD. The risk of IBD increased significantly with the number of overlapping epidemics: The adjusted risk ratio for CD with 3 concurrent epidemics was 8.17, (95% CI 1.97-33.89) and for UC was 2.77 (95% CI 1.43-5.36). No combinations with chickenpox were found to be significantly associated with IBD.

For SSPE, animal exposure in childhood has been described as a risk factor. Dogs infected with canine distemper virus (which has a close antigenic resemblance to measles virus) and bird ownership were found to be significantly associated with subsequent SSPE. (163)

Animal contact has been studied in relationship with IBD in several studies. The multinational study by Gilat found that keeping a rodent as a pet was a significant risk for UC, but not other animal exposures. (47) Having a bird as a pet was significantly associated with CD in another study. (82) A twin study also describes a significant increase in overall animal exposure of the affected twin, compared to the unaffected twin (Odds ratio 6.42, 95% CI 1.7-35). (173)

Epidemiological studies-measles vaccination

The possible impact of monovalent measles vaccination on the development of inflammatory bowel disease has been investigated in 4 studies and forms the basis of one of the studies in this thesis. Measles vaccination was started at 1-2 years of age in England and Wales in 1968. Uptake of the monovalent vaccine increased from 50-60% (before 1980) to 70% by 1986. The vaccine is a live attenuated virus of either Schwartz or Enders Edmonton strains. It results in approximately 95% seroconversion. Since

1988, measles vaccine in the United Kingdom has been combined with rubella and mumps in the MMR, with an uptake rate of 92% in 1992 (177).

The earliest study to specifically examine the possible association between monovalent measles vaccine and IBD was performed by Thompson et al. This group examined the prevalence of Crohn's disease, ulcerative colitis, coeliac disease and peptic ulcer in people who had received live measles vaccine as part of a measles vaccine trial of 3545 people, born in 1960-63 (Medical Research Council trial). (11) A longitudinal birth cohort of 11,407 unvaccinated subjects from the National Child Development Study, born in 1958, were used for comparison, as were 2541 partners of those vaccinated. The relative risk of developing Crohn's disease in the vaccinated group was 3.01 (95% CI 1.45-6.23) and of developing ulcerative colitis were 2.53 (95% CI 1.15-5.55). There was also a non-significant increase in inflammatory bowel disease (but not coeliac disease or peptic ulcers) in vaccinated subjects compared with their partners. This study had some important potential methodological problems that may have influenced the results. Loss to follow up (although similar in both groups) and different methods of questioning regarding IBD status in the vaccinated and unvaccinated groups may have resulted in case ascertainment and selection bias. The younger cohort is also likely to have a higher prevalence of IBD due to temporal trends. An extremely high prevalence of IBD in the NCDS cohort at age 33 years (who were unvaccinated) was recorded, of 254 per 100,000. This suggests the case ascertainment overall was likely to have been rigorous.

In contrast, Feeney et al found no such association in a case-control study in one English region. (178) Some 140 patients with IBD, born after 1968, were compared with 280 age and sex matched controls from general practice (GP). Vaccination history before age 5 years was obtained retrospectively from GP records and community health vaccination records. Vaccination rates for pertussis, diphtheria/tetanus and measles did not differ significantly between cases and controls. Some concern over possible systematic biases and unreliable ascertainment of vaccination status may have influenced these findings. It is also notable that this study was undertaken on subjects born after 1968, compared with the study by Thompson, hence temporal changes in the epidemiology of IBD and wild measles and differing material circumstances in childhood

may also be responsible for the different findings to Thompson's study. Some of the controls may also yet develop IBD, as the study group was also too young to identify those at peak age of developing IBD.

A multicentre study of early risk factors looked at retrospective vaccination history until 6 years in several countries with differing vaccination schedules. No significant association was found between BCG, diphtheria, pertussis, tetanus or measles vaccine and IBD. Smallpox vaccination was significantly less common in CD patients than controls. However, the vaccination hypothesis was not *a priori* here and further data were not published. (47)

A prospective follow-up study in Finland investigated gastrointestinal symptoms following measles, mumps and rubella vaccine (MMR).(179) This vaccine contained a live attenuated strain of the Enders Edmonton measles virus and was given at 14-18 months and again at 6 years to approximately 3 million children. Adverse events in the weeks following vaccination were reported. 31 children had gastrointestinal symptoms and these children were traced a mean of 9 years following vaccination (maximum 15 years). None were found to have IBD, although such short follow-up is unlikely to detect any cases of IBD, as paediatric IBD is still relatively rare. The prevalence of IBD in those children who did not report adverse reaction was also not recorded., and there was no unvaccinated control group. It is also unclear why only those reporting GI in the 3 weeks post vaccination were chosen for long-term follow up as this did not appear to be part of the hypothesis tested.

A case-control study, as part of a vaccine safety project in America, studied 155 cases with UC or CD born between 1958 and 1989 and age and sex-matched controls. No significant association was found between previous vaccination with any measles containing vaccine (MMR or other measles containing vaccines) or age at vaccination and subsequent IBD. However, those vaccinated at an older age appeared at increased risk of CD than those vaccinated <12 months, the converse being true for UC. (180)

Studies of monovalent measles vaccine and MMR are unlikely to be comparable. The monovalent vaccine was introduced in at time when wild measles was endemic, and was given at different age. MMR was started in this country following 30 years of monovalent measles vaccine, when the nature of wild measles infection is likely to have

been changed. The immunogenic effects of three live attenuated vaccines given simultaneously are also likely to differ from a single monovalent vaccine. The possibility of interaction between these paramyxoviruses has already been discussed in the context of atypical measles exposures above, although this has not yet been studied for the MMR vaccine. The strain of measles vaccine used in the MMR is also variable. The above study used the Enders Edmonton strain, whilst in the UK, Moraten strain is used. It would be unwise to assume that findings from studies on monovalent vaccines can be generalised to the MMR, as the age at vaccination, strain, route and adjuvant type are all important parameters in determining the subsequent immune response to vaccines. (181)

It is unknown whether *age* at measles vaccination has any influence in delayed disease such as SSPE or potentially IBD. Whether the timing of exposure to vaccine strains of infections is an important factor for later IBD is untested, but the age at vaccination may be related to the development of other chronic disorders such as diabetes mellitus, predominantly in animal studies. (182;183)

The presence of measles virus -histopathological and immunological studies

Work by the Inflammatory Bowel Disease Study Group at the Royal Free Hospital School of Medicine has shown that the pathology found in Crohn's disease is a chronic granulomatous vasculitis. (129;184) A vascular pathogenesis has also been identified for ulcerative colitis. (185) The finding of granulomas in the lumen of blood vessels in CD has been suggested as the primary site of infection in CD, rather than luminal infections. Subsequent studies confirm that granulomatous vasculitis and multifocal gastrointestinal infarction may explain many of the pathological hallmarks of CD. These include 'skip' lesions and transmural inflammation, (186;187) (188) aphthoid ulceration, (189) mesenteric marginal ulceration, (190) anastamotic recurrence (191) (192) and thrombogenesis. (193) (194) (195) (187) (196) (49) According to Wakefield, these studies suggest that the granuloma is a localised response to infection, and that the responsible infection may reside in the intestinal blood vessels endothelium in CD. (49)

Wakefield proposes that it is biologically plausible that measles virus is an infection that could be responsible for the pathological findings described. (2) Measles

virus has specific tropism for the gut during primary infection, and the virus induces vasculitis in the mesenteric microvascular endothelium. (197) Measles virus can result in the histopathological changes similar to CD, namely vasculitis, giant cell formation, and distribution throughout the gastrointestinal tract. Following measles infection, secondary lymphoid follicles develop with overlying necrosis, producing Koplik's spots. These are similar to aphthoid ulcers of CD. (198) Measles virus is also able to persist in the lymphoid tissue, particular of the gut. (199)

Identification of measles virus within tissue from inflammatory bowel disease may be necessary in some traditional criteria for causality, but not others (200;201). Studies from different centres conflict in their conclusions, which in some cases may reflect different methodological processes.

Measles virus-like particles have been identified ultrastructurally in intestine from patients with Crohn's disease using electron microscopy in two separate centres. (49) (202) In-situ hybridisation and immunohistochemistry using mono- and polyclonal antibodies against different measles virus proteins identified elements of measles virus in granulomata of CD tissue, but not healthy controls (203) or other chronic inflammatory bowel diseases (including UC and intestinal tuberculosis). (204) Immunogold electron microscopy and in situ hybridisation for genomic RNA support these ultrastructural findings in some studies. (49;205) However, concerns have been raised about the specificity of these techniques in detecting specific viral proteins and in the ambiguity in discriminating viral particles from cellular structures using electron microscopy.

A recent Japanese study reported finding 'measles related antigen', an unidentified human protein, by immunohistochemistry. This was present in CD, UC and other forms of colitis but not in healthy controls. The antibody and methods were different to those of previous studies: - in particular Crohn's granulomata and lymphoid follicles were not examined. (206) The authors of the paper speculate that this antigen may be responsible for the autoimmune response, perhaps via molecular mimicry, which is found in inflamed bowel tissue that is not specific to CD. This is not contrary to Wakefield's hypothesis –such mechanisms may explain why enteric infections often appear to trigger the onset of IBD. Wakefield speculates that susceptible individuals

primed by early atypical measles infection may later suffer enteric infections that result in expression of 'measles related antigen' proteins and fuel the ongoing immune response. (207)

In contrast to SSPE, few of the cells within the granulomata appear infected with measles, and the viral copy number is very low. (205;207;208) Reverse transcriptase polymerase chain reaction (RT-PCR) methods have therefore been used to detect measles virus RNA in Crohn's disease tissue. Five studies have not found evidence of measles RNA, (209) (210) (211) (211) (212) whilst two studies have found measles RNA in intestine (203) and peripheral blood. (213) (213) Differences in methods and the possible presence of measles in very low copy numbers may explain the discrepancies between these studies as discussed by Wakefield (2;214)

The immune response to measles virus has been considered in IBD patients in several studies. Some studies have shown an increase in measles virus IgM reactivity in CD and UC patients compared with controls. This may reflect heightened immune responsiveness in patients with IBD rather than evidence of persistent measles infection. (203) (215) (216) (217)Other studies have not replicated these findings. One did not find raised measles antibodies using a complement fixation test.(218) Two other studies failed to find raised measles IgM titres in a family with multiple members affected with Crohn's disease. (156;219) In a multicentre Israeli study, IgG antibodies to measles were present more frequently in CD than UC or controls but this was not statistically significant. (220)

Overall, at present there is insufficient evidence to either confirm or refute the measles hypothesis for inflammatory bowel disease. Some of the epidemiological, ultrastructural and immunohistochemical evidence seem compelling but lack of consistent gene sequencing of measles virus in the intestinal tissue of patients with IBD is inconsistent and contradictory.

Problems with interpreting epidemiological studies

A recent review highlights the problems assessing the global epidemiology of IBD (221). The lack of routinely collected incidence data in most countries has resulted in most studies being conducted retrospectively by interested specialists. These are often based on small numbers of cases from hospital inpatient records, which can often be misleading, as IBD is increasingly being diagnosed and managed in an outpatient setting. Some studies are not age standardised, making comparisons difficult. In addition, case definitions, age of onset of disease (which may differ from age at diagnosis by several years) and geographical boundaries may be unclear.

Difficulty in interpreting apparently changing patterns of disease over time may also be due to the improvements in diagnostic techniques (radiological and endoscopic). In addition, a change in the pattern of infectious diseases that were previously misdiagnosed as IBD may also affect incidence risks.

Mortality figures for IBD have been used in some studies to reflect incidence patterns. However, deaths from IBD are extremely rare (42) and changing figures are more likely to reflect improving clinical practice or changing patterns of disease complications.

Methods

The 1970 British Cohort Study

Description of the 1970 British Cohort Study – birth to age 16 years

This study used data from the 1970 British Cohort Study (BCS70). This ongoing national study follows all those born during one week (5-11th April) in 1970 who live in Great Britain. The study was established by the National Birthday Trust Fund and the Royal College of Obstetricians and Gynaecologists. This was following the success of the1958 National Child Development Study. This was a similar birth cohort used to investigate perinatal mortality. The Centre for Longitudinal Studies at the Institute of Education now administers the BCS70.

Information was requested on all babies born after the 24th week of gestation from midnight on 5th April to midnight on 11th April 1970. Some 16954 live births and 242 foetal deaths were recorded and it is thought that only 2-5% of all births were not included in the study.

In the birth survey, questionnaires were completed by interview with the mother, usually conducted by a midwife. These related to antenatal care, delivery, socio-demographic data of the parents, and the first seven days post-partum.

At 22 and 42 months further surveys were undertaken using a 10% sample of the birth cohort, with addition of all multiple births, post-mature and low birthweight babies. These data were not used in this thesis.

At 5 years, the cohort members were again traced, primarily through the family practitioner committees. 13,135 of an estimated cohort size of 16284 (80.7%) were traced and interviewed by health visitors on or shortly after their fifth birthday. The interview comprised a maternal self-completion questionnaire (asking about the child's behaviour, mother's health and opinions), a home parental interview (asking about social and medical history), and a test booklet for the child. A developmental history was also taken from child health clinics where available. Those who were not traced at age 5 years did not significantly differ in social class at birth, or sex from those that were traced. At age 7

years 1915 of these untraced children were located and it was found that were more likely to have been children of single mothers, and be of ethnic minorities. (222)

At 10 years, 14,875 cohort members were traced out of a predicted target population of 16,500 (93%). A self-completion questionnaire by child, parent and schoolteacher, an interview with the parents by a health visitor, medical examination of the child by school doctor and educational tests were all carried out. Those cohort members who responded at age 10 years did not significantly differ in social class at birth from non-responders, but those from ethnic minorities, who had single mothers; teenage and older mothers and unemployed fathers were again slightly under-represented.

At 16 years, 13,000 cohort members were traced out of a predicted 16,500 (79%). A self-completion questionnaire by child, parent and schoolteacher, an interview with the parents by a health visitor, medical examination of the child by school doctor and educational tests were again all carried out. Young men and those from lower social classes were under-represented in this sample, as well as some regional variation.

Description of the 1970 British Cohort Study – 26 year sweep

During earlier follow-up of the cohort in 1975,1980 and 1986, cohort members were traced predominantly through schools. However after age 16 years attempts to continue contact were made annually with a birthday card, which was used to confirm their address. This maintained contact with about 9,000 of the target 16,000-cohort members up until 1996. To improve follow-up at age 26 years, collaboration with the Royal Free Hospital Medical School and the Driver and Vehicle Licensing Agency (DVLA) enabled tracing letters to be sent to all cohort members identified by their database of addresses. Some 9,803 out of a target of 16,000 (61%) subjects were identified in this manner.

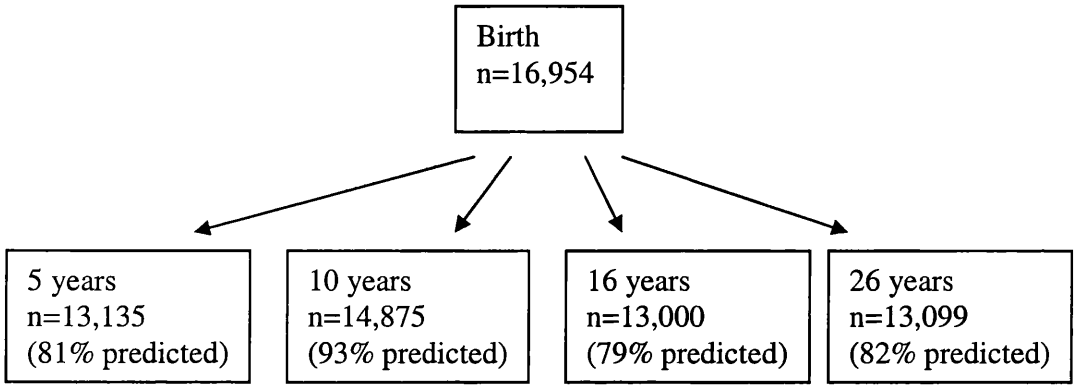
Further telephone tracing exercises and matching via Family Health Service Authorities in England and Wales and the health Boards in Scotland later traced addresses a total of some 13,099-cohort members of a target 16,000 (82%). These additional subjects form part of this thesis. The representativeness of those traced at age 26 years compared with the earlier cohorts will be discussed in detail in the results section. However, not surprisingly, those born outside Britain, those from ethnic

minorities, those born to single, teenage mothers and unemployed fathers, those from lower social classes, those with lower school achievement and poorer housing conditions are under-represented at age 26 years. Further details of the mode of data collection at age 26 years are described in forthcoming sections. See Figure 6 for summary.

The National Child Development Study (NCDS)

This birth cohort study was used in addition to the BCS70 for the analysis of handedness in this thesis only. Other data from this cohort has previously been analysed and published and so is not described in further detail.(128) The birth cohort was established in 1958, and was made of 17,414 infants born in Great Britain from 3rd to 9th March 1958. It represented 98% of births during this period. (223) At the time of this study, there have been five major 'sweeps' (comprised of an interview and questionnaires) to the cohort members or their parents, the last being in 1991. In 1991, 13,444 subjects were traced of 15,666 cohort members (85.8%) thought to remain in the target population.

Fig 6 Follow-up of the BCS70 members from birth to age 26 years



Survey instruments, case ascertainment and ethical approval

Survey instruments

A single postal questionnaire was sent to all 13,099 traced cohort members in 1995-6 when cohort members were aged 25 to 26 years. This asked if they had *"ever had or been told by a doctor that they had any of these illnesses: Crohn's disease, ulcerative colitis, appendicitis that required surgical removal of your appendix or diabetes requiring insulin injections"*. A further question asking, *" Has a doctor ever said that you had pneumonia? If yes, did you spend one or more nights in hospital because of this pneumonia?"*

Reminders were sent if there was no response after 3 weeks and a second reminder after a further month. Later in the year a further questionnaire regarding other socio-medical factors was also sent to cohort members, although the data from this was not available for this study.

Case ascertainment

All self-reported cases of IBD were contacted again by post to confirm their responses and to record their age at diagnosis. Permission was also sought to contact their physician to confirm the diagnosis. The age at which the cohort member was first told they had inflammatory bowel disease was requested in the same questionnaire. Again, reminders were sent if there was no response after 3 weeks and a second reminder after a further month.

In addition, data collected from earlier BCS70 survey was used to identify further cohort members with IBD who had reported Crohn's disease, ulcerative colitis or inflammatory bowel disease in free text as part of the medical survey at 16 years.

Cohort members reporting insulin dependent diabetes mellitus (IDDM) were used as chronic disease controls. No further information was sought to confirm these diagnoses.

Standard questionnaires were then sent to the named physicians provided by those cohort members permitting us access to their records. Written and telephone reminders

after 1 month were carried out if there was no initial response. These questionnaires were based on the criteria described by Riiss (9) as described in the introduction and were identical to those used by Thompson et al. (11;45) In addition the areas affected by the disease and the age at diagnosis were requested. Histopathological samples, copies of histology, microbiology and radiology reports were also requested.

(See Appendix 5 for copies of questionnaires).

Ethical approval

The ethical practices committee of the Royal Free Hampstead NHS Trust approved the study.

Outcome measures

Case ascertainment has been described above. Subjects who responded to the survey at age 26 years as having CD or UC and whose doctors confirmed the diagnosis according to the criteria described (9) were considered to be confirmed cases.

Subjects who responded to the survey at age 26 years but who did not give permission to contact their physician or who did not respond to this request were considered to be possible cases. The age at disease diagnosis was taken from the self-reported questionnaire, and from the doctor's confirmation details. The disease extent was taken from the doctor's confirmation record.

Histological specimens were obtained for 27/52 subjects. An independent histological diagnosis was made at the Royal Free Hospital (PD) who did not have access to clinical information on the patient at the time of specimen review, but was aware of the likely diagnosis of IBD. Further details are given in the results section.

Those who reported IDDM at age 26 years were not further contacted and so were all considered as definite cases.

Explanatory variables and potential confounding factors

Demographic measures and socioeconomic status

Sex

This was determined from the maternal interview during the birth survey.

Parental social class at birth

This was classified by the Registrar general's classification and recorded by midwives at birth.

I	Professional occupation
II	managerial and other professionals
III NM	non-manual skilled occupations
III M	skilled manual workers
IV	semi-skilled workers
V	unskilled workers
Other	
Unsupported	single parent, not working
Housewives	

Parental education

The age of each parent at which full time education was completed, including college or university, was recorded as part of the birth survey. This was divided into the following categories: <12, 13-15, 16-18 and over 19 years.

Maternal age at delivery

Maternal age at birth of the cohort member was recorded in the birth survey. This was considered both as a continuous variable and a categorical variable (divided into the following categories: under 19 years, 20 to 29 years and over 30 years).

Region of Birth

This was recorded at birth and divided into the following regions:

North, Yorkshire and Humberside, North West, East Midlands, West Midlands, East Anglia, South West, South Wales, North Wales, South East, London, Scotland, Northern Ireland, Overseas births.

Person per room ratio

Health visitors at the home interview recorded the number of rooms and number of persons living in the household at age 5 and age 10 years. A person per room ratio was calculated and this was divided into fifths of the distribution to form a categorical variable for statistical analysis.

Ethnic origin

When the cohort members were 10 years, ethnic origin of the child was recorded at parental interview and categorised as British (English, Welsh, Scottish or Northern Irish), Irish, Other European, West Indian or Guyanese, Indian, Pakistani or Bangladeshi, and other ethnic group (including mixed parentage).

Measures of genetic predisposition - family history of IBD

A family history of IBD was obtained from the maternal self-completion questionnaire when the cohort members were 16 years of age. This was defined as those with a first degree relative with a diagnosis of ulcerative colitis or Crohn's disease before 1987. We were unable to confirm family histories from medical records. Only those cohort members who responded at both age 16 and age 26 years were included in the analysis.

Material and cultural circumstances in childhood

Smoking

Data on maternal smoking in pregnancy, and parental smoking when the children were 5, 10 and 16 years were collected prospectively by interview with health visitors. Cigarette smoking was defined as smoking an average of one or more cigarettes per day.

At the birth interview, the mothers were asked, "has (the mother) smoked during this pregnancy?" The responses coded were "yes", "no" and "not known" (excluded from analysis). At age 5 years, at parental home interview, parents were asked, "do either N's mother or father smoke at all at present?"

At age 10 years, the cohort member's parents were asked "Does the mother (father) smoke cigarettes or cigars or a pipe at present" and "Do any other members of the household smoke at present?" The cohort member was also asked "How many do you smoke a week?"

At age 16 years, the cohort members themselves were asked "how many cigarettes do you smoke a week?" and "Does your mother (father) smoke?" "Does your brother(s) (sister(s)) smoke?" Data on smoking habit at age 26 years were not available at the time of this study.

A combined variable of exposure to smoke by age 5, 10 and 16 years was derived from the above. Smoke exposure was considered to have been present if any of the household members reported smoking at any of the interviews. Potential confounding factors, sex, father's social class at birth, crowding variable at age 10 years and ethnic origin of the child at age 10 years were adjusted for in the multivariate model (smoke exposure by age 16 years only).

Birth Order

Data regarding number of siblings was obtained prospectively from health visitors at age 5 years, and from parental interview at age 10 years. Father's social class (at birth) and crowding ratio (at age 5) were also obtained at this time and were considered to be potential confounding factors, as were sex and mothers ethnic origin (from age 10 data). All were modelled as categorical variables. Cross-tabulation and multiple logistic regression was used to investigate the relationship between number of siblings, number of older siblings and number of younger siblings with later CD or UC. The number of older and younger siblings were coded as none, one, two or more siblings ('none' used as the baseline), with adjustment for potential confounders. Two-tailed Fisher's exact test was used to assess significance were small numbers in some cells were evident. The Chi squared test for trend was also used when analysing the age 10 data. The possible effect

of older siblings on disease phenotype was examined by comparing older siblings in cohort members with CD and those with UC, with adjustment for sex and social class as above. Analysis of birth order of cohort members age 10 years has previously been reported by Montgomery in this cohort (1), the data collection was performed by myself and the results are included for completeness.

Parity

Parity was defined as the number of previous pregnancies experienced by the mother, excluding miscarriages and abortions in early pregnancy, but including stillbirths. This was obtained by from the medical notes the midwives at the time birth. For analysis, parity was divided into three groups: 0,1 and 2 or more previous pregnancies. Cross-tabulation and multiple logistic regression was used to investigate the relationship between maternal parity and IBD. Maternal parity was coded as none, one, two or more ('none' used as the baseline), with adjustment for potential confounders, sex, father's social class at birth and mothers ethnic origin (taken from the age 10 data). The possible effect parity on disease phenotype was examined by comparing maternal parity in cohort members with CD and those with UC.

Nursery Attendance

At age 5 the cohort members' parent's were asked whether the child had attended a nursery or playgroup since birth for duration of 3 months or longer. The age the child first started such a placement was also recorded. Age at starting nursery was considered as a continuous variable and a categorical variable, when it was divided into 0-2 yrs, 3 yrs and 4-5yrs. Linear and logistic regression, Cross-tabulation and the chi-squared test were used assess any association, 2-tailed p values are reported.

Perinatal events

Birth weight and weight for gestational age

Birthweight in grams and gestational age in weeks were recorded by the midwife at the time of birth and were considered as continuous variables.

Weight for gestational age was calculated by dividing the birthweight in grams by the gestational age of the baby in weeks. The gestational age was determined as the number of full weeks of pregnancy from the last menstrual period to the date of birth.

Subsequent growth:weight, height and head circumference

Weight in kg was also measured at the time of the medical examination at age 10 and age 16 years. Height in cm was also measured at the time of the medical examination at age 5, 10 and age 16 years. Head circumference in cm was recorded at the time of the medical examination at age 5, 10 and 16 years.

Unpaired t-tests were used to examine the differences between the mean weight, height and head circumference in cohort members with IBD and the whole cohort. Where the data was not normally distributed the Mann-Whitney U test for non-parametric data was used.

Neonatal Feeding

Data on infant feeding practices were obtained from the medical records at birth by the midwives and on maternal questionnaire at age 5 years.

From the medical records, the types of feed the baby had for each 24-hour period after birth for the first seven days were recorded. All types of feeds were recorded and divided into breast fed (with or without additional feeds) and not breast fed in the first day (received colostrum) and first week of life.

At age 5 years the mother was asked by a health visitor "was (the cohort member) breast fed partly or wholly, even for a few days?" The responses were coded yes-for less than 1 month, yes for 1-3months, yes for 3 months or more, yes but cannot remember how long, no, and not known.

Univariate analysis using crosstabulation, Chi-squared test and Chi-squared test for trend were used to investigate any relationship with CD,UC, diabetes or IBD combined.

Potential confounding factors for the possible associations between breastfeeding and CD or UC were considered to be ethnic origin (from age 10 data), crowding ratio (from age 5 data), birthweight (in fifths of the distribution, from birth data) and parity

(divided into 0,1 or 2+ previous pregnancies from the birth data). Colostrum on the first day and reported breastfeeding (ever or never) from the age 5 data were used in the final model. Multiple logistic regression analysis was used to examine any association between these factors and later CD, UC diabetes or IBD.

Appendicectomy and Tonsillectomy

Data on appendicectomy were collected at age 10 years (When parents were asked if the cohort members had ever had an appendicectomy) and at age 26 years. At age 26 years appendicectomy was defined from the answer to the postal survey 'Have you ever had appendicitis-that required surgical removal of your appendix?'
Potential confounding factors were considered to be exposure to smoke in childhood, sex, father's social class at birth and crowding variable at age 10 years. Data on current smoking habit at age 26 years were not available at the time of this study.

Data on Tonsillectomy were collected at age 5, 10 and 16 years. At age 5 and 10 years the parents were specifically asked if the child had ever had a 'Tonsillectomy or T's and A's'. At age 16 years the cohort members themselves were asked if they had 'ever had any illnesses/accidents/operations for as long as you can remember' and asked to list these in free text.

Perinatal infections and illnesses

From the birth survey, data were used regarding maternal and neonatal infections as recorded by the midwives at birth using the clinical notes and at maternal interview in the first week of birth.

The questions asked about he mother were 'during the first seven days after delivery did the mother have: any urinary infection? Any genital infection? any venous complications in the legs? Any other morbidity or illness?' The answers were coded yes, no or not known.

The questions asked about the neonate were 'Did the baby have "sticky eyes"?', 'Did the baby have a discharge from the umbilicus?' and 'were there any other illnesses or conditions of the baby?' The answers were coded yes, no or not known.

Cross-tabulation and Chi-squared tests were used to investigate any relationship with CD, UC or IBD. Fisher's exact test was used due to the small numbers in some cells.

Where the neonate spent the first night after birth

Data from the birth survey was used to identify where the baby spent the first night after birth. Separation from the mother was used as a proxy measure of risk of early exposure to nonfamilial microorganisms (at a low dose or for a limited duration). This was classified into three groups. The first were those who spent the day with the mother, but the night in the infant nursery cared for by nursing staff, the second were those who spent both day and night by their mother's bed. The third group were those babies who did not fit into the above, but who were either in the ward nursery all the time, in the special care or surgical unit or at home.

Potential confounding factors were considered to be sex, father's social class at the birth, crowding ratio in fifths of the distribution (from the age 5 data), maternal parity (divided into 0, 1 or 2 or more previous pregnancies), birthweight in 10ths of the distribution, maternal age (<30, 31-35 and 36+years) and breastfeeding practices. Two measures of breastfeeding were used. The first was whether the baby had received colostrum or not (see above) and the second was a categorical variable of duration of breastfeeding from the age 5 data (see above).

Cross-tabulation and multiple logistic regression were used to investigate the association with inflammatory bowel disease or diabetes and spending the first night in the nursery. In the adjusted model all variables were modelled as a series of binary dummies. Only cohort members with complete data for all the variables in the model were included in the final analysis.

Childhood Illnesses

Childhood eczema, hay fever and wheezing

At age 5 years, cohort member's parents were asked about specific medical conditions since birth. The questions used were 'Eczema, hay fever or sneezing attacks'. The parents were also asked 'has the child had one or more attacks in which she/he has had wheezing on the chest, regardless of the cause'. The responses code were 'yes', 'no never' and 'not known'.

At age 10 years, cohort member's parents were asked, 'has the child ever had any of the following:-eczema, hay fever'. The parents were also asked 'has the child ever had one or more attacks in which there was wheezing or whistling in the chest'. The responses codes were 'yes', 'no never' and 'not known'. Cross-tabulation and Chi-squared tests were used to investigate any relationship with CD, UC or IBD. Where appropriate, Fisher's exact test was used due to the small numbers in some cells. Multivariate analysis was not performed as it was outside the remit of this thesis.

Non-specific childhood infections

At age 5 years, cohort member's parents were asked about specific medical conditions since birth. The questions used were 'Has the child had any of the following in the past years or previous to past year:- Ear discharge (pus not wax), repeated sore throats requiring medical attention, bronchitis, pneumonia, meningitis'. The responses code were 'yes', 'no never' and 'not known'. Cross-tabulation and Chi-squared tests were used to investigate any relationship with CD, UC or IBD. Fisher's exact test was used due to the small numbers in some cells.

At age 10 years, cohort member's parents were asked, 'has the child ever had any of the following:- recurrent sore throats, middle ear infection/glue ear, bronchitis, pneumonia, any other significant illness or disability'. The responses code were 'yes', 'no never' and 'not known'. Cross-tabulation and Chi-squared tests were used to investigate any relationship with CD, UC or IBD. Fisher's exact test was used due to the small numbers in some cells.

Childhood infections and vaccinations

Viral infections in childhood and age of measles infection

When the cohort members were 10 years old, their parents were interviewed by health visitors and questioned about whether their child had ever suffered from specific infections, namely measles, mumps, pertussis (whooping cough) and chickenpox. The age at which these were experienced was also recorded in years.

Age at measles infection was considered both as a continuous variable and as a categorical variable, with age at infection divided into never, under 1 year, 1, 2 or 3years, and 4 years over.

Further analysis was also performed with the age groups divided into never, under 2 years, 2 to 5 years and 6 to10 years. This grouping was chosen, as these ages are known to represent a risk for subacute sclerosing pan-encephalitis. (162)

Cross-tabulations and the chi-squared test were used for univariate analyses of categorical variables, with multiple logistic regression to adjust for potential confounding factors. The unpaired t-test was used to compare the mean age of measles infection between Crohn's disease and ulcerative colitis.

Age of other infections and concurrent infections

The age of infection with mumps, chickenpox, pertussis and meningitis have also been investigated in this cohort as part of another study. They have not been further analysed here. Concurrent infection with measles, mumps and chickenpox within one year of life were also examined but are again not part of this work, although they have been alluded to. (48)

Childhood vaccinations and age at vaccination

Information on childhood vaccination history was collected by health visitors from home parental interviews at 5 years (n=13,135) and 10 years (n=13,697). When the cohort members were 5-years old their parents were asked, "At what ages did (your child) receive immunisation, against what diseases and where?" A checklist of immunisations against specific diseases was supplied. At 10 years, the parents were asked, "Has the child ever received any form of immunisation or vaccination...if yes,

against which of the following diseases has the child been immunised?" It was not possible to assess false-positive vaccination histories.

The age at measles vaccination as recorded at age 5 years was used as both a continuous and categorical variable. For the categorical variable, the age at measles vaccination reported at age 5 years was divided into categories: under 2 years, 2, 3 and 4-5 years.

Cross-tabulations and the chi-squared test were used for univariate analyses of categorical variables, with multiple logistic regression to adjust for potential confounding factors. The Mann-Whitney U test was used to compare the mean age of measles vaccination between Crohn's disease and ulcerative colitis.

The reliability of parental recall of vaccination was assessed by comparing parental response at age 5 and 10 years.(see results for details)

It was not possible to validate data further from medical records, as these were unavailable.

Age at first exposure to measles as vaccine or wild infection

A Combined variable was constructed using the age at measles infection reported at 10 years and the age at measles vaccination reported at 5 years to give the age at first reported exposure to measles in either form. If both measles infection and measles vaccination were reported, the earliest age was used. This variable was divided into the following categories: no exposure, 0-1 year, 2 years, 3 years and 4-10 years.

Measles vaccination and measles infection

Children whose parents reported both measles vaccination by age 5 years and measles infection by age 10 years were compared with those who had reported either measles infection or measles vaccination alone, to see if such double exposure conferred any excess risk of inflammatory bowel disease. A variable of type of measles exposure was created from the measles vaccination data age 5 years and the measles infection data at age 10 years. Only subjects with data for both variables were included in this analysis.

Logistic regression analysis was used to assess the relationship between type of exposure to measles (infection, vaccination, both or neither) and subsequent

inflammatory bowel disease. Crohn's disease and ulcerative colitis were considered as the dependant variables and type of measles exposure as the independent variable. Those who reported neither measles vaccination nor infection were used as the baseline.

Adverse reactions following vaccinations

A history of adverse reactions to vaccinations was documented at age 10 years. Parents were asked if their child had ever had any form of reaction to any vaccination. Where a reaction was reported, details on the disease being vaccinated against, the age of the child, the length of time between the vaccination and the start of the reaction and a description of the reaction were recorded. Cross-tabulation and the chi-squared test were used assess any association, and Fisher's 2-tailed p values are reported due to small numbers in some cells.

Other putative risk factors

Contraceptive pill

Data regarding contraceptive pill use in female cohort members was only available at age 16 years. Cohort members themselves were asked if they had ever been on the contraceptive pill and asked to circle yes or no.

Hand, foot and eye preference

This study used data from two nationally representative birth cohort studies: the 1970 British Cohort Study (BCS70) as previously described, and the National Child Development Study (NCDS). These prospective ongoing studies follow all those born during one week (5-11th April 1970 for the BCS70 and 3-9th March 1958 for the NCDS), who lived in Great Britain.(224)

For the BCS70, a postal self-completion survey was conducted in 1995-6 when cohort members were aged 25 to 26 years as previously described. All self-reported cases of IBD were contacted again by post to confirm their responses and to seek permission to contact their physician to confirm the diagnosis.

The response rate of those subjects traced at age 26 years in the BCS70 cohort was 77% Of the 8150 subjects from the BCS70 used in these analyses, 21 had Crohn's disease and 19 had ulcerative colitis.

For the NCDS, the diagnosis of inflammatory bowel disease was established by using the international coding of diseases codes reported at face-to-face interview when the subjects were 23 or 33 years old. Physicians did not confirm these diagnoses. The response rate of those subjects traced at age 33 years in the NCDS cohort was 85%. Of the 9771 subjects from the NCDS used in these analyses, 17 had Crohn's disease and 16 had ulcerative colitis.(225;226)

Despite loss to follow-up in both cohorts since their inception, cohort members for whom data was available were broadly representative of the original cohorts, with approximately two-thirds of both cohorts used in the analyses having a father with a manual social class.

Midwives at birth in 1958 (NCDS) or 1970 (BCS70) recorded the sex of each subject.

For the BCS70, handedness and foot preference were ascribed following a medical examination and interview at age 10 years. The child was asked: *"which hand is used for writing?"* and *"which foot is used for kicking a ball?"* For eye preference, the children were asked, "Can you show me what you do with a telescope?" Responses of right, left, either or unknown were recorded.

For the NCDS, the response of parents at interview with a health visitor was recorded in 1965, when the children were 7-years old. The question *"does the mother think the child is: right-handed, left-handed, mixed right and left or don't know"* was used. Eye preference was not requested in the NCDS survey.

Responses of 'either' in the BCS70 or 'mixed right and left' in the NCDS were excluded from the analysis.

The two cohorts were combined to increase statistical power. Cross-tabulation was used to investigate the relationship between sex and inflammatory bowel disease and sex and handedness, as sex was considered to be a potential confounding factor. Adjustment was similarly made for cohort.

Cross-tabulation and Pearson's Chi-squared test were used to assess the relationships between handedness and ulcerative colitis, Crohn's disease and inflammatory bowel disease. These were performed after combining both cohorts. Two-tailed Pearson's p-values were used. Similar methods were used to assess foot preference to kick a ball and eye preference to view a telescope in the BCS70. Relative odds were calculated with 95% confidence intervals. All p values reported were 2-tailed. Logistic regression analysis was used to adjust for sex and birth cohort.

Statistical analysis

Specific analyses have been described in more detail above, and where relevant in the results section. Univariate analyses for categorical variables used cross-tabulation and the chi-squared test. 2-tailed Pearson's p-values and relative odds with 95% confidence intervals are stated in most cases, unless otherwise described. Fisher's exact test and p-values are stated when there are expected counts of less than 5 in any of the cells.

Multivariate analyses using multiple logistic regression was used to adjust for potential confounding factors where stated. All variables were modelled as a series of binary dummies. Relative odds with 95% confidence intervals are also stated. Statistical analyses were performed using the SPSS for Windows version 9.

Results

Demographic data, histology, prevalence and response rate

Responders characteristics at age 26 years compared with the original birth cohort

Whilst there was inevitable loss to follow up of approximately 3000 cohort members from birth to age 26 years, some13, 099-cohort members of a target 16,000 (82%) were traced. Those responding to our survey remained largely representative of the original birth cohort. The main losses were those from the most disadvantaged as expected. (See table 5)

Table 5

Comparison of demographic characteristics of cohort members at birth, and in those responding at age 26 years

Characteristic	Birth		Responders at age 26 years		2-tailed p value
	No	%	No	%	
Sex					**p=0.0003 χ^2=12.88**
Male	9281	48.8	4834	49.5	
Female	8632	45.4	4921	50.4	
Missing	1097	5.8	2	0.1	
Total	19010	100	9757	100	
Social Class Father					**p<0.0001 χ^2=103.9**
I	820	4.3	507	5.2	
II	1906	10.0	1151	11.8	
III Non-manual	1924	10.1	1172	12.0	
III Manual	7544	39.7	3980	40.8	
IV	2473	13.0	1186	12.2	
V	1106	5.8	451	4.6	
Other	502	2.6	255	2.6	
Unsupported	824	4.3	284	2.9	
Missing	1911	10.1	41	0.4	
Total	19010	100	9757	100	
Maternal age					**p<0.0001 χ^2=22.08**
<19	1662	8.7	717	7.3	
20-29	11357	59.7	6120	62.7	
30+	4074	21.4	2141	21.9	
Missing	1917	10.1	779	8.0	
Total	19010	100	9757	100	
Age mother completed education					**p<0.0001 χ^2=27.19**
<12	203	1.1	70	0.7	
13-15	11029	58.0	5603	57.4	
16-18	4773	25.1	2677	27.4	
19+	1044	5.5	623	6.4	
Missing	1961	10.3	784	8.0	
Total	19010	100	9757	100	

Characteristic	Birth		Responders at age 26 years		2-tailed p value
	No	%	No	%	
Age father completed education					**p<0.0001 χ^2=90.01**
<12	123	0.6	70	0.7	
13-15	10560	55.5	5603	57.4	
16-18	4087	21.5	2677	27.4	
19+	1505	7.9	623	6.4	
Missing	2735	14.4	784	8.0	
Total	19010	100	9757	100	
Child's Ethnic origin					**p=0.0042 χ^2=17.2**
British	13020	68.5	8178	83.8	
Irish	75	0.4	49	0.5	
Other European	80	0.4	42	0.4	
West Indian	164	0.9	72	0.7	
Indian, Bangladeshi or Pakistani	321	1.7	150	1.5	
Other	53	0.3	25	0.3	
Missing	5297	27.9	1241	12.7	
Total	19010	100	9757	100	
Region of residence					
North	1023	5.4	593	6.1	
Yorks & Humberside	1485	7.8	809	8.3	
North West	2170	11.4	1191	12.2	
East Midlands	1035	5.4	556	5.7	
West Midlands	1745	9.2	895	9.2	
East Anglia	539	2.8	353	3.6	
South West	1049	5.5	629	6.4	
South Wales	615	3.2	342	3.5	
North Wales	264	1.4	158	1.6	
South East	2895	15.2	1674	17.2	
London	2121	11.2	1010	10.4	
Scotland	1617	8.5	804	8.2	
Northern Ireland	626	3.3	10	0.1	
Overseas	12	0.1	3	0.0	
Missing	1814	9.5	730	7.5	
Total	19010	100	9757	100	

Response at age 26 years and prevalence of IBD and diabetes

Some 13,099 cohort members were traced at age 26 years, approximately 82% of the predicted target population of 16,000. Of these, 9803 completed questionnaires were returned. 309 addresses were incorrect and 12 cohort members refused to participate. The Driver and Vehicle Licensing Agency provided 2373 addresses that could not be supplied by the social statistics research unit at City University (who supplied the remaining 7430). When invalid and untraced addresses were excluded, the response rate was 77%.

There were 32 members reporting Crohn's disease and 27 reporting ulcerative colitis. The subjects themselves (5 cases) or their physicians (3 cases) subsequently refuted 2 reports of CD and 5 of UC when further questioned.

21/30 members reporting CD and 12/22 reporting UC gave permission to contact their physicians-all of who confirmed the diagnosis according to the criteria described. (9) Those who did not give permission (9 CD, 10 UC) where considered as having probable IBD.

For those with confirmed disease, the prevalence per 10,000 was 21.4 (95% CI 12.3 to 30.6) for CD, 12.24 (95% CI 5.3 to 19.2) for UC and 33.7 (95% CI 22.2 to 45.1) for inflammatory bowel disease overall.

If the same disease specific false positive rate as the whole sample is taken for the unconfirmed cases with probable IBD, the overall estimated prevalence per 10,000 were 29.8 (95% CI 19.0 to 40.6), 19.4 (95% CI 10.5 to 28.1) and 49.2 (95% CI 35.3 to 63.0) for CD, UC and IBD respectively. (See table 6)

Some 40cohort members reported diabetes that required injection of insulin at age 26 years. These diagnoses were not confirmed, but assuming them all to be accurate, a disease prevalence of 41 per 10,000 (95% CI 28.3 to 53.7) was found.

Table 6 Prevalence of inflammatory bowel disease amongst 26 year olds and relationship with sex and father's social class at birth

Characteristics	No IBD (%)	Crohn's disease (%)		Ulcerative colitis (%)	
		All cases	Confirmed	All cases	Confirmed
Social Class Father					
I	504 (5.6)	1 (3)		2 (9)	1 (8)
II	1144 (12.8)	4 (13)	3 (14)	3 (14)	3 (25)
III Non-manual	1167 (13.1)	5 (17)	5 (24)		
III Manual	3959 (44.3)	11 (37)	9 (43)	10 (46)	4 (33)
IV	1180 (13.2)	4 (13)	2 (10)	2 (9)	2 (17)
V	449 (5.0)	1 (3)	1 (5)	1 (5)	
Other	254 (2.8)			1 (5)	
Unsupported	284 (3.2)				
Missing	771 (8.1)	4 (13)	1 (5)	3 (14)	2 (17)
Sex					
Male	4808 (49.5)	14 (47)	9 (43)	13 (59)	7 (58)
Female	4896 (50.5)	16 (53)	12 (57)	9 (41)	5 (42)
Total	9704 (100)	30 (100)	21 (100)	22 (100)	12 (100)
Prevalence per 10,000 (95%CI)		29.8 (19.0-40.6)	21.4 (12.3 -30.6)	19.4 (10.5 -28.1)	12.2 (5.3 -19.2)

Histological diagnosis

Table 7 shows the comparison between the clinical diagnosis according to the Riis criteria (9) (Table 1), the histological diagnosis made at the hospital the patient attends and the independent histological diagnosis made at the Royal Free Hospital (PD) who did not have access to clinical information on the patient at the time of specimen review.

Table 7 Histological diagnosis –comparison with independent pathologist.

No	Clinical diagnosis (Riis criteria)	Specimen	Pathological Diagnosis	Granuloma present	Independent Pathological Diagnosis
1	CD	Colon	CD	Yes	CD
2	CD	Colon	CD	Yes	missing
3	CD	Colectomy	CD	Yes	CD
4	CD	Colon	CD	No	missing
5	CD	Anus	CD	Yes	CD
6	CD	Right hemicolectomy	CD	Yes	CD
7	CD	Ileal resection	CD	Yes	CD
8	CD	Rectum	CD	No	CD
9	CD	Ileal resection	CD	Yes	missing
10	CD	Ileal Resection	CD	No	missing
11	CD	Right hemicolectomy	CD	No	CD
12	CD	Right hemicolectomy	CD	Yes	CD
13	CD	Colon	CD	Yes	CD
14	CD	Right hemicolectomy	CD	Yes	CD
15	CD	Colon	CD	Yes	CD
16	CD	Colon	Normal	No	normal
17	CD	Rectum	Normal	No	normal
18	UC	Rectum	UC	No	IBD non-specific
19	UC	Caecum	IBD non-specific	No	IBD non-specific
20	UC	Colon	UC	No	UC
21	UC	Colon	IBD non-specific	No	Normal
22	UC	Colon	UC	No	Missing
23	UC	Rectum	UC	No	IBD ?CD
24	UC	Rectum	UC	No	IBD non-specific
25	UC	Rectum	UC	No	IBD non-specific
26	UC	Colon	UC	No	UC
27	UC	Colon	IBD non-specific	yes	IBD non-specific

Histological specimens were obtained for 27/52 subjects. Some 17 specimens were available for Crohn's disease. Of these, 11/17 showed granuloma formation. The pathological and clinical diagnoses correlated in all cases, with the independent pathologist agreeing with the diagnosis of the initial pathologist in all available specimens. Two normal rectal biopsies were also reviewed in subjects with isolated small bowel disease.

Some 10 specimens were available for ulcerative colitis. The initial pathological diagnosis and clinical diagnoses correlated in 7/10 cases. In the remaining three cases the pathology was described as inflammatory bowel disease of non-specific type. The independent pathologist agreed with the diagnosis of the initial pathologist in 4/9 available specimens. In those five where the diagnoses were different, three were described as inflammatory bowel disease of non-specific type and one as IBD with possible CD by the independent pathologist, but as UC on the initial diagnosis. The remaining case had a normal colon biopsy reviewed by the independent pathologist but unfortunately specimens from the initial diagnosis were unavailable. One cohort member was clinically initially thought to have *Campylobacter* colitis, but subsequent follow-up revised this to UC. The histological biopsies were consistent with IBD but a single granuloma was found, making the pathological diagnosis unclear.

Disease distribution and age of onset

Disease extent

The disease extent was available for 21/32 (65.6%) cohort members reporting Crohn's disease.

The disease extent was available for 12/20 (60%) cohort members reporting ulcerative colitis. (Figure 7 and Table 8)

Fig 7 Crohn's disease extent

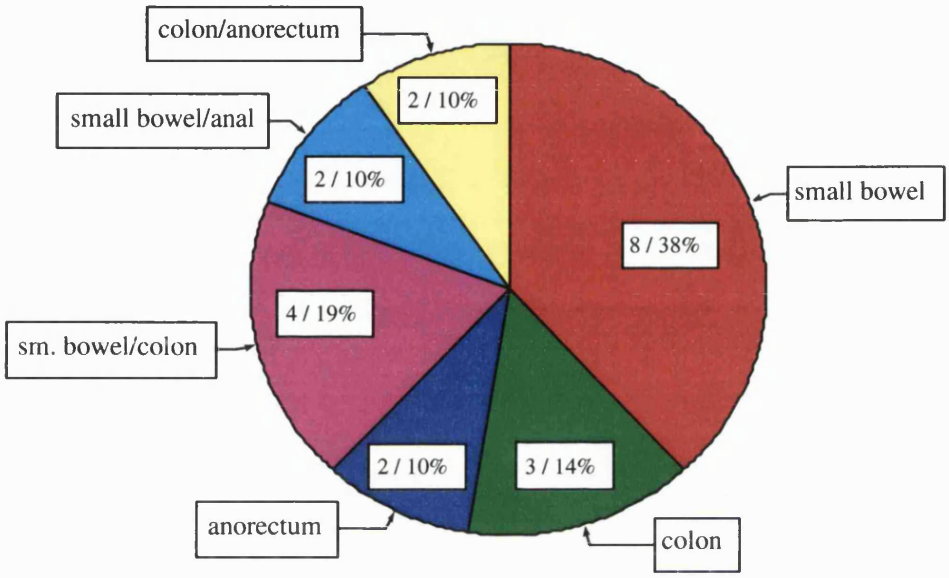


Table 8 Extent of Ulcerative colitis

Site	Frequency	%
Rectum	8	66.7
Left colon	3	25.0
Pancolitis	1	8.3
Total	12	100

Age at diagnosis of disease

The age at disease diagnosis was recorded in 22/32 (68.8%) subjects with Crohn's disease and 13/20 (65%) with UC. The mean age at disease diagnosis for Crohn's disease was 20.59 years, (range 12 to 26 years, standard deviation 3.79). The mean age at disease

diagnosis for ulcerative colitis was 20.62 years, (range 15 to 25 years, standard deviation 3.5). The mean age at disease diagnosis for IBD overall was 20.60 years, (range 12 to 26 years, standard deviation 3.63).

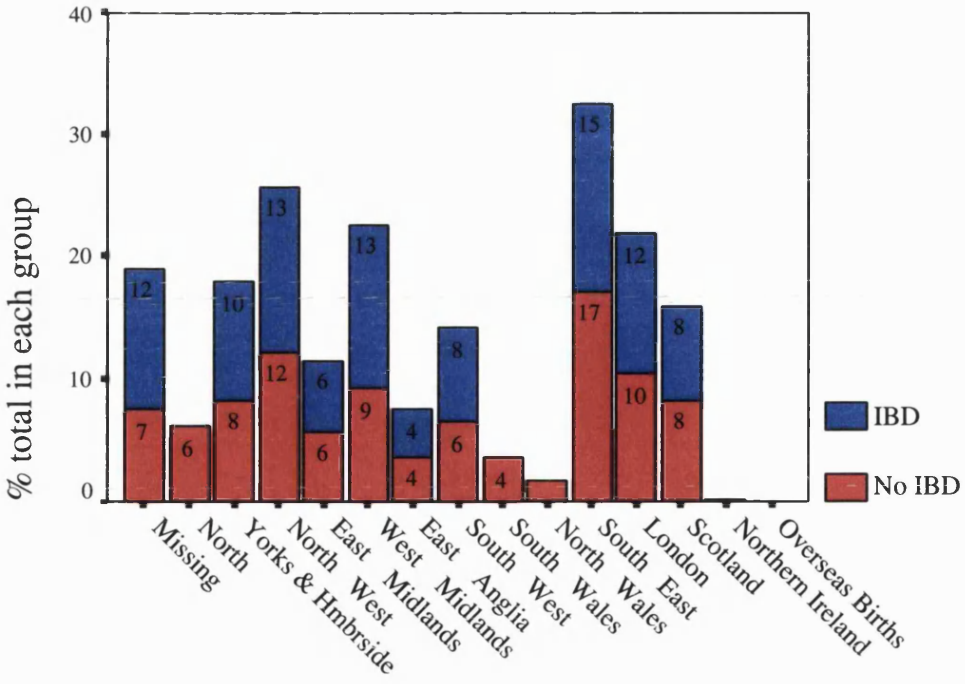
5 cohort members had their disease diagnosed before age 16 years (3 with UC and 2 with CD). The youngest patient was diagnosed with Crohn's disease at age 12 years. The crude prevalence of paediatric IBD (16 years or under) reported at age 26 years was 5.12 per 10,000.

Demographic measures

Region of birth

The region of birth was available for 46/52 (88%) cohort members with IBD (26/30 with CD and 20/22 with UC) and 36/40 (90%) with diabetes. There was no association between region of birth and any of the outcome diseases (see fig 8)

Fig 8 Region of Residence of Mother in 1970



Region of residence of the mother

Sex

Sex was not significantly associated with CD, UC, IBD or IDDM. The odds ratios and 95% confidence intervals for male sex and CD, UC, IBD and IDDM were 0.68 (0.29 to 1.59, p=.370), 1.21 (0.58 to 2.52, p=0.619), 0.94 (0.55 to 1.63, p=0.838) and 0.65 (0.35 to 1.23, p=0.185) respectively.
See Table 6 above.

Social class, maternal age and parental education

Parent's social class was not associated significantly with any of the outcome diseases. Pearson's χ^2 for the association between fathers social class and IBD was 2.06, 2-tailed p-value 0.957, and for mothers social class 2.68, p=0.848 respectively. For IDDM, the same statistics were χ^2=10.38, p=0.168 for fathers social class and χ^2=5.14, p=0.526 for mothers social class.

Maternal age at delivery was also not significantly associated with inflammatory bowel disease but older maternal age was associated with diabetes. The odds ratio for later diabetes in those with maternal age 30+ was 2.26 (95% CI 1.15 to 4.46, p=0.018), compared with mothers aged 20-29 years. When considered as a continuous variable, the odds ratio for diabetes for each 1-year increase in age at delivery was 1.07 (95% CI 1.01 to 1.13, p=0.017).

Mother's age at completion of full-time education was significantly associated UC (χ^2=22.6, p<0.001), but not CD or diabetes. Father's age at completion of full-time education was significantly associated with UC only (χ^2=9.46, p=0.024), but not CD, IBD overall or diabetes. (See Table 9 and 10)

Table 9 The association between maternal age and parental education and later inflammatory bowel disease or Diabetes

Characteristic	Whole sample (%)	IBD (%)	Statistic For IBD	IDDM (%)	Statistic For IDDM
Maternal age			χ^2=0.85 p=0.654		χ^2=6.33 **p=0.042**
<19	717 (7.3)	5 (10.9)		2 (5.6)	
20-29	6120 (62.7)	32 (69.6)		19 (52.8)	
30+	2141 (21.9)	9 (19.6)		15 (41.7)	
Total	8978	46		36	
Age mother completed education			χ^2=21.69 **p<0.001**		χ^2=2.04 p=0.564
<12	70 (0.8)	3 (6.5)		1 (2.9)	
13-15	5603 (62.4)	26 (56.5)		22 (62.9)	
16-18	2677 (29.8)	16 (34.8)		10 (28.6)	
19+	623 (6.9)	1 (2.2)		2 (5.7)	
Total	8973	36		35	
Age father completed education			χ^2=3.11 p=0.375		χ^2=4.75 p=0.191
<12	44 (0.5)	1 (2.3)		1 (2.9)	
13-15	5437 (62.5)	28 (63.6)		24 (68.6)	
16-18	2344 (27)	10 (22.7)		7 (20)	
19+	870 (10)	5 (11.4)		3 (8.6)	
Total	8695	44		35	

Table 10 Odds ratios for UC and CD according to parental age at completing education

Characteristic	Whole sample (%)	CD (%)	OR for CD (95% CI) p-value	UC (%)	OR for UC (95% CI) p-value
Age mother completed education			p=0.162		**p=0.005**
<12	70 (0.8)	1 (3.8)	6.23 (0.80-48.3) p=0.080	2 (10)	12.65 (2.80-57.12) **p=0.010**
13-15	5603 (62.4)	13 (50)	1.0	13 (65)	1.0
16-18	2677 (29.8)	12 (46.2)	1.94 (0.88-4.25) p=0.636	4 (20)	0.64 (0.21-1.98) p=0.441
19+	623 (6.9)	0 (0)	-	1 (5)	0.69 (0.09-5.29) p=0.722
Total	8973	26		20	
Age father completed education			p=0.951		**p=0.024**
<12	44 (0.5)	0 (0)	-	1 (5.3)	11.48 (1.45-90.82) **p=0.021**
13-15	5437 (62.5)	17 (68)	1.0	11 (57.9)	1.0
16-18	2344 (27)	6 (24)	0.82 (0.32-2.08) p=0.819	4 (21.1)	0.84 (0.27-2.65) p=0.771
19+	870 (10)	2 (8)	0.73 (0.17-3.19) p=0.680	3 (15.8)	1.71 (0.48-6.13) p=0.413
Total	8695	25		19	

Household Crowding

This was considered at age 5 and age 10 years. At age 5 years, only Crohn's disease was associated significantly with household crowding overall (χ^2=12.59, p=0.0.013). Those in the second and third fifths of the distribution being at increased risk of subsequent CD, when compared with those living in the most crowded conditions, although the stratified relative odds were not statistically significant. (See Table 11). There was no such association for UC (χ^2=2.22, p=0.696), or diabetes (χ^2=2.66, p=0.617).

At age 10 years there was no statistical association between the person per room ratio (divided into fifths of the distribution) and subsequent CD (χ^2=4.81, p=0.307), UC (χ^2=1.41, p=0.843), or diabetes (χ^2=8.89, p=0.064).

There was also no statistical association between the person per room ratio when comparing UC against CD at age 5 (χ^2=3.05, p=0.549) or at age 10 years (χ^2=3.25, p=0.518).

Table 11 Odds ratios for Crohn's disease according to person per room ratio at age 5 years (in fifths of the distribution)

Person/room ratio in 5ths distribution	Crohn's Disease (%)	Whole sample (%)	Odds ratio	95% CI
1	1 (4.5)	1318 (16.6)	0.44	0.04-4.80
2	11 (50)	1626 (20.5)	3.89	0.86-17.59
3	5 (22.7)	2077 (26.2)	1.38	0.27-7.12
4	3 (13.6)	1773 (22.3)	0.97	0.16-5.81
5	2 (9.1)	1145 (14.4)	1.0	-
Total	22 (100)	7939 (100)		

Ethnic origin

There were 8516/9757 (87.3%) cohort members with data available for ethnic origin. Some 8178/8516 (96%) were British (21/23 with CD, 16/19 with UC), 148/8516 (1.8%) were Indian, Pakistani or Bangladeshi (2/23 with CD,2/19 with UC), 72/8516 (0.8%) were West Indian (1/19 with UC), 49/8516 Irish (0.6%), 42/8516 (0.5%) Other European and 25/8516 (0.3%) Other. There was a statistically significant relationship between Asian ethnic origin (Indian, Pakistani or Bangladeshi) and subsequent UC (χ^2 =13.24, p=0.021) and IBD (χ^2 =16.47, p=0.006) but not CD (χ^2 =6.86, p=0.231). The unadjusted relative odds for CD, UC and IBD respectively in those of Asian origin using British as baseline were 5.25 (95% CI 1.22-22.6, p=0.027) 6.89 (95% CI 1.57-30.25, p=0.011) and 6.03 (95%CI 2.12-17.13, p=0.0007). Those of West Indian origin showed increased relative odds for UC only (OR 7.18, 95% CI 0.94-54.91, p=0.057), although this was based on a single case, and did not reach the 5% level of statistical significance.

Analysis using maximum numbers including individual Asian subgroups (Indian, Pakistani or Bangladeshi) is shown in table 12 below. There is significant increased risk of IBD in the Indian subgroup, compared with the British group. A non-significant increase in relative odds of 6.11 is also found in the Pakistani group. For UC there is a significant increased relative odds of 14.17 in the Pakistani subgroup. For CD there is a significant increased relative odds of 7.40 in the Indian subgroup. The overall χ^2 =10.84, p=0.146 for CD, χ^2 =17.60, p=0.014 for UC and χ^2 =17.38, p=0.015 for IBD.

After excluding those with missing data for sex and crowding variables there were 8432/9757 (86.4%) cohort members with complete data for analysis. Table 12 shows the relationship between ethnic origins reported at age 10 years and inflammatory bowel disease. Amongst the Asian group there were 6 Bangladeshi's (none with IBD), 36 Pakistanis (1 with UC), and 105 Indians (one with UC and two with CD). 1 of 70 West Indian cohort members had UC, and none of the remaining cohort members from other ethnic groups reported IBD by age 26 years.

There was a significant increase in risk IBD in those of Asian ethnic origin compared with those from the British group (unadjusted Odds ratio 6.10, 95% CI 2.14-17.33, Fisher's p=0.006). Adjustment for sex or household crowding at age 10 years increased the Odds ratio for IBD in the Asian group to 7.28 (95% CI 2.52-21.03). The

relative odds for both Crohn's disease and UC were significantly increased in Asian subjects (see table 13).

Those of West Indian origin showed increased relative odds for UC only, although this was based on a single case, and did not reach the 5% level of statistical significance.

If only those with a physician-confirmed diagnosis of IBD were included, the relationship between Asian origin and subsequent IBD persisted (OR 6.77, 95% CI 2.02-22.67, Fisher's p=0.013).

Family history of IBD (a first degree relative with IBD reported by age 16 years) was also considered as a potential confounding factor. Complete data for this variable as well as the crowding and sex variables was available for only 6864 of 9757 responding at age 26 years (70%), 6623 of whom were British and 112 Asian origin. 31 of these cohort members reported IBD (29 British, 2 Asian ethnic origin). Some 16 cohort members reported a family history of IBD, and these were all of British origin. 2 of these 16 cohort members had IBD themselves (one with UC and one with CD). When family history of IBD was included in the regression model with sex and household crowding, the odds ratio for IBD in those of Asian origin, compared with the British group, remained statistically significant (OR 5.23, 95% CI 1.17-23.31, p=0.025). In the same model, the relative odds for IBD at age 26 years in those with a first degree relative with IBD was 35.26 (95% CI 7.45 to 166.84, p<0.000)

The relationship between family history and IBD will be further described in a subsequent section.

Table 12 The relative odds for inflammatory bowel disease by ethnic origin using maximum numbers

Ethnic origin	Whole sample (%)	CD/UC or IBD	N	Unadjusted Relative Odds (95% CI)	2-tailed p-value
British	8178 (96.9)	CD	21 (50.0)	1.0	-
		UC	16 (38.0)	1.0	-
		IBD	37 (88.1)	1.0	-
West Indian	72 (0.8)	CD	0	*	*
		UC	1 (5.3)	7.18 (0.94-54.91)	0.057
		IBD	1 (2.4)	3.10 (42-22.90)	0.268
Indian	107 (1.3)	CD	2	7.40 (1.71-31.96)	0.007
		UC	1 (5.3)	4.81 (0.63-36.62)	0.129
		IBD	3 (7.1)	6.35 (1.93-20.91)	0.002
Pakistani	37 (0.4)	CD	0	*	*
		UC	1 (5.3)	14.17 (1.83-109.70)	0.011
		IBD	1 (2.4)	6.11 (0.82-45.76)	0.078
Bangladeshi	6 (0.1)	IBD	0	*	*
Irish	49 (0.5)	IBD	0	*	*
Other European	42 (0.4)	CD	0	*	*
Other	25 (0.3)	CD	0	*	*
Total	8516		42		

*Relative Odds not calculated due to empty cells.

Table 13 The relative odds for inflammatory bowel disease by ethnic origin. Adjustment for sex, and household crowding

Ethnic origin	Whole sample (%)	CD/UC or IBD	N (%)	Unadjusted Relative Odds (95% CI)	Adjusted Relative Odds (95% CI)
British	8100 (96.90)	CD	21 (50.0)	1.0	1.0
		UC	16 (38.0)	1.0	1.0
		IBD	37 (88.1)	1.0	1.0
West Indian	70 (0.008)	CD	0	*	*
		UC	1 (2.38)	7.32 (.96-56.00)	7.57 (0.98-58.37)
		IBD	1 (2.38)	3.16 (.43-23.30)	3.55 (.48-26.30)
Indian, Pakistani or Bangladeshi	147 (0.017)	CD	2 (4.76)	5.31 (1.23-22.84)	7.05 (1.60-31.03)
		UC	2 (4.76)	6.97 (1.59-30.59)	7.35 (1.64-32.99)
		IBD	4 (9.52)	6.10 (2.14-17.33)	7.28 (2.52-21.03)
Irish	49 (0.006)	CD	0	*	*
		UC	0	*	*
		IBD	0	*	*
Other European	41 (0.005)	CD	0	*	*
		UC	0	*	*
		IBD	0	*	*
Other	25 (0.003)	CD	0	*	*
		UC	0	*	*
		IBD	0	*	*
Total	8432		42		

*Relative Odds not calculated due to empty cells.

Genetic Predisposition and Family History of IBD

Only those cohort members who responded at both age 16 and age 26 years were included in the analysis. 38 cohort members with IBD (20 with CD and 18 with UC) were therefore included along with 7681 unaffected cohort members. Overall, 18 cohort members reported a family history of IBD with one currently unaffected subject reporting both parents were affected (one with UC and one with CD). See table 14.

Table 14 Family history of inflammatory bowel disease in 7719 cohort members responding at age 16 and 26 years

Relationship to cohort member	Crohn's disease	Ulcerative colitis	IBD
Mother	2	9	11
Father	3	3	6
Sibling	0	2	2
Total	5	14	19

However, only 2/38 cohort members with IBD themselves reported a family history of IBD. One male subject had small and large bowel Crohn's disease, and reported a mother with CD. This subject reported an age at diagnosis of 14 years. This was significantly younger than the mean of 20 years for the 15 subjects who had both age at diagnosis and family history data available (one-sample t-test, t=5.84 on 14 degrees of freedom, p=0.000). The second cohort member with a family history of IBD was female. She was diagnosed at age 15 years with UC and had reported a brother also with UC. This was significantly younger than the mean of 20 years for the 12 subjects who had both age at diagnosis and family history data available (one-sample t-test, t=6.20 on 11 degrees of freedom, p=0.000).

The overall odds ratio of having IBD by 26 yrs if any first-degree relative has the disease was 26.6 (95 % CI 5.9 to 120). If the relative was a parent, the odds ratio was 13.8, with 95% CI 1.8 to 107.3. The small numbers of relatives with IBD in this study

made it impossible to interpret more detailed analysis of the type of relationship most at risk. See tables 15 and 16.

The relationship between family history in a first degree relative and subsequent IBD at age 26 years was also found to be strengthened when adjustment for sex, crowding and ethnicity were made (OR for IBD=35.26, 95% CI 7.45 to 166.84, $p<0.000$). See section on ethnicity for further details.

Table 15 Family History of IBD in cohort members with and without IBD themselves at age 26 years

Disease State of Cohort member at 26 years	Family History of CD (%)	Family History of UC (%)	Family History of IBD (%)
CD	1/20 (5%) *		
UC		1/18 (5.6%) **	
IBD			2/38 (5.3%) ***
Currently unaffected	4/7699 (0.1%)	13/7701 (0.2%)	16/7681 (0.2%) $

* Fishers exact test p=0.013 **Fishers exact test p=0.032

***Fishers exact test p=0.003 $ one cohort member has both parents with IBD

Table 16 Unadjusted relative odds for inflammatory bowel disease at 26 years in those with a first degree relative or parent with IBD

	CD in cohort member age 26 yrs		UC in cohort member age 26 yrs		IBD in cohort member age 26 yrs	
	OR (95% CI)	**Fisher's p value**	**OR (95% CI)**	**Fisher's p value**	**OR (95% CI)**	**Fisher's p value**
Any first degree relative	101.3 (10.8 to 948)	0.013	34.8 (4.3 to 281)	0.032	26.6 (5.9 to 120)	0.003
Parent	101.3 (10.8 to 948)	0.013	_	_	13.8 (1.8 to 107)	0.076

Material and cultural circumstances in childhood

Availability of hot water and hygiene facilities in the home

All subjects with IBD and diabetes had access to hot water, in the home, sole use of a kitchen, and sole use of a bathroom and indoor toilet at age 5 years. This did not differ significantly from the whole cohort. The prevalence of hygiene facilities in the home is shown below. The relative odds for CD, UC and Diabetes have not been shown.

Table 17 Table of availability of hot water and hygiene facilities in the home at age 5 years

	Hot water	Indoor toilet	Kitchen	Bathroom
Sole use	7754 (98%)	7571 (96.6%)	7863 (99.3%)	7697 (97.1%)
Shared	58 (0.7%)	59 (0.8%)	50 (0.6%)	67 (0.8%)
None	104 (1.3%)	200 (2.6%)	10 (0.1%)	164 (2.1%)
Total	7916	7830	7923	7927
Missing	1841	1927	1834	1829

Birth Order

Some 8049/9757 (82.5%) responding cohort members at age 26 years had data available on number of older and younger siblings at age 5 years. 22/32 and 15/20 cohort members with CD and UC respectively had sibling data available at age 5 years. There were 4836 (49.3%) cohort members reporting one or more than one older siblings and 3498 (34.8%) reported one or more younger siblings.

A report of any sibling, older or younger, was not significantly associated with later CD. 864/8049 cohort members overall and 21/22 cohort members with CD reported

siblings (OR 2.53, 95% CI 0.34-18.83, Fisher's 2-tailed p-value 0.504). Similarly there was no significant association with siblings and later UC (15/15 reported siblings) or diabetes (36/37 reported siblings, OR 4.35, 95% CI 0.6-31.7, Fisher's 2-tailed p-value 0.176).

When older siblings only were considered at age 5 years, using maximum numbers, 3213/8049 (39.9%) reported no older siblings, 2870/8049 (35.7%) reported one older sibling and 1966/8049 (24.4%) reported two or more than two older siblings. Some 6/22, 14/22 and 2/22 cohort members with CD reported none, one and 2 or more older siblings respectively. Using the Chi squared test there was a significant association between having older siblings and later Crohn's disease, (Pearsons χ^2 =7.851, 2-tailed p-value=0.020). Having one older sibling appeared to be a risk for CD (unadjusted OR 2.62, 95% CI 1.01-6.83, p=0.049), whilst having 2 or more than 2 older siblings appeared to be protective against CD (Unadjusted OR=0.55, 95% CI 0.11-2.70, p=0.457).

Some 3/15, 7/15 and 5/15 cohort members with UC reported none, one and 2 or more than 2 older siblings respectively at age 5 years. Using the Chi squared test there was no association between having older siblings and later Crohn's disease, (Pearsons χ^2 =2.49, 2-tailed p-value=0.288). Using maximum numbers, having one older sibling appeared to be a non-significant risk for UC (unadjusted OR 2.61, 95% CI .68.01-10.10, p=0.164), as did having 2 or more than 2 older siblings (Unadjusted OR=2.72, 95% CI 0.65-11.39, p=0.170).

Combining UC and CD together, there was a significant increased risk of IBD in cohort members reporting older siblings at age 5 years (Pearsons χ^2 =7.37, 2-tailed p-value=0.025). The unadjusted relative odds for IBD (using maximum numbers) with one older sibling were 2.62 (95% CI 1.20-5.73, p=0.016) and for two or more siblings were 1.27 (95% CI 0.47-3.42). There was no association between diabetes and number of older siblings.

Adjustment was made for potential confounders, sex, crowding variable at age 5, and father's social class at birth. Only subjects with complete data for all variables were used in the analysis. A baseline of 0 older sibling was used for comparison. See Table 18.

A second model including mother's ethnic origin, sex and father's social class as potential confounders was also examined. This reduced the number of cases for analysis to 7087 (19 with CD, 14 with UC). The adjusted relative odds for CD and for UC were

again not significant overall (p=0.168 and p=0.248 respectively), but a similar pattern was observed. The relative odds for CD in those with 2 or more older siblings were 0.56, 95% CI .11-2.79, p=0.474, and for UC were 3.56, (95% CI 0.67-18.84, p=0.135). None of the other variables in this model were significantly associated with CD or UC.

Further analysis was performed to assess the relationship between IBD phenotype (UC or CD) and number of older siblings. Compared to those without older siblings, having 2 or more older siblings was protective against CD (OR 0.2, 95% CI 0.02-1.71, p=0.142) and a risk for UC (OR 5.00, 95% CI 0.58-50), although this was not statistically significant overall (Pearsons χ^2 = 3.417, Fisher's p=0.181). Adjusting for sex and social class did not affect this relationship. The adjusted OR for those with 2 or more older siblings and CD were 0.07(95% CI 0.00-1.59, p=0.096) and for UC were 14.29, 95% CI 0.63-294).

When younger siblings only were considered, 4551/8049 (56.5%) reported no older siblings, 3068/8049 (38.1%) reported one younger sibling and 430/8049 (5.3%) reported 2 or more than 2 younger siblings. Some 15/22, 7/22 and 0/22 cohort members with CD reported none, one and 2 or more younger siblings respectively. Using the Chi squared test there was no significant association between having younger siblings and later Crohn's disease, (Pearsons χ^2 =1.937, 2-tailed p-value=0.380).

For UC, 11/15, 3/15 and 1/15 cohort members with UC reported none, one and 2 or more younger siblings respectively. Using the Chi squared test there was no significant association between having younger siblings and later UC, (Pearsons χ^2 =2.09, 2-tailed p-value=0.351).

For diabetes, 17/26, 6/26 and 3/26 cohort members with diabetes reported none, one and 2 or more younger siblings respectively. Using the Chi squared test there was no significant association between having younger siblings and later diabetes, (Pearsons χ^2 =3.79, 2-tailed p-value=0.150).

Previous analysis performed by Montgomery using data from this cohort regarding family structure when the cohort members were age 10 years found a similar pattern. (1) This is shown in Table 19 for completeness. Cohort members with 2 or more older siblings were significantly associated with UC (Unadjusted OR 3.79, 95% CI 1.11-12.98, Fisher's p=0.044) and a significant test for trend with increasing number of older

siblings (p=0.024). The relative odds for UC in those with 2 or more older siblings after adjusting for sex and social class were 3.60 (95% CI 1.05-12.30, p for trend 0.036). An inverse association was seen with number of older siblings and CD. Having 2 or older siblings was associated with a reduced risk of CD, although this was not statistically significant. Younger siblings were not associated with UC or CD.

Among subjects with IBD reporting siblings at age 10, 2/27 with CD and 7/19 with UC reported 2 or older siblings. A larger number of older siblings (2 or more) were predictive of disease phenotype. The relative odds were 0.08 (95% CI 0.01-0.56, Fisher's p=0.011) and 12.25 (95% CI 1.79-83.95) for Crohn's disease and ulcerative colitis respectively. The test for trend was also significant (p=0.007). Adjustment for social class and sex further increases the relative odds for 2 or more siblings and subsequent UC to 14.45 (95% CI 1.92-108.9), with a p for trend of 0.008.

Table 18 **Unadjusted and adjusted relative odds for CD and UC according to number of older siblings reported at age 5 years**

Number of older siblings	Whole sample (%)	With Disease (%)	Unadjusted OR 95% CI p-value	Adjusted OR* 95% CI p-value
Crohn's disease			P=0.036 Pearsons χ^2 = 6.63	P=0.110
0	3087/7723 (40%)	6/21 (28.6%)	-	-
1	2758/7723 (35.7%)	13/21 (61.9%)	2.43 (0.92-6.40) p=0.072	2.22 (0.84-5.88) P=0.109
2+	1878/7723 (24.3%)	2/21 (9.5%)	0.55 (0.11-2.72) p=0.461	0.60 (0.11-3.33) P=0.559
Ulcerative colitis			P=0.285 Pearsons χ^2 = 2.51	P=0.437
0	3087/7723 (40%)	3/15 (20.0%)	-	-
1	2758/7723 (35.7%)	7/15 (46.7%)	2.61 (0.68-10.10) p=0.164	2.36 (0.60-9.24) P=0.217
2+	1878/7723 (24.3%)	5/15 (33.3%)	2.74 (0.65-11.47) p=0.168	2.33 (0.50-10.92) P=0.284
IBD			P=0.041 Pearsons χ^2 = 6.37	P=0.093
0	3087/7723 (40%)	9/36 (25.0%)	-	-
1	2758/7723 (35.7%)	20/36(55.6%)	2.50 (1.13-5.49) p=0.023	2.29 (1.04-5.07) P=0.040
2+	1878/7723 (24.3%)	7/36 (19.4%)	1.28 (0.48-3.44) p=0.626	1.29 (0.44-3.76) P=0.646

*Adjusted for sex, father's social class at birth, crowding variable.

Table 19 Unadjusted Relative Odds for CD and UC according to number of older siblings reported at age 10 years (1)

Number of older siblings	No without IBD (%)	With Disease (%)	Unadjusted OR 95% CI Fisher's p-value	χ^2 for trend
Crohn's disease				P=0.182
0	4111/9031 (46%)	14/27 (52%)	1.00	
1	3014/9031 (33%)	11/27 (41%)	1.07 (0.49-2.36) p=1.000	
2+	1906/9031 (21%)	2/27 (7%)	0.31 (0.70-1.36) p=0.113	
Ulcerative colitis				**P=0.024**
0	4121/9039 (46%)	4/19 (21%)	1.00	
1	3017/9039 (33%)	8/19 (42%)	2.73 (0.82-9.08) p=0.140	
2+	1901/9039 (21%)	7/19 (37%)	3.79 (1.11-12.98) p=0.044	

Parity

Data regarding parity of the cohort members' mother was available for 9023/9757 (92.5%) responding cohort members at age 26 years (26/ 30 reporting CD and 20/22 with UC). Some 3496/9023 (38.7%) mothers overall were nulliparous. Using logistic regression analysis with 0 previous pregnancies as baseline, and maximum number of cases, there was a non-significant association between maternal parity and IBD. The relative odds for CD were reduced for children whose mothers had 2 previous pregnancies, compared with cohort members whose mothers had none. On combining CD and UC, there was a significant risk for IBD at the 5% level in cohort members whose mother reported one or 2 previous pregnancies, compared with those who were reported none. See table 20. There was no significant association between diabetes and maternal parity.

Adjustment was made for potential confounders, sex and father's social class at birth. See Table 21. Only subjects with complete data for all variables were used in the analysis. A baseline of 0 previous pregnancies was used for comparison.

A second model including mother's ethnic origin, sex and father's social class as potential confounders was also examined. This reduced the number of cases for analysis to 7936 (19 with CD, 15 with UC). The adjusted relative odds for CD and for UC were again not significant overall (p=0.300 and p=0.426 respectively), but a similar pattern was observed. The relative odds for CD in those with maternal parity of 2 or more were 0.36, 95% CI .08-1.71, p=0.198, and for UC were 2.03, (95% CI 0.48-8.70, p=0.338). . Only female sex was significantly associated with CD in the multivariate model (OR 2.8, 95% CI 1.01-7.80, p=0.048).

Parity was also considered as a continuous variable, and those with no previous pregnancies excluded. The relative odds for Crohn's disease for each additional pregnancy was 0.43, 95% CI 0.18 to 1.06, p=0.067. The relative odds for UC for each additional pregnancy was, 0.80 95% CI 0.46-1.40, p=0.441.

Further analysis was performed to assess the relationship between IBD phenotype (UC or CD) and maternal parity. A parity of 2 or more was protective against CD (OR 0.33, 95% CI 0.06-2.00, p=0.232) and a risk for UC (OR 3.00, 95% CI 0.50-18 17), although this was not statistically significant overall (Pearsons χ^2 = 1.55, Fisher's p=0.460).

Table 20 Unadjusted Relative Odds for CD, UC, and IBD according to maternal parity (Maximum numbers)

Number previous pregnancies	Whole sample (%)	With disease (%)	Unadjusted OR 95% CI p-value
Crohn's disease			P=0.092
0	3496/9023 (38.7)	9/26 (34.6)	-
1	3108/9023 (34.4)	14/26 (53.8)	1.75 (0.76-4.05) p=0.190
2+	2419/9023 (26.8)	3/26 (11.5)	0.48 (0.13-1.78) p=0.273
Ulcerative colitis			P=0.316
0	3496/9023 (38.7)	5/20 (25.0)	-
1	3108/9023 (34.4)	10/20 (50.0)	2.25 (0.77-6.60) p=0.138
2+	2419/9023 (26.8)	5/20 (25.0)	1.45 (0.42-5.00) p=0.560
IBD			P=0.044
0	3496/9023 (38.7)	14/46 (30.4)	-
1	3108/9023 (34.4)	24/46 (52.2)	1.94 (1.00-3.75) p=0.050
2+	2419/9023 (26.8)	8/46 (17.4)	0.83 (0.35-1.97) p=0.666

Table 21 Unadjusted and adjusted Relative Odds for CD and UC according to maternal parity

Maternal parity	Whole sample (%)	With Disease (%)	Unadjusted OR 95% CI p-value	Adjusted OR* 95% CI p-value
Crohn's disease			P=0.094 Pearsons χ^2 = 4.74	P=0.127
0	3487/9007 (39%)	8/24 (33%)	-	-
1	3103/9007 (34%)	13/24 (54%)	1.83 (0.76-4.42) p=0.180	1.76 (0.73 –4.26) P=0.207
2+	2417/9007 (27%)	3/24 (13%)	0.54 (0.14-2.04) p=0.364	0.53 (0.14-2.01) P=0.349
Ulcerative colitis			P=0.158 Pearsons χ^2 = 3.69	P=0.238
0	3487/9007 (39%)	3/17 (18%)	-	-
1	3103/9007 (35%)	9/17 (53%)	3.30 (0.91-12.43) p=0.068	3.07 (0.83-11.37 P=0.093
2+	2417/9007 (27%)	5/17 (29%)	2.40 (0.57-10.04) p=0.230	2.07 (0.49-8.72) P=0.320

*Adjusted for sex and father's social class at birth.

Nursery Attendance

Data regarding nursery or school attendance by age 5 years were available for 7932/9757 (81%) subjects responding at 26 years. 21/30 (70%) and 15/22 (68%) and 25/40 (63%) cohort members with CD and UC and diabetes respectively had nursery data available at age 5 years.

7597/7932 (95.8%) cohort members reported nursery or school attendance by age 5 years. Some 20/21 (95%), 15/15(100%) and 23/25 (92%) cohort members with CD, UC and diabetes respectively reported nursery attendance by 5 years. There was no significant association between nursery or school attendance by age 5 years and subsequent Crohn's disease (OR 0.88, 95% CI 0.12-6.59, Fisher's p=0.596), ulcerative colitis, or diabetes (OR 0.50, 95% CI 0.12-2.15, Fisher's p=0.284).

The age at starting nursery, when considered as a continuous variable was not significantly associated with any of the outcome diseases. The relative odds for each additional year at starting nursery were 0.89, (95% CI 0.51 to 1.54, p=0.667), 1.92 (95% CI 0.97 to 3.84, p=0.061), and 0.86 (95% CI 0.51 to 1.44, p=0.561), for CD, UC and diabetes respectively.

When age at starting nursery was considered as a categorical variable again there was no statistically significant association between age at staring nursery and any of the outcome diseases. See table 22.

Table 22 Unadjusted Relative Odds for CD, UC, and Diabetes according to age at starting nursery (using age 3yrs as baseline)

Age at starting nursery	Whole sample (%)	With disease (%)	Unadjusted OR	95% CI	2-tailed p-value
Crohn's disease					P=0.370
0-2 yrs	1135/7597 (14.9%)	2/20 (10%)	0.51	(0.11-2.25)	0.371
3 yrs	3743/7597 (49.3%)	13/20 (65%)	-	-	-
4-5yrs	2719/7957 (35.8%)	5/20 (25%)	0.53	(0.19-1.48)	0.226
Ulcerative colitis					P=0.326
0-2 yrs	1135/7597 (14.9%)	1/5 (6.7%)	0.55	(0.07-4.57)	0.580
3 yrs	3743/7597 (49.3%)	6/15 (40%)	-	-	-
4-5yrs	2719/7957 (35.8%)	8/15 (53.3%)	1.84	(0,64-5.30)	0.260
Diabetes					P=0.947
0-2 yrs	1135/7597 (14.9%)	4/23 (17.4%)	1.20	(0.38-3.78)	0.755
3 yrs	3743/7597 (49.3%)	11/23 (47.8%)	-	-	-
4-5yrs	2719/7957 (35.8%)	8/23 (34.8%)	1.00	(0.40-2.50)	0.996

Smoking

Maternal smoking in pregnancy was not significantly associated with Crohn's disease (OR 0.99 95% CI 0.46-2.15), ulcerative colitis (0.90 95% CI 0.37-2.2) or IDDM (OR 0.76 95% CI 0.39-1.51).

Cigarette smoking that was reported by the cohort member themselves at age 10 or 16 years was not significantly associated with UC, CD or IDDM. 95 children (1 with UC) out of 7752 responding to questioning at age 10 reported smoking cigarettes. Some1061children (3CD, 1UC, 4 IDDM) of 4526 responding at age 16 reported smoking cigarettes.

There was no significant association between smoking exposure at any individual age, (5, 10 or 16 years) or with any specific relationship with the cohort member and subsequent UC, CD or diabetes. See table 23.

Exposure to smoke by 5 years (any exposure in pregnancy or at 5 years survey), 10 years (any exposure in pregnancy or at 5 year or 10 year surveys) or by 16 years (any exposure in pregnancy or at 5 year or 10 year or 16 year surveys) was also considered. There was a statistically significant protective effect of smoke exposure by age 16 years with subsequent Crohn's disease (unadjusted OR=0.30, 95% CI 0.1-0.8, Fisher's p=0.026). A similar trend was found with smoke exposure by age 5 and 10 years and later CD, which did not reach conventional significance levels (OR 0.83, 95% CI 0.4-1.8, p= 0.214 and OR 0.48, 95% CI 0.2-1.1, p=0.075 by 5 and 10 years respectively). See table 24.

The relationships between smoke exposures by age 16 years and subsequent CD, UC and diabetes was further examined in relation to potential confounding factors. These were sex, father's social class at birth, crowding variable at age 10 years and child's ethnic origin age 10 years. A total of 6625/9757 (67.8%) cohort members had complete data available for all variables in the multivariate model. Exclusions due to missing data did not affect the proportion of those born to fathers in social class V (5.0 %). Of the 6625 subjects that had complete data available, 17 reported Crohn's disease (CD), 13 reported ulcerative colitis (UC) and 29 reported insulin dependent diabetes mellitus (IDDM). Asian ethnic origin was known to be a risk factor for inflammatory bowel disease in this cohort (see previous results). However in the multivariate model, only

exposure to smoke by age 16 years was found to have a significant independent protective association with later Crohn's disease after adjusting for all the other variables. (Adjusted OR 0.30, 95% CI 0.1-0.89, p=0.030). West Indian ethnic origin was significantly associated with UC (OR16.2, 95% CI 1.8-140.0, p=0.011) and European ethnic origin was significantly associated with later insulin dependant diabetes (OR 3.48, 95% CI 1.4-98.1, p=0.024) but these were based on single cases only. See Table 25.

When smoke exposure by age 16 was compared between UC (14/15, 93%) and CD (18/23, 78%) there was no statistically significant difference. (OR for CD in smoke exposed=0.26, 95% CI 0.03-2.5).

Table 23 Relationship between parental smoking in pregnancy, and at 5, 10 and 16 years with subsequent IBD or diabetes (unadjusted relative odds)

Age	Relation to child	Whole sample (%)	Crohn's Disease (%) OR (95%CI)	Ulcerative colitis (%) OR (95%CI)	Diabetes (%) OR (95%CI)
Pregnancy	Mother	3824/8985 (42.6)	11/26 (42.3) 0.99 (0.5-2.2)	8/20 (40.0) 0.90 (0.4-2.2)	13/36 (36.1) 0.76 (0.3-1.5)
At age 5yrs	Mother	2930/7977 (36.7)	8/22 (36.4) 0.98 (0.4-2.3)	7/15 (46.7) 1.51 (0.5-4.2)	6/26 (23.1) 0.52 (0.2-1.3)
	Father	3157/7860 (40.2)	10/22 (45.5) 1.24 (0.5-2.9)	8/15 (53.3) 1.7 (0.6-4.7)	10/26 (38.5) 0.93 (0.4-2.1)
At age 10 yrs	Child	95/7752 (1.2)	0/23 -	1/18 (5.6) 4.74 (0.6-35.3)	0/30 -
	Mother	3120/8353 (37.4)	7/23 (30.4) 0.73 (0.3-1.8)	4/19 (21.1) 0.45 (0.1-1.3)	13/34 (38.2) 1.0 (0.5-2.1)
	Father	4248/8024 (52.9)	10/23 (43.5) 0.68 (0.3-1.6)	10/17 (58.8) 1.3 (0.5-3.3)	18/36 (50.0) 0.89 (0.5-1.7)
	Anyone in house	5465/2342 (70.0)	11/21 (52.4) 0.46 (0.2-1.1)	10/16 (62.5) 0.71 (0.3-2.0)	24/31 (77.4) 1.47 (0.6-3.4)
At age 16 yrs	Child	1061/4526 (23.4)	3/13 (23.1) 0.98 (0.3-3.6)	1/8 (12.5) 0.47 (0.1-3.8)	2/18 (11.1) 0.41 (0.1-1.8)
	Mother	1453/4157 (35)	4/13 (30.8) 0.83 (0.3-2.7)	1/5 (20.0) 0.47 (0.1-4.2)	2/16 (12.5) 0.27 (0.1-1.2)
	Father	1891/4174 (45.3)	4/13 (30.8) 0.54 (0.2-1.7)	4/7 (57.1) 1.61 (0.4-7.2)	4/17 (23.5) 0.37 (0.1-1.1)

Table 24 Univariate association between any reported smoke exposure by age 5, 10 and 16 years and subsequent CD, UC or diabetes

Any smoke exposure	N (%)	Unadjusted OR (95% CI)
Up to 5 yrs		
Whole sample	5485/8331 (65.8)	1.00
Crohn's disease	16/26 (61.5)	0.83 (0.38-1.83)
Ulcerative colitis	10/15 (66.7)	1.04 (0.36-3.03)
Diabetes	21/28 (75.0)	1.56 (0.66-3.66)
Up to 10 yrs		
Whole sample	6750/8250 (81.7)	1.00
Crohn's disease	17/25 (68.0)	0.48 (0.2-1.1)
Ulcerative colitis	14/16 (87.5)	1.56 (0.4-6.9)
Diabetes	27/31 (87.1)	1.51 (0.5-4.3)
Up to 16 yrs		
Whole sample	7161/7749 (92.4)	1.00
Crohn's disease	18/23 (78.3)	0.30 (0.1-0.8)*
Ulcerative colitis	14/15 (93.3)	1.15 (0.2-8.7)
Diabetes	29/31 (93.5)	1.19 (0.3-5.0)

* 2-tailed Fishers exact test p=0.026

Table 25 **Multivariate analysis of exposure to smoke by age 16 years and subsequent CD, UC or Diabetes. Adjusted for sex, ethnic origin of child at age 10, fathers social class and crowding variable.**

Any smoke Exposure by age 16 years	**N (%)**	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)**
Whole sample	6040/6625 (91.2)	1.00	1.00
Crohn's disease	12/17 (70.6)	0.23 (0.1-0.7)*	0.30 (0.1-0.9)**
Ulcerative colitis	12/13 (92.3)	1.16 (0.2-8.9)	1.25 (0.2-10.1)
Diabetes	27/29 (93.1)	1.30 (0.3-5.5)	1.50 (0.4-6.5)

Only subjects with complete data for all variables were included in the analysis

*2-tailed Fishers exact test p=0.013 **p=0.030

Appendicectomy and Tonsillectomy

Appendicectomy

At age 5 years, 27/7763 (0.3%), age 10 years 131/6321 (2.1%), age 16 years 149/5288 (2.8%) and age 26 years, 566/9749 (5.8%) responding cohort members reported appendicectomy.

Appendicectomy by age 26 years was significantly associated with maternal smoking in pregnancy, maternal smoking at 5 and 10 years and any exposure to smoke in the home by age 16 years (see table 26). Appendicectomy at this age was not associated with male sex (OR 0.96, 95% CI 0.82-1.13), crowding variable at age 10 (Pearson's χ^2 =4.4, p=0.354) or father's social class at birth (Pearson's χ^2 =5.723. p=0.678). See Table 21.

Table 26 Appendicectomy age 26 years and association with smoke exposure in childhood

	Total (%)	With Appendicectomy age 26 yrs (%)	Unadjusted OR (95% CI)	2-tailed p-value
Mother smoked in pregnancy	3821/8980 (42.6)	252/523 (48.2)	1.26 (1.06-1.48)	0.007
Mother smoked age 5 years	2927/7972 (36.7)	200/458 (43.7)	1.34 (1.12-1.60)	0.001
Mother smoked age 10 years	3118/8349 (37.3)	206/478 (43.1)	1.27 (1.07-1.51)	0.007
Any exposure to smoke by age 16 years	7158/7746 (92.4)	436/458 (95.2)	1.63 (1.07-2.48)	0.020

Table 27 Appendicectomy by age 10 and age 26 years and association with CD, UC and Diabetes

	No with Appendicectomy (%)	Unadjusted OR (95% CI)	Adjusted OR[$] (95% CI)
Age 10 years			
Whole sample	131/6321 (2.1)	-	-
Crohn's disease	0/14	-	-
Ulcerative colitis	1/12 (7.7)	3.96 (0.5-30.7)	-
Diabetes	2/29 (6.9)	3.54 (0.8-15.0)	-
Age 26 years			
Whole sample	391/6624 (5.9)	1.00	1.00
Crohn's disease	2/16 (12.5)	2.28 (0.5-10.1)	2.43 (0.5-10.9)
Ulcerative colitis	1/12 (8.3)	1.45 (0.2-11.3)	1.46 (0.2-11.4)
Diabetes	7/29 (24.1)	5.15 (2.2-12.1)*	5.45 (2.3-13.0)*

*Fisher's $p<0.0001$

[$] Adjusted for sex, father's social class, crowding variable at age 10 and smoke exposure by age 16 years.

There was no statistically significant association between appendicectomy reported at age 10 or 26 years and subsequent CD or UC. Appendicectomy by age 26 years was significantly associated with Diabetes. (See table 27)

After adjustment for potential confounding factors (sex, father's social class, crowding variable at age 10 and smoke exposure by age 16), again there was no statistically significant relationship between appendicectomy reported at 26 years and CD or UC. The relationship between appendicectomy and diabetes was strengthened by

adjustment for these factors. See Table 27. Total numbers are smaller at age 26 years as only those with complete data for all the variables in the model were used in this analysis. Only smoke exposure by age 16 remained independently associated with Crohn's disease after adjustment for all the other variables in the model (OR 3.94, 95% CI 1.32-11.81, p=0.014).

Tonsillectomy

At age 5 years, 175/7807 (2.2%), age 10 years 864/7054 (12.2%), and age 16 years 234/5373 (4.4%) responding cohort members reported tonsillectomy. As the response at age 16 years was thought to be unreliable, further analysis of this data was not undertaken.

Tonsillectomy at age 5 years was not significantly associated with maternal smoking in pregnancy, maternal smoking at 5 or 10 years or any exposure to smoke in the home by age 16 years. However, tonsillectomy reported at age 10 years was significantly associated with maternal smoking in pregnancy, maternal smoking at age 5 years and maternal smoking at age 10 years. (See table 28)

Table 28 Tonsillectomy age 5 and 10 years and association with smoke exposure in childhood

	Total (%) Age 5 yrs	With Tonsillectomy Age 5 yrs (%)	Unadjusted OR (95% CI)	Total (%) Age10 yrs	With Tonsillectomy Age 10 yrs (%)	Unadjusted OR (95% CI)
Mother smoked in pregnancy	3183/7558 (42.1)	79/170 (46.5)	1.19 (0.89-1.61) p=0.245	2763/6612 (41.8)	371/798 (46.5)	1.21 (1.06-1.38) **p=0.004**
Mother smoked age 5 years	2836/7739 (36.6)	69/173 (39.9)	1.15 (0.85-1.55) p=0.371	2142/6015 (35.6)	296/736 (40.2)	1.21 (1.06-1.40) **p=0.005**
Mother smoked age 10 years	2561/4407 (36.8)	62/155 (40.0)	1.15 (0.84-1.58 p=0.397	2556/6921 (36.9)	359/846 (42.4)	1.26 (1.11-1.43) **p=0.000**
Any exposure to smoke by age 16 years	5890/6463 (91.1)	138/145 (95.2)	1.92 (0.90-4.08) p=0.084	5332/5840 (91.3)	665/717 (92.7)	1.22 (1.93-1.59) p=0.142

Table 29 Tonsillectomy by age 5 and age 10 years and association with CD, UC and Diabetes

	No with Tonsillectomy (%)	Unadjusted OR	95% CI	2-tailed p-value
Age 5 years				
Whole sample	174/7807 (2.2)	1.00	-	-
Crohn's disease	1/22 (4.5)	2.08	0.28-15.57	0.393
Ulcerative colitis	0/15	-	-	-
Diabetes	0/26	-	-	-
Age10 years				
Whole sample	864/7054 (12.2)			
Crohn's disease	5/19 (26.3)	2.57	0.92-7.15	0.073
Ulcerative colitis	1/13 (7.7)	0.60	0.08-4.60	1.000
Diabetes	2/29 (6.9)	0.53	0.13-2.23	0.571

Tonsillectomy age 5 and 10 was significantly associated with male sex (OR 1.56, 95% CI 1.15-2.10). There was no significant association between tonsillectomy at age 5 or 10 years and crowding variable at age 10 (Pearson's χ^2 =5.28, p=0.260 and Pearson's χ^2 =6.09, p=0.192 respectively). There was no significant association between tonsillectomy at age 5 or 10 years and father's social class at birth (Pearson's χ^2 =4.30, p=0.821 and Pearson's χ^2 =7.66, p=0.467 respectively).

There was no statistically significant association between tonsillectomy reported at age 5 or 10 years and subsequent CD or UC. (See table 29). Adjustment for sex and smoke exposure was not performed as the number of cases remaining for analysis after excluding those with missing variables would have been too small.

Perinatal events

Birthweight

Birthweight was available in 9020/9757 (92.4%) cohort members responding at age 26 years. The mean birthweight for all cohort members was 3321.34g (s.d. 521.91). The mean birth weight for cohort members with CD, UC, IBD and diabetes did not differ significantly from that of the entire cohort. See table 30.

Table 30 Unpaired t-tests between mean birthweight of the whole cohort and those with inflammatory bowel disease and diabetes.

	Mean birthweight g (s.d)	Mean difference	95% CI of the difference	T	2-tailed p value
Whole cohort n=9020	3321.3 (521.9)	-		-	-
CD n=26	3308.3 (571.2)	-13.07	-214 to 188	-0.127	0.899
UC n=20	3385.0 (484.1)	63.80	-165 to 293	0.546	0.585
IBD n=46	3341.7 (530.7)	20.42	-131 to 172	0.265	0.791
Diabetes n=36	3290.4 (616.8)	-30.94	-202 to 178	-0.355	0.723

Weight for gestational age

Weight for gestational age was available in 7432/9757 (76.2%) cohort members responding at age 26 years. The mean birthweight for gestational age for all cohort members was 85.02g per week gestation (s.d. 12.85). Again, the mean birth weight for gestational age in cohort members with CD, UC, IBD and diabetes did not differ significantly from that of the entire cohort. See table 31.

Table 31 Unpaired t-tests between mean birthweight for gestational age of the whole cohort and those with inflammatory bowel disease and diabetes.

	Mean birthweight for gest. age (s.d)	Mean difference	95% CI of the difference	T	2-tailed p value
Whole cohort n=7432	83.99 (12.1)	-		-	-
CD n=22	85.02 (12.8)	1.03	-4.04 to 6.12	0.400	0.689
UC n=17	84.69 (8.9)	0.70	-5.07 to 6.47	0.237	0.812
IBD n=39	84.88 (11.2)	0.89	-2.92 to 4.70	0.458	0.647
Diabetes n=32	84.76 (12.5)	0.78	-3.43 to 4.98	0.362	0.717

Subsequent growth: weight, height and head circumference

Unpaired t-tests were used to examine the differences between the mean weight, height and head circumference in cohort members with IBD and the whole cohort. Where the data was not normally distributed the Mann-Whitney U test for non-parametric data was used. See tables 32, 33 and 34.

Weight at age 10 and age 16 years

There was no significant difference in weight between cohort members with CD, UC or IBD combined compared with the remaining cohort at either age 10 or age 16 years. Some 7828/9757 (80.2%) subjects responding at age 26 years had data on weight at age 10 and 4087/9757 (41.9%) at age 16years.None of the cohort members had a diagnosis of IBD made by 10 years. Five cohort members had IBD diagnosed by age 16 years (two with CD and three with UC).

Height at age 5, 10 and 16 years

There was no significant difference in weight between cohort members with CD, UC or IBD combined compared with the remaining cohort at age5, 10 or age 16 years.

Some 8049/9757 (82.5%), 8024/9757 (82.2%) and 3947/9757 (40.5%) subjects responding at age 26 years had data on weight at age 5,10 and age 16years respectively.

Head Circumference at age 5 and 10 years

There was no significant difference in head circumference between cohort members with CD, UC or IBD combined compared with the remaining cohort at age5 or 10 years. Some 7905/9757 (81%), 7979/9757 (81.8%) subjects responding at age 26 years had data on weight at age 5 and 10 years respectively.

Table 32 **Unpaired t-tests between mean weight at age 10 and 16 years in those with inflammatory bowel disease compared with the whole cohort.**

	Mean weight kg (s.d)	Mean difference	95% CI of the difference	T	2-tailed p value
Age 10 yrs					
Whole cohort n=7828	32.7 (5.32)	-	-	-	-
CD n=20	33.0 (5.90)	0.37	-1.96 to 2.71	0.31	0.764
UC n=19	33.3 (6.34)	0.67	-1.73 to 3.06	0.55	0.586
IBD n=39	33.2 (6.04)	0.52	-1.16 to 2.19	0.61	0.596
Age 16 yrs					
Whole cohort n=4087	59.2 (9.71)	-	-	-	-
CD n=13	56.8 (12.49)	-2.40	-7.69 to 2.89	-0.89	0.374
UC n=9	58.1 (11.12)	-1.12	-7.48 to 5.23	-0.35	0.729
IBD *n=22*	57.3 (11.69)	-1.88	-5.95 to 2.19	-0.91	0.365

Table 33 **Unpaired t-tests between mean height at age 10 and 16 years in those with inflammatory bowel disease compared with the whole cohort.**

	Mean height cm (s.d)	Mean difference	95% CI of the difference	T	2-tailed p value
Age 5 yrs					
Whole cohort n=8049	107.2 (14.82)	-	-	-	-
CD n=22	107.9 (5.78)	0.64	-5.56 to 6.84	0.20	0.840
UC n=15	107.3 (5.96)	0.11	-7.40 to 7.62	0.03	0.978
IBD n=37	107.7 (5.77)	0.42	-4.36 to 5.21	0.17	0.862
Age 10 yrs					
Whole cohort n=8024	138.9 (6.52)	-	-	-	-
CD n=21	138.6 (6.81)	-0.29	-3.08 to 2.50	-0.20	0.839
UC n=19	140.3 (7.80)	1.39	-1.55 to 4.32	0.93	0.355
IBD n=40	139.4 (7.25)	0.51	-1.52 to 2.54	0.49	0.624
Age 16 yrs					
Whole cohort n=3947	168.9 (9.72)	-	-	-	-
CD n=12	166.4 (9.71)	-2.51	-8.01 to 3.00	-0.89	0.372
UC n=9	167.4 (6.28)	-1.52	-7.87 to 4.84	-0.47	0.640
IBD *n=21*	166.8 (8.99)	-2.09	-6.26 to 2.08	-0.98	0.326

Table 34 **Unpaired t-tests between head circumference at age 5 and 10 in those with inflammatory bowel disease compared with the whole cohort.**

	Mean head Circumference In cm (s.d)	**Mean difference**	**95% CI Of the difference**	**T/Z***	**2-tailed p value**
Age 5 yrs					
Whole cohort n=7905	51.81 (1.83)	-	-	-	-
CD n=22	52.18 (1.76)	0.37	-0.39 to 1.14	0.95	0.340
UC* n=15	50.33 (3.85)	-1.48	-3.61 to 0.65	-0.81*	0.073*
IBD* n=37	51.43 (2.90)	-0.38	-1.35 to 0.59	-0.79*	0.608*
Age 10 yrs					
Whole cohort n=7979	53.51 (1.94)	-	-	-	-
CD n=21	52.69 (4.26)	-0.83	-2.77 to 1.11	-0.45*	0.650*
UC n=19	53.23 (1.83)	-0.28	-1.15 to 0.59	-0.63	0.530
IBD *n=40*	52.95 (3.30)	-0.57	-1.63 to 0.49	-0.88*	0.379*

*Mann-Whitney U test used due to non-parametric data-Z score shown

Neonatal feeding

Data were available on type of feed given in the first day of life from the birth records of all 9757 cohort members responding at 26 years. Data regarding breast feeding duration reported when the cohort were age 5 years was available for 7980/9757 (81.8%) cohort members.

Some 3103/9757 (31.8%) received colostrum on the first day. There was no significant association with any of the outcome diseases. 13/30 (43.3%), 6/22(27.3%), 19/52 (36.5%) and 13/40 (32.5%) cohort members with CD, UC, IBD and diabetes respectively reported receiving colostrum. Using maximum numbers, the unadjusted relative odds were 1.64 (95% CI 0.80 –3.39 p=0.174), 0.80 (95% CI 0.31–2.06, p=0.648), 1.24 (95%CI 0.70-2.18, p=0.462) and 1.03 (95%CI 0.53-2.01, p=0.922) for Crohn's disease, ulcerative colitis, IBD and diabetes respectively.

Receiving colostrum on the first day did not discriminate between phenotype of IBD. Some 6/22 with UC and 13/30 with CD received colostrum. The relative odds for CD for those with IBD receiving colostrum were 2.04 (95% CI 0.63 –6.67, p=0.235) and for UC were 0.49 (95% CI 0.15-1.60, p=0.235).

Using data from the age 5 maternal survey, 3140/7980 (39.3%) cohort members overall, 11 /22 (50%) with CD, 11/15 (26.7%) with UC and 10/26 with diabetes mothers reported ever breastfeeding. Using maximum numbers, the relative odds for disease in breastfed children compared with those not breastfed were 1.54 (95% CI 0.67-3.56, p=0.306), 0.56 (95%CI 0.18-1.76, p=0.314) and 1.05 (95%CI 0.54-2.03, p=0.882) for CD, UC and IBD respectively.

A report of breastfeeding ever from the age 5 data did not discriminate between phenotype of IBD. Some 11/15 with UC and 11/22 with CD reported being breastfed. The relative odds for CD for those with IBD who were breastfed were 2.75 (95% CI 0.67 –11.56, p=0.156) and for UC were 0.36 (95% CI 0.09-1.50, p=0.156). Breast feeding in the first week (from birth survey) and retrospective reporting of breast feeding duration when the cohort were aged 5 years were also not associated with IBD or diabetes. For breast-feeding duration, those not breast-fed were used as baseline. See table 35 below.

Although not statistically significant, there was a consistent increased relative odds for Crohn's disease in breastfed babies in all the measures (colostrum on the first

day, breast feeding in the first week and breastfeeding reported at age 5 years.) The relative odds for later Crohn's disease also increased with duration of breastfeeding from the age 5 data, although this was not statistically significant (χ^2 =2.359, p for trend=0.125).

Table 35 Unadjusted Relative Odds for CD, UC, and IBD according to breastfeeding practices reported at birth and at 5 years

	Whole sample (%)	With Disease (%)	Unadjusted OR	95% CI p-value
Breast fed in first week				
Crohn's Disease				
Yes	4601/9757 (47.2)	15/30 (50.0)	1.12	0.55-2.30 p=0.755
No	5156/9757 (52.8)	15/30 (50.0)	-	-
Ulcerative colitis				
Yes	4601/9757 (47.2)	7/22 (31.8)	0.52	0.21-1.28 p=0.149
No	5156/9757 (52.8)	15/22 (68.2)	-	-
IBD				
Yes	4601/9757 (47.2)	22/52 (42.3)	0.82	0.47-1.43 p=0.483
No	5156/9757 (52.8)	30/52 (57.7)	-	-
Breast fed duration				
Crohn's Disease				P=0.598
<1 month	1309/7980 (16.4)	3/22 (13.6)	1.01	0.28-3.62 p=0.990
1<3 months	836/7980 (10.5)	3/22 (13.6)	1.58	0.44-5.68 p=0.483
>=3months	976/7980 (12.2)	5/22 (22.7)	2.26	0.78-6.52 p=0.131
Duration unknown	19/7980 (0.2)	0/22	-	-
Not breast fed	4840/7980 (60.7)	11/22 (50.0)	-	-
Ulcerative colitis				P=0.134
<1 month	1309/7980 (16.4)	0/15	-	-
1<3 months	836/7980 (10.5)	0/15	-	-
>=3months	976/7980 (12.2)	4/15 (26.7)	1.81	0.57-5.69 p=0.312
Duration unknown	19/7980 (0.2)	0/15	-	-
Not breast fed	4840/7980 (60.7)	11/15 (73.3)	-	-
IBD				P=0.178
<1 month	1309/7980 (16.4)	3/37 (8.1)	0.50	0.15-1.69 p=0.266
1<3 months	836/7980 (10.5)	3/37 (8.1)	0.79	0.24-2.64 p=0.701
>=3months	976/7980 (12.2)	9/37 (24.3)	2.04	0.94-4.44 p=0.073
Duration unknown	19/7980 (0.2)	0/37	-	-
Not breast fed	4840/7980 (60.7)	22/37 (59.5)	-	-

The potential confounding factors for the association between breastfeeding and CD or UC were considered to be ethnic origin (British as baseline), crowding ratio (least

crowded as baseline), birthweight ranked in fifths of the distribution (lightest fifth as baseline) and parity (no previous pregnancies as baseline). Maternal smoking in pregnancy and father's social class were not included in the model as they were not associated with any of the outcome measures in this study. A multivariate model using colostrum on the first day from the birth data and ever breastfed from the age 5 survey is shown in table 36. Again there was no significant association between breastfeeding (either measure) and later UC, CD or IBD. The numbers of cases are reduced in the model, as only those with complete data for all variables were included. Only mothers' ethnic origin (West Indian) was significantly associated with UC (OR 10.53, 95% CI, 1.09-102.15, p=0.042).

Perinatal infections and illnesses

There was no association between maternal history of urinary or genital tract infection and subsequent CD, UC or IBD. 8828 cohort members (44 with IBD) and 8701 cohort members (45 with IBD) had data available for maternal history of urinary or genital tract infection respectively. The unadjusted odds ratios for IBD were 2.63 (95% CI 0.82-8.43 Fisher's p=0.116), and 2.21 (95% CI 0.54-9.07, Fisher's p=0.237) for urinary or genital tract infection respectively. A maternal history of venous complications in the legs was also not associated with CD, UC or IBD. 8788 cohort members (44 with IBD) had data available for venous complications in the legs. The unadjusted odds ratios for IBD were 2.28 (95% CI 0.89-5.82 Fisher's p=0.084). On specific questioning, 149/8777-cohort member's mothers had recorded evidence of perinatal infection, including infection associated with hypertension and puerperal psychosis. None of the cohort members who later developed IBD had such infections recorded.

8807 cohort members (43 with IBD) and 8897 cohort members (43 with IBD) had data available for the neonate having umbilical discharge or fits in the first week. None of the cohort members who later developed IBD had an umbilical discharge or fits recorded. 8787 cohort members (24 with CD, 19 with UC) had data available for a history of sticky eyes in the first week. A history of sticky eyes was not associated with CD, UC or IBD. The unadjusted odds ratio for IBD in those with sticky eyes reported was 2.00 (95% CI 0.84-4.75 Fisher's p=0.135). None of the cohort members with later IBD reported any other neonatal illness or condition.

Table 36 Unadjusted and adjusted relative odds for CD, UC, IBD and diabetes according to breastfeeding practices reported at birth (colostrum on the first day) and at 5 years (ever breastfed)

	Whole sample (%)	With Disease (%)	Unadjusted OR 95% CI p-value	Adjusted OR* 95% CI p-value
Colostrum on the first day				
Crohn's disease				
No colostrum	5096 (73.4)	12 (63.2)	-	-
Had colostrum	1850 (26.6)	7 (36.8)	1.61 (0.63-4.09) p=0.313	1.26 (0.37-4.24) p=0.712
Ulcerative colitis				
No colostrum	5096 (73.4)	11 (78.6)	-	-
Had colostrum	1850 (26.6)	3 (21.4)	0.75 (0.21-2.69) p=0.659	1.08 (0.20-5.97) p=0.928
IBD				
No colostrum	5096 (73.4)	23 (69.7)	-	-
Had colostrum	1850 (26.6)	10 (30.3)	1.20 (0.57-2.52) p=0.633	1.20(0.44-3.23) p=0.724
Diabetes				
No colostrum	5094 (73.4)	19 (76.0)	-	-
Had colostrum	1848 (26.6)	6 (24.0)	0.87 (0.35-2.18) p=0.766	0.97 (0.30-3.20) p=0.962
Ever Breastfed				
Crohn's disease				
Never breastfed	4214 (60.7)	9 (47.4)	-	-
Breastfed	2732 (39.3)	10 (52.6)	1.72 (0.70-4.23) p=0.235	1.52 (0.47-4.95) p=0.487
Ulcerative colitis				
Never breastfed	4214 (60.7)	10 (71.4)	-	-
Breastfed	2732 (39.3)	4 (28.6)	0.62 (0.19-1.97) p=0.409	0.57 (0.12-2.76) p=0.481
IBD				
Never breastfed	4214 (60.7)	19 (57.6)	-	-
Breastfed	2732 (39.3)	14 (42.4)	1.14 (0.57-2.27) p=0.715	1.04 (0.41-2.65) p=0.937
Diabetes				
Never breastfed	4213 (60.7)	16 (64.0)	-	-
Breastfed	2729 (39.3)	9 (36.0)	0.89 (0.38-1.97) p=0.734	1.0 (0.35-2.90) p=1.000

* Adjusted for birthweight, parity, crowding ratio and ethnic origin

Where the neonate spent the first night after birth

Data on where the baby spent the first night after birth were available for 8947/9757 (91.7%) cohort members responding at age 26 years. This included 20/22 (90.9%) with UC, 26/30 (86.6%) with CD, and 36/40 (90%) with diabetes. Some 2173/8947 (24.3%) spent the day and night with the mother, 3537/8947 (39.5%) spent the day with the mother and the night in the nursery and 3237/8947 (36.2%) were elsewhere (see methods for description).

Univariate analysis using the maximum number of cases (n=46 with IBD, 26 with CD, 20 with UC), showed a non-significant increased relative odds for CD, UC and IBD combined in babies who spent there first night in the nursery, compared with those who remained with their mother day and night. The unadjusted relative odds for IBD were 1.78 (95% CI 0.83-3.81, p= 0.137). There was a significantly reduced relative odds for diabetes in those who were in the nursery at night. See table 37.

Table 38 shows the unadjusted and adjusted relative odds for all the potential confounding factors and inflammatory bowel disease combined. The relative odds in this table are shown adjusted and unadjusted for all of the potential confounding factors listed. A combined variable of IBD was used for this model, as there were small numbers of cohort members with disease after excluding those with missing data. This may be appropriate because CD and UC share many common genetic and environmental risk factors and both have been associated with improved conditions in childhood (77;78) and specific patterns of viral infections.(48)There is also an increased relative odds for both CD and UC in those spending the first night in the nursery compared with those with there mothers all the time supporting the appropriateness of using a combined variable.

Although not significant at the 5% level, there was an increased unadjusted relative odds for IBD (1.87, 95% CI 0.79-4.40, p=0.153) in those who spent the first night in the nursery compared with those who remained with their mother. After adjustment for potential confounding factors (sex, father's social class, mother's age, parity, crowding, birthweight, breastfeeding in the first day and duration of breastfeeding) the adjusted relative odds for IBD increased to 2.11 (95% CI 0.88-5.06, p=0.094). None of the other factors were significantly associated with IBD

Table 37 **Unadjusted Relative Odds for CD, UC, IBD and diabetes according to where the baby spent the first night after birth (maximum numbers)**

	Whole sample (%)	With Disease (%)	Unadjusted OR (95% CI)	p-value
Crohn's Disease				χ^2=2.41 P=0.299
Mother's bed-Day and night	2173/8947 (24.3)	4/26 (15.4)	-	-
Mother's bed-Day only	3537/8947 (39.5)	14/26 (53.8)	2.15 (0.71-6.55)	P=0.176
Other	3237/8947 (36.2)	8/26 (30.8)	1.34 (0.40-4.47)	P=0.630
Ulcerative colitis				χ^2 =4.61 p=0.100
Mother's bed-Day and night	2173/8947 (24.3)	5/20 (25.0)	-	-
Mother's bed-Day only	3537/8947 (39.5)	12/20 (60.0)	1.48 (0.52-4.20)	P=0.465
Other	3237/8947 (36.2)	3/20 (15.0)	0.40 (0.10-1.69)	P=0.214
IBD				χ^2 =5.72 p=0.057
Mother's bed-Day and night	2173/8947 (24.3)	9/46 (19.6)	-	-
Mother's bed-Day only	3537/8947 (39.5)	26/46 (56.5)	1.78 (0.83-3.81)	P=0.137
Other	3237/8947 (36.2)	11/46 (23.9)	0.82 (0.34-1.98)	P=0.660
Diabetes				χ^2 =6.51 p=0.039
Mother's bed-Day and night	2172/8942 (4.3)	15/36 (41.7)	-	-
Mother's bed-Day only	3535/8942 (39.5)	9/36 (25.0)	0.37 (0.16-0.84)	P=0.018
Other	3223/8942 (36.2)	12/36 (33.3)	0.54 (0.25-1.15)	P=0.108

Table 38 Relative odds of developing inflammatory bowel disease by where the baby spent the first night of life, with adjustment for multiple potential confounding factors

	Whole sample N=7525 (%)	With IBD N=36 (%)	Unadjusted OR 95% CI p-value	Adjusted OR* 95% CI p-value
First night of life			P=0.071	P=0.086
Mother's bed-Day and night	1843 (24.5)	7 (19.4)	-	-
Mother's bed-Day and night	2968 (39.4)	21 (58.3	1.87 (0.79-4.40) p=0.153	2.11 (0.88-5.06) p=0.094
Other	2714 (36.1)	8 (22.2)	0.78 (0.28-2.14) p=0.625	0.97 (0.88-5.06) p=0.954
Crowding ratio-5ths			P=0.077	P=0.112
1 (low)	1249 (16.6)	2 (5.6)	-	-
2	1543 (20.5)	14 (38.9)	5.71 (1.30-25.16) p=0.021	5.60 (1.25-24.98) P=0.024
3	1988 (26.4)	8 (22.2)	2.52 (0.53-11.88) p=0.243	2.38 (0.49-11.55) P=0.282
4	1682 (22.4)	8 (22.2)	2.98 (0.63-14.05) p=0.168	3.11 (0.63-15.44) p=0.166
5 (high)	1063 (14.1)	4 (11.1)	2.35 (0.43-12.88) p=0.323	2.81 (0.47-16.96) p=0.260
Parity			P=0.088	P=0.181
0 prev pregnancy	2920 (38.8)	10 (27.8)	-	-
1 prev pregnancy	2628 (34.9)	19 (52.8)	2.11 (0.98-4.56) p=0.055	2.01 (0.90-4.46) p=0.088
2 or more prev pregnancies	1977 (26.3)	7 (19.4)	1.03 (0.39-2.72) p=0.946	1.19 (0.39-4.62) p=0.764
Father's social class			P=0.993	P=0.994
I	423 (5.6)	3 (8.3)	-	-
II	985 (13.1)	5 (13.9)	0.71 (0.17-3.00) p=0.646	0.76 (0.18-3.24) P=0.707

Table 38 (cont) **Relative odds of developing inflammatory bowel disease by where the baby spent the first night of life, with adjustment for multiple potential confounding factors**

	Whole sample N=7525 (%)	With IBD N=36 (%)	Unadjusted OR 95% CI p-value	Adjusted OR* 95% CI p-value
Father's social class (Continued)				
III non-manual	1005 (13.4)	4 (11.1)	0.56 (0.12-2.51) p=0.448	0.58 (0.13-2.65) P=0.478
III manual	3390 (45.0)	17 (47.2)	0.71 (0.21-2.42) P=0.579	0.80 (0.22-2.92) p=0.741
IV	996 (13.2)	5 (13.9)	0.71 (0.17-2.97) P=0.635	0.79 (0.18-3.55) P=0.759
V	362 (4.8)	1 (2.8)	0.39 (0.04-3.74) P=0.413	0.46 (0.04-4.63) P=0.506
Other	171 (2.3)	1 (2.8)	0.82 (0.09-7.97) P=0.867	0.89 (0.09-8.93) P=0.923
Unsupported	193 (2.6)	0	-	-
Sex				
Male	3708 (49.3)	17 (47.2)	-	-
Female	3817 (50.7)	19 (52.8)	1.09 (0.56-2.09) p=0.805	1.07 (0.55-2.08) p=0.850
Colostrum on first day				
No	5534 (73.5)	25 (69.4)	-	-
Yes	1991 (26.5)	11 (30.6)	1.22 (0.60-2.49) p=0.576	0.98 (0.35-2.71) p=0.965
Breast-feeding			P=0.201	P=0.262
Less than 1 month	1221 (16.2)	3 (8.3)	0.54 (0.16-1.80) p=0.312	0.54 (0.14-2.08) p=0.373
1 month up to 3 months	789 (10.5)	3 (8.3)	0.83 (0.25-2.78) p=0.761	0.86 (0.22-3.45) p=0.835
3 months or more	919 (12.2)	9 (12.2)	2.15 (0.98-4.70) p=0.056	2.21 (0.75-6.57) p=0.151
Breastfed-duration unsure	18 (0.2)	-	-	-
Never breast-fed	4578 (60.8)	21 (58.3)	-	-

Table 38 (cont) **Relative odds of developing inflammatory bowel disease by where the baby spent the first night of life, with adjustment for multiple potential confounding factors**

	Whole sample N=7525 (%)	With IBD N=36 (%)	Unadjusted OR 95% CI p-value	Adjusted OR* 95% CI p-value
Mother's age at delivery			P=0.678	P=0.719
0-30 years	6065 (80.6)	31 (86.1)	-	-
31-35 years	986 (13.1)	3 (8.3)	0.59 (0.18-1.94) p=0.390	0.60 (0.17-2.07) p=0.420
36 years and over	474 (6.3)	2 (5.6)	0.82 (0.20-3.46) p=0.792	0.85 (0.19-3.81) p=0.834
Birthweight (10ths)			P=0.574	P=0.565
1 (low)	727 (9.7)	1 (2.8)	6.63 (0.81-53.96) p=0.077	0.33 (0.04-3.01) p=0.324
2	774 (10.3)	7 (19.4)	4.03 (0.45-36.10) p=0.213	1.74 (0.49-6.17) p=0.390
3	725 (9.6)	4 (11.1)	2.72 (0.28-26.15) p=0.388	1.03 (0.25-4.26) p=0.958
4	805 (10.7)	3 (8.3)	5.13 (0.60-44.04) p=0.136	0.66 (0.14-2.99) p=0.587
5	712 (9.5)	5 (13.9)	0.99 (0.06-15.84) p=0.994	1.21 (0.32-4.61) p=0.780
6	735 (9.8)	1 (2.8)	3.69 (0.41-33.08) p=0.243	0.23 (0.03-2.09) p=0.192
7	791 (10.5)	4 (11.1)	4.92 (0.57-42.18) p=0.146	0.85 (0.21-3.45) p=0.820
8	743 (9.9)	5 (13.9)	2.00 (0.18-22.13) p=0.571	1.23 (0.32-4.63) p=0.764
9	726 (9.7)	2 (5.6)	3.71 (0.41-33.29) p=0.241	0.46 (0.08-2.53) p=0.369
10 (high)	786 (10.4)	4 (11.1)	-	-

Childhood illness and non-specific childhood infections

Childhood eczema, hay-fever and wheezing

Eczema, hay fever and wheezing were examined at age 5 and 10 years. See table below. Eczema was significantly associated with UC and IBD at age 10 years. Wheezing at age 10 showed a significant negative association with CD and IBD overall.

Table 39 Unadjusted relative odds for IBD in cohort members reporting atopic illnesses at age 5 or 10 years.

	Age 5		Age 10	
	No with atopic disease (%)	**Unadjusted OR (95% CI)**	**No with atopic disease (%)**	**Unadjusted OR (95% CI)**
Eczema Whole sample	970/7690 (12.6)	-	1125/8214 (13.7)	-
Crohn's disease	3/22 (13.6)	1.09 (0.32-3.70)	3/23 (13.0)	0.95 (0.28-3.19)
Ulcerative colitis	4/14 (28.6)	2.78 (0.87-8.88)	7/18 (38.9)	4.03 (1.56-10.41) p=0.007
IBD	7/36 (19.4)	1.68 (0.73-3.84)	10/41 (24.4)	2.04 (1.00-4.18) p=0.046
Hay fever Whole sample	337/7661 (4.4)	-	919/8155 (11.3)	-
Crohn's disease	2/20 (9.1)	2.18 (0.51-9.37)	3/23 (13.0)	1.18 (0.35-3.98)
Ulcerative colitis	0/13	-	1/17 (5.9)	0.49 (0.07-3.71)
IBD	2/35 (5.7)	1.32 (0.32-5.52)	4/40 (10.0)	0.87 (0.31-2.46)
Wheezing Whole sample	1600/7970 (20.1)	-	1672/8128 (20.6)	-
Crohn's disease	3/22 (13.6)	0.63 (0.19-2.13)	0/22	- p=0.014
Ulcerative colitis	3/15 (20.0)	1.00 (0.28-3.53)	3/19 (15.8)	0.72 (0.21-2.48)
IBD	6/37 (16.2)	0.77 (0.32-1.85)	3/38 (7.3)	0.31 (0.09-0.99) p=0.035

Non-specific childhood infections

7702 cohort members (35 with IBD) and 7698 (35 with IBD) had data available at age 5 years regarding pneumonia and meningitis respectively. None of the cohort member who later developed IBD gave a history of pneumonia or meningitis. 7716 (36 with IBD), 7765 (36 with IBD) and 7744 (36 with IBD) cohort members had data available at age 5 years regarding ear discharge, recurrent sore throats or bronchitis respectively. There was no association between any of these conditions by age 5 years and subsequent CD, UC or IBD. The unadjusted odds ratios for IBD were 1.60 (95% CI 0.66-3.85 Fisher's p=0.285), 0.78 (95% CI 0.33-1.88, Fisher's p=0.683) and 1.25 (95% CI 0.55-2.86, Fisher's p=0.648) for ear discharge, sore throats and bronchitis respectively.

At age 10, data were available for 8108 (41 with IBD) and 7974 (38 with IBD) cohort members regarding pneumonia and meningitis respectively. None of the cohort member who later developed IBD gave a history of pneumonia or meningitis. 8051 cohort members (22 with CD, 19 with UC) had data regarding ear infections by age 10 years. There was a significant negative association between ear infections by age 10 and later Crohn's disease (unadjusted OR 0.16, 95% CI 0.02-1.16, Fisher's p=0.041). This was based on only one cohort member with CD who gave a history of ear infections. UC and IBD combined were not associated with a previous history of ear infections. 8057 cohort members (41 with IBD) had data available at age 10 years regarding recurrent sore throats. There was no significant association between recurrent sore throats by age 10 and later IBD (unadjusted OR 1.12, 95% CI 0.58-2.17, Fisher's p=0.732). On specific questioning about other acute fevers, 20 cohort members reported a history of gastro-enteritis or dysentery by age 10 years. None of these cohort members subsequently developed IBD.

Specific infections in childhood including measles

Viral infections

The relationship between childhood infections by age 10 years and subsequent IBD and diabetes by age 26 years was considered using the Chi-squared test, with calculation of relative odds for disease and 95% confidence intervals. The earliest age at diagnosis of IBD in any of the cohort members was age 12 years. The summarised medical records at the age 10 interviews were reviewed and there was no evidence of significant illness or symptoms of IBD or immunodeficiency. No statistically significant association was found between any of the specific fevers (measles, mumps, chickenpox, and pertussis) and the outcome diseases. (See table 40). Exclusion of cohort members with missing data did not greatly affect the socio-economic background-the proportion of those in social class V only dropped from 5.1 to 4.7%.

Some 46.8% (4256/7996) cohort members responding at age 26 years reported having had measles infection when questioned at age 10 years (by parental interview). This compares with 55.2% (2193/4898) of those not responding at age 26 years. The relative odds for measles infection in responders compared with non-responders were 0.71 (95% CI 0.66 to 0.77, p=0.000).

Table 40 Univariate analysis for the association between childhood infections by age 10 years and subsequent IBD or Diabetes by age 26 years (Maximum numbers)

Infection	Whole sample n (%)	CD n(%) OR (95% CI)	UC n (%) OR (95% CI)	IBD n (%) OR (95% CI)	Diabetes n (%) OR (95% CI)
Measles	3740/7996 (46.8%) OR=1.00	11/22 (50.0%) OR=1.14 (0.49-2.63)	9/17 (52.9%) OR=1.28 (0.49-3.32)	20/39 (51.3%) OR=1.20 (0.63-2.25)	11/34 (32.4%) OR=0.54 (0.26-1.12)
Mumps	3810/8069 (47.2%) OR=1.00	10/22 (45.5%) OR=0.93 (0.40-2.16)	10/17 (58.8%) OR=1.60 (0.61-4.24)	20/39 (51.3%) OR=1.18 (0.63-2.21)	18/36 (50.0%) OR=1.12 (0.58-2.15)
Chickenpox	5255/8225 (63.9%) OR=1.00	10/22 (45.5%) OR=0.47 (0.20-1.09)	15/19 (78.9%) OR=2.12 (0.70-6.40)	25/41 (61.0%) OR=0.88 (0.47-1.66)	26/36 (72.2%) OR=1.47 (0.71-3.05)
Pertussis	628/8014 (7.8%) OR=1.00	2/20 (9.1%) OR=1.18 (0.27-5.05)	1/17 (5.9%) OR=0.74 (0.10-5.55)	3/39 (7.7%) OR=0.98 (0.30-3.30)	1/35 (2.9%) OR=0.35 (0.05-2.52)

Potential confounding factors were considered to be sex, father's social class at birth and household crowding (person per room ratio in fifths of the distribution, taken from the parental interview at age 5 years). Multiple logistic regression was therefore used to assess the effects of these potential confounding factors. The independent variables were measles, mumps, chickenpox, pertussis, sex, and father's social class at birth and household crowding. All variables were modelled as a series of binary dummies. Only cohort members with data for all variables in the model were included in the analysis. No significant association was found between any of the specific fevers and IBD or diabetes after adjustment for potential confounding factors. The adjusted relative odds for IBD and diabetes are shown in table 41.

Table 41 **Multivariate analysis for the association between childhood infections by age 10 years and subsequent IBD or Diabetes by age 26 years (Adjusted for sex, fathers social class and household crowding)**

Infection	Whole sample n (%)	CD n(%) Adjusted OR (95% CI)	UC n (%) Adjusted OR (95% CI)	IBD n (%) Adjusted OR (95% CI)	Diabetes n (%) Adjusted OR (95% CI)
Measles	3035/6600 (46.0%) OR=1.00	9/19 (47.4%) OR=1.21 (0.49-3.03)	7/13 (53.8%) OR=1.40 (0.46-4.27)	16/32 (50%) OR=1.28 (0.63-2.60)	8/23 (34.8%) OR=0.71 (0.30-1.68)
Mumps	3214/6671 (48.2%) OR=1.00	9/19 (47.4%) OR=0.85 (0.34-2.10)	8/13 (61.5%) OR=1.73 (0.56-5.36)	17/32 (53.1%) OR=1.13 (0.56-2.29)	12/25 (48.0%) OR=0.97 (0.44-2.13)
Chickenpox	4383/6797 (64.5%) OR=1.00	9/19 (47.4%) OR=0.46 (0.19-1.14)	11/14 (78.6%) OR=1.97 (0.54-7.14)	20/33 (60.6%) OR=0.80 (0.40-1.62)	19/25 (76.0%) OR=1.62 (0.64-4.08)
Pertussis	517/6625 (7.8%) OR=1.00	2/19 (10.5%) OR=1.33 (0.30-5.79)	1/13 (7.7%) OR=1.02 (0.13-7.92)	3/32 (9.4%) OR=1.21 (0.37-4.01)	1/24 (4.2%) OR=0.52 (0.07-3.90)

Age of measles infection

The age of measles infection was recorded in 9 cases with CD (mean 5.00 yrs sd 1.87), 9 cases of UC (mean 3.22 yrs sd 2.68), 18 cases overall with IBD (mean 4.11, sd 2.42) 9 cases of diabetes (mean 4.56yrs sd 2.30) and in 3567 overall responding cohort members without IBD (mean 4.46 yrs sd 2.42).

The mean age of measles infection in those responding at age 26 years was 4.47, (sd 2.49), and 4.47 (sd 2.42) in those who did not respond at age 26 years.

There was no significant difference between the mean age of measles infection in patients with CD compared with UC using a paired t-test ($t=1.631$ on 16 df, $p=0.122$).

No significant association was found between age of measles infection and any of the outcome diseases when analysed using both categorical and continuous variables. (See table 42)

Adjustment for sex, father's social class at birth, and crowding ratio did not significantly alter these results. Only cohort members with complete data for all variables were included in these analyses. Unadjusted and adjusted relative odds for CD and UC are shown in tables 43 and 44.

Table 42 **Age of measles infection in cohort members with and without Crohn's disease, ulcerative colitis, IBD combined and diabetes (maximum numbers).**

Age at measles Infection	Outcome disease	N (%)	Unadjusted OR	95% CI
No measles infection	Whole sample	4254/7839 (54.3)	-	-
	CD	11/20 (55.0)	0.85	0.33-2.19
	UC	8/17 (47.1)	0.86	0.28-2.64
	IBD	19/37 (51.4)	0.85	0.41-1.76
	Diabetes	23/32 (71.9)	2.07	0.84-5.10
<1 yr	Whole sample	175/7839 (2.2)	-	-
	CD	0/20 (0)	-	-
	UC	2/17 (11.8)	5.29	1.02-27.44
	IBD	2/37 (5.4)	2.19	0.49-9.89
	Diabetes	1/32 (3.1)	2.19	0.26-19.31
1 yr	Whole sample	282/7839 (3.6)	-	-
	CD	0/20 (0)	-	-
	UC	1/17 (5.9)	1.63	0.19-13.98
	IBD	1/37 (2.7)	1.51	0.42-5.38
	Diabetes	0/32 (0)	-	-
2 yrs	Whole sample	380/7839 (4.8)	-	-
	CD	2/20 (10.0)	1.73	0.36-8.34
	UC	1/17 (5.9)	1.21	0.14-10.35
	IBD	3/37 (8.1)	1.51	0.42-5.38
	Diabetes	0/32 (0)	-	-
3 yrs	Whole sample	457/7839 (5.8)	-	-
	CD	0/20 (0)	-	-
	UC	0/17 (0)	-	-
	IBD	0/37 (0)	-	-
	Diabetes	2/32 (6.3)	1.67	0.34-8.32
4 yrs and over	Whole sample	2291/7839 (29.2)	-	-
	CD	7/20 (35)	Baseline	Baseline
	UC	5/17 (29.4)	Baseline	Baseline
	IBD	12/37 (32.4)	Baseline	Baseline
	Diabetes	6/32 (18.8)	Baseline	Baseline

Table 43 **Age of measles infection in cohort members with and without Crohn's disease. adjusted and unadjusted for fathers social class, sex, and crowding ratio**

Age at measles Infection	Subjects with CD (%)	Whole sample (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
No measles infection	10/17 (58.8)	3563/6469 (55.1)	1.05 (0.36-3.08)	0.96 (0.32-2.83)
<1 year	0/17	136/6469 (2.1)	0.00	0.00
1 year	0/17	225/6469 (3.5)	0.00	0.00
2 years	2/17 (11.8)	314/6469 (4.9)	2.39 (0.46-12.40)	2.54 (0.49-13.21)
3 years	0/17	358/6469 (5.5)	0.00	0.00
4 years and over	5/17 (29.4)	1873/6469 (29.0)	1.00 Baseline	1.00 Baseline

Table 44 **Age of measles infection in cohort members with and without ulcerative colitis. Adjusted and unadjusted for fathers social class, sex, and crowding ratio.**

Age at measles Infection	Subjects with UC (%)	Whole sample (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
No measles infection	6/13 (46.2)	3563/6469 (55.1)	0.79 (0.22-2.00)	0.78 (0.22-2.80)
<1 yr	1/13 (7.7)	136/6469 (2.1)	3.46 (0.38-31.18)	4.28 (0.47-39.21)
1 year	1/13 (7.7)	225/6469 (3.5)	2.09 (0.23-18.74)	2.37 (0.26-21.42)
2 years	1/13 (7.7)	314/6469 (4.9)	1.49 (0.17-13.4)	1.54 (0.17-13.89)
3 years	0/13	358/6469 (5.5)	0.00	0.00
4 years and over	4/13 (30.8)	1873/6469 (29.0)	1.0 Baseline	1.0 Baseline

Further analysis was also performed with the age groups divided into never, under 2 years, 2 to 5 years and 6-10 years. This grouping was chosen, as these ages are known to represent a risk for subacute sclerosing pan-encephalitis. (164) See Table 45 below.

Table 45 Unadjusted relative odds for Ulcerative Colitis, Crohn's disease and diabetes by age of measles infection

Age (yrs)	Whole sample	Crohn's disease		Ulcerative colitis		Diabetes	
		N (%)	OR (95% CI)	N (%)	OR (95% CI)	N (%)	OR (95% CI)
Never	4254/7839 (54.3)	11 (55%)	1.00	8 (47%)	1.00	23 (72%)	1.00
<2	457/7839 (5.8)	0	-	3 (18%)	3.51 (0.93-13.27)	1 (3%)	0.40 (0.05-3.00)
2-5	1911/7839 (24.4)	5 (25%)	1.01 (.35-2.92)	5 (29%)	1.39 (0.45-4.26)	5 (16%)	0.48 (0.18-1.27)
6-10	1217/7839 (15.5)	4 (20%)	1.27 (.40-4.00)	1 (6%)	0.44 (0.05-3.49)	3 (9%)	0.45 (0.14-1.51)
Total	7839	20		17		32	

When age of measles infection was considered as a continuous variable, and those who denied measles infection were excluded, there was also no statistically significant association found. The relative odds for CD for each year increase in age of measles infection were 1.10 (95% CI 0.84-1.44). The relative odds for UC for each year increase in age of measles infection were 0.80 (95% CI 0.60-1.07). The relative odds for IBD for each year increase in age of measles infection were 0.94 (95% CI 0.78-1.14). The relative odds for diabetes for each year increase in age of measles infection were 1.01 (95% CI 0.77-1.33).

Age of other infections

Age of infection with chickenpox and pertussis were not associated with IBD or diabetes. Only age at mumps infection was significantly associated with ulcerative colitis The relative odds for UC was 25.12, 95% CI 6.35-99.36, (Fisher's p=0.001) in those

experiencing mumps under 2 years of age compared with those who did not report mumps infection by 10 years. 3 (18%) responding cohort members with UC experienced this pattern of mumps exposure whilst only 64 (1%) of the unaffected cohort members reported mumps under age 2 years.

Childhood vaccinations including monovalent measles

Some 4611/7616 (60.5%) subjects responding at age 26 years reported having had measles vaccination by 5 years. Those responding at 26 years were significantly more likely to have reported measles vaccination by age 5 years than non-responders (OR=1.14, 95% CI 1.07-1.21).(227) See table 46.

Table 46 Measles vaccination status and age of measles vaccination by age 5 years in those responding at 26 years compared with original birth cohort.

Variable		Original birth cohort (%)	Responded at age 26 years (%)
Measles vaccine reported by age 5 years	Vaccinated	6856 (57.4%)	4611 (60.5%)*
	Unvaccinated	5092 (42.6%)	3005 (39.5%)
	Total	11948	7616
Age at measles vaccination	0-1 year	5866 (49.1%)	3862 (52.2%)
	2 years	653 (5.5%)	412 (5.6%)
	3 years	217 (1.8%)	138 (1.9%)
	4 years and over	116 (0.9%)	69 (0.9%)
	Total	6852	4481

*$p<0.0001$ $\chi^2=19.16$

Recall Error for vaccination at age 5 and age 10 years

The error in recall of vaccination status at different ages was assessed for measles vaccination by cross-tabulation of the parent's response at age 5 years with that at 10 years. There was some discrepancy in parental report of vaccination status at 5 and 10 years. For measles vaccination, 13.2% who reported measles vaccination at 5 years failed to do so at 10 years. Some discrepancy was apparent for all vaccinations, although more marked for measles vaccine and BCG. See table 47.

Table 47 **Error in recall of vaccine status between age 5 and age 10 years**

Vaccine status reported at age 5 years		Vaccine status reported at age 10 years		Total
		Yes	No	
Measles	Yes	3672 (86.8%)	559 (13.2%)	4231
	No	660 (24.5%)	2031 (75.5%)	2691
	Total	4332	2590	6922
Pertussis	Yes	6228 (95.9%)	266 (4.1%)	6494
	No	134 (36.7%)	231 (63.3%)	365
	Total	6362	497	6859
Diphtheria	Yes	6898 (99.4%)	39 (0.6%)	6937
	No	91 (52%)	84 (48%)	175
	Total	6989	123	7112
Polio	Yes	6805 (99.2%)	55 (0.8%)	6860
	No	183 (72.6%)	69 (27.4%)	252
	Total	6988	124	7112
Tetanus	Yes	6877 (99.1%)	64 (0.9%)	6941
	No	122 (63.2%)	71 (36.8%)	193
	Total	6999	135	7134
BCG	Yes	348 (82.1%)	76 (17.9%)	424
	No	372 (5.6%)	6287 (94.4%)	6659
	Total	720	6363	7083

Vaccination at age 5 and age 10 years- association with inflammatory bowel disease and diabetes

The unadjusted relative odds for CD, UC, IBD, and IDDM with 95% confidence intervals were calculated for cohort members responding at 5 and 10 years, for each

vaccine type. Whilst the recall error is apparent at age 10 years, making the results difficult to interpret, the unadjusted OR are included here for completeness (Table 49). It was not possible to assess false-positive vaccination histories, as medical notes were not available. Multiple logistic regression analysis was used to adjust for potential confounding factors. These were sex, father's social class at birth and household crowding variable at age 5 years (person per room ratio in fifths of the distribution). All variables were modelled as a series of binary dummies. Only those with complete data for each variable were included in this analysis. Unadjusted and adjusted relative odds are reported. (Table 48)

Measles vaccination history was available at age 5 years in 7616/9757 cohort members (21/30 subjects with CD, 15/22 with UC, and 24/40 with IDDM). If those subjects with missing data for potential confounding factors were excluded, measles vaccination history was available for 7319 cohort members (20 with CD, 15 with UC and 23 with IDDM). Those who did not have available vaccination histories at age 5 years did not differ significantly in sex or social class from those for whom data were available.(226) There was no statistically significant association between measles vaccination by 5 years and CD. Using maximum numbers, the unadjusted odds ratios were 0.72, (95% CI 0.30 to 1.69), 0.57, (95% CI 0.21 to 1.57), 0.65, (95% CI 0.34 to 1.25) and 0.91, (95% CI 0.40 to 2.05) for CD, UC, IBD and diabetes respectively. This was unaffected by adjusting for social class, sex and crowding (Numbers are reduced by excluding those with missing data for any of the variables). There was no statistically significant association between any of the other vaccines by 5 years and any of the outcome diseases. Only measles, pertussis and diphtheria have been shown. (Table 48)

Table 48 Vaccine recipients by age 5 years and subsequent inflammatory bowel disease and diabetes

	No. Reporting Vaccine (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Measles vaccine			
Whole sample	4431/7319 (61%)	-	-
Crohn's disease	11/20 (55%)	0.80 (0.3-1.9)	0.67 (0.3-1.6)
Ulcerative colitis	7/15 (47%)	0.57 (0.2-1.6)	0.57 (0.2-1.6)
IBD	18/35 (51%)	0.69 (0.4-1.3)	0.62 (0.3-1.2)
Diabetes Mellitus	13/23 (57%)	0.85 (0.4-1.9)	0.75 (0.3-1.7)
Pertussis vaccine			
Whole sample	6862/7264 (94.5%)	-	-
Crohn's disease	19/21 (90.5%)	0.56 (0.1-2.4)	0.44 (0.1-1.9)
Ulcerative colitis	14/15 (93.3%)	0.82 (0.1-6.3)	0.84 (0.1-6.5)
IBD	33/36 (91.7%)	0.64 (0.2-2.1)	0.57 (0.2-1.9)
Diabetes Mellitus	23/24 (95.8%)	1.35 (0.2-10.0)	1.15 (0.2-8.6)
Diphtheria vaccine			
Whole sample	7339/7534 (97.4%)	-	-
Crohn's disease	20/21 (95.2%)	0.53 (0.1-4.0)	0.35 (0.0-2.8)
Ulcerative colitis	14/15 (93.3%)	0.37 (0.0-2.8)	0.38 (0.1-3.0)
IBD	34/36 (94.4%)	0.45 (0.1-1.9)	0.37 (0.1-1.6)
Diabetes Mellitus	24/25 (96%)	0.63 (0.1-4.7)	0.51 (0.1-3.9)

*Adjusted for potential confounding factors sex, social class at birth and crowding in childhood. Subjects with missing data for any of the variables were excluded

Table 49 **Vaccine recipients by age 10 years and subsequent inflammatory bowel disease and diabetes**

	No. Reporting Vaccine (%)	**Unadjusted OR (95% CI)**
Measles vaccine		
Whole sample	5233/8492 (61.6%)	-
Crohn's disease	15/23 (65.2%)	1.17 (0.5-2.8)
Ulcerative colitis	13/19 (68.4%)	1.35 (0.5-3.6)
IBD	28/42 (66.7%)	1.25 (0.7-2.4)
Diabetes Mellitus	27/36 (75.0%)	1.87 (0.9-4.0)
Pertussis vaccine		
Whole sample	7761/8480 (91.5%)	-
Crohn's disease	21/23 (91.3%)	0.97 (0.2-4.2)
Ulcerative colitis	18/18 (100%)	-
IBD	39/41 (95.1%)	1.81 (0.4-7.5)
Diabetes Mellitus	35/36 (97.2%)	3.25 (0.4-23.8)
Diphtheria vaccine		
Whole sample	8282/8480 (97.7%)	-
Crohn's disease	22/23 (95.7%)	0.53 (0.1-3.9)
Ulcerative colitis	18/18 (100%)	-
IBD	40/41 (97.6%)	0.96 (0.1-7.0)
Diabetes Mellitus	35/36 (97.2%)	0.84 (0.1-6.1)

Vaccinations using doctor confirmed cases of IBD only

If doctor confirmed cases of IBD only were used in the analysis, again no association was seen between any of the vaccines by age 5 and subsequent IBD (see table 50)

Table 50 Relationship between measles vaccination by age 5 and age 10 and inflammatory bowel disease using doctor confirmed cases only

	No reporting measles vaccine (%)	**Unadjusted OR (95% CI)**
Age 5		
Whole sample	4611/7616 (61%)	-
Crohn's disease	9/17 (53%)	0.73 (0.3-1.9)
Ulcerative colitis	2/7 (29%)	0.26 (0.1-1.3)
IBD	11/24 (46%)	0.55 (0.2-1.2)
Age 10		
Whole sample	5233/8492 (62%)	-
Crohn's disease	12/18 (67%)	1.25 (0.5-3.3)
Ulcerative colitis	6/10 (60%)	0.93 (0.3-3.3)
IBD	18/28 (64%)	1.12 (0.5-2.4)

Measles vaccination excluding those with a family history of IBD or a history of concurrent measles and mumps infections

As described previously, both family history and a history of concurrent measles and mumps in the same year of life have been significantly associated with IBD in this study. Subjects with such histories were therefore excluded from the analysis to examine any relationship between measles vaccination and IBD independent of these factors. Again no statistically significant relationship was evident. (See table 51)

Table 51 Relationship between measles vaccination by age 5 and age 10 and inflammatory bowel disease, excluding those reporting concurrent measles and mumps infection or family history of IBD

	Excluding concurrent measles and mumps infection		**Excluding those with a family history of IBD**	
	No reporting measles vaccine (%)	**Unadjusted OR (95% CI)**	**No reporting measles vaccine (%)**	**Unadjusted OR (95% CI)**
Age 5				
Whole sample	3679/5901 (62%)	-	3832/6213 (62%)	-
Crohn's disease	9/15 (60%)	0.91 (0.3-2.5)	9/15 (60%)	0.93 (0.3-2.6)
Ulcerative colitis	5/9 (56%)	0.76 (0.2-2.8)	6/13 (46%)	0.53 (0.2-1.6)
IBD	14/24 (58%)	0.85 (0.4-1.9)	15/28 (54%)	0.72 (0.3-1.5)
Age 10				
Whole sample	4573/7254 (63%)	-	5221/8465 (62%)	-
Crohn's disease	12/17 (71%)	1.41 (0.5-4.0)	15/22 (68%)	1.33 (0.5-3.3)
Ulcerative colitis	9/13 (69%)	1.32 (0.4-4.3)	12/18 (67%)	1.24 (0.5-3.3)
IBD	21/30 (70%)	1.37 (0.6-3.0)	27/40 (68%)	1.29 (0.7-2.5)

Age at measles vaccination

The age at measles vaccination and later CD, UC and IDDM was examined by multiple logistic regression and using the chi-square test for trend. The age at measles vaccination reported at age 5 years was divided for analysis into categories: under 2 years, 2, 3 and over 4 years. Multiple logistic regression analysis was used to adjust for potential confounding factors. These were sex, father's social class at birth and household crowding variable at age 5 years (person per room ratio in fifths of the distribution). All variables were modelled as a series of binary dummies. Only those with complete data for each variable were included in this analysis. Unadjusted and adjusted relative odds are reported.

Age of vaccination was also examined as a continuous variable. The same analysis was performed after excluding those with a history of measles and mumps infections in the same year of life, as this had previously been identified as an independent risk factor for IBD.

The age at vaccination against measles amongst vaccinees was recorded in the survey at age 5 years in 4610 subjects also responding at 26 years (mean age at vaccination 17.6 months, sd 7.4). There were 11 cases with CD (mean age at vaccination 21.8 months, sd 13.8), 7 cases of UC (mean age at vaccination 16.6 months, sd 2.9) and 14 cases of diabetes mellitus (mean age at vaccination 15.5 months, sd 4.8). After excluding cohort members with missing data for potential confounding factors there were 4430 subjects for analysis (11 with CD, 7 with UC and 13 with IDDM). There was a statistically significant trend (p=0.040) with increasing age of measles vaccination for risk of Crohn's disease, but not UC or IDDM, although there were small numbers of cases in some cells making interpretation difficult. There were 8 subjects with CD vaccinated before age 2 years, and one each at age 2, 3 and 4 years respectively. The unadjusted relative odds for Crohn's disease in those reporting measles vaccination were 1.17 (95% CI 0.15 to 9.35), 3.53 (95% CI 0.44 to 28.40), and 7.11 (95% CI 0.88 to 57.62), when vaccinated at 2, 3 and over 4 years respectively, with under 2 years used as the baseline. Adjusting for the potential confounders, social class at birth, sex and crowing ration did not significantly affect these findings. Caution must be taken in interpretation of the results, as the number of cases in each cell was so small. (Table 52)

There was a statistically significant association between age at vaccination entered as a continuous variable and Crohn's disease, after adjusting for potential confounders sex, social class at birth and crowding ratio (relative odds for CD for each unit increase in age 1.05, 95% CI 1.00 to 1.10, p=0.049).

When age at vaccination as a continuous variable was compared between CD and UC using the Mann Whitney U test, there was no statistically significant difference between the 2 groups (U=38.0, Z=-0.046, p=0.964).

None of the subjects with Crohn's disease who reported measles vaccination over age 2 years gave a history of measles infection by 10 years although 2 had reported mumps infection (one at age 2 years and one over 4 years of age). Excluding those with a history of mumps and measles infection in the same year of life (n=297), the unadjusted OR for CD in those reporting measles vaccination was increased to 1.54 (0.18 to 12.89), 4.84 (0.55 to 42.45) and 8.92 (1.02 to 77.67) at 2, 3 and over 4 years, respectively (Chi-square test for trend, p=0.015). See Figure 9.

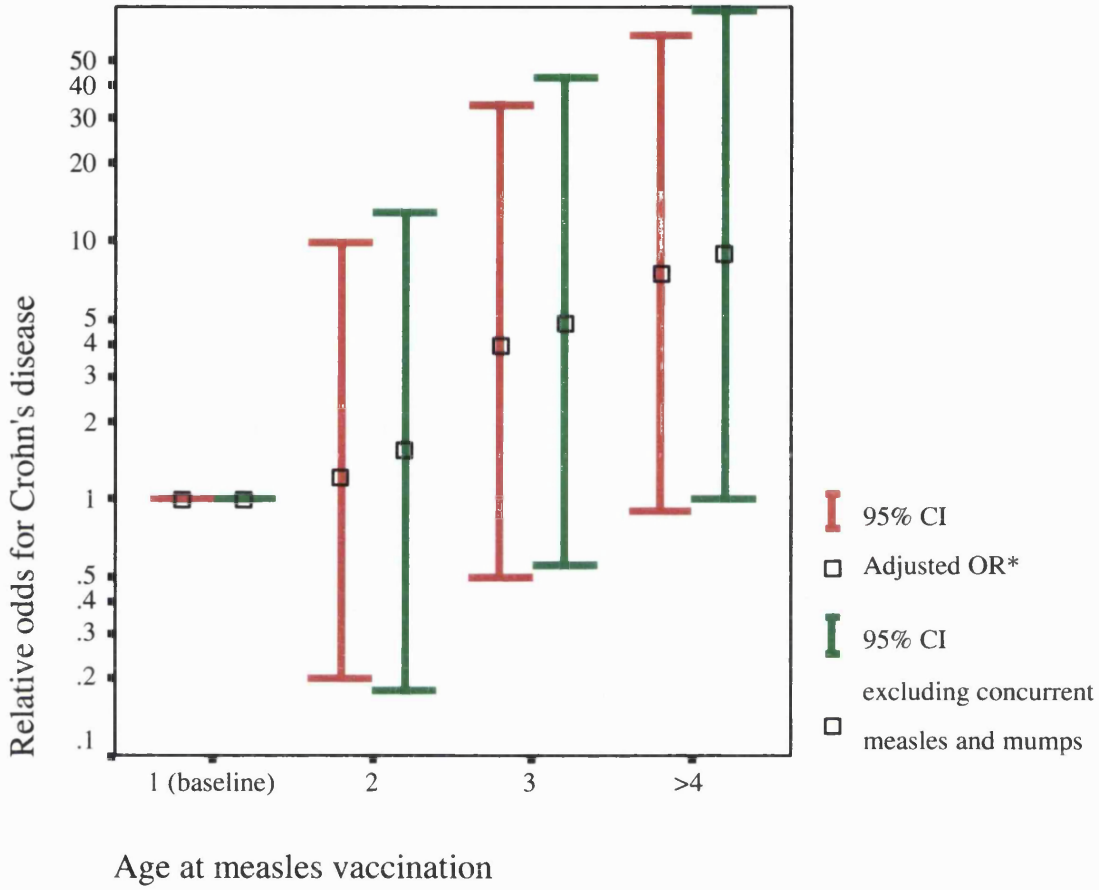
Table 52 Age at measles vaccination and subsequent Crohn's disease, ulcerative colitis

Age at measles vaccination	Whole sample reporting measles vaccine (%)	No. with IBD reporting measles vaccine (%)	Unadjusted OR (95% CI)	Adjusted OR[$] (95% CI)
Crohn's disease				
0-1 year	3817 (86.2%)	8 (72.7%)	-	-
2 years	409 (9.2%)	1 (9.1%)	1.17 (0.1-9.4)	1.22 (0.2-9.8)
3 years	136 (3.1%)	1 (9.1%)	3.53 (0.4-28.4)	3.95 (0.5-33.1)
4-5 years	68 (1.5%)	1 (9.1%)	7.11 (0.9-57.6)*	7.43 (0.9-61.9)**
Total	4430	11		
Ulcerative Colitis				
0-1 year	3817 (86.2%)	7 (100%)	-	-
2 years	409 (9.2%)	0	-	-
3 years	136 (3.1%)	0	-	-
4-5 years	68 (1.5%)	0	-	-
Total	4430	7	-	-

*p for trend=0.040 ** p for trend=0.045

[$] Adjusted for sex, father's social class and crowding variable

Figure 9 **Relative odds for Crohn's disease by age of measles vaccination**



*Adjusted for sex, father's social class and crowding variable

Age at first reported exposure to measles in vaccine or wild infection

Only those cohort members with complete data for all variables were used in the analysis. There was no statistically significant relationship between age at first exposure to measles (either wild infection or vaccination) in subjects with Crohn's disease, ulcerative colitis or diabetes. This was unaffected by adjustment for potential confounding factors (sex, father's social class and crowding variable). See table 53.

Table 53 Age at first reported exposure to measles (vaccine or wild infection) and subsequent Crohn's disease and ulcerative colitis

Age at first measles exposure	Whole sample reporting measles exposure (%)	Nos reporting measles exposure (%)	Unadjusted OR (95% CI)	Adjusted OR[$] (95% CI)
Crohn's disease No exposure	616 (10.0%)	2 (11.8%)	1.62 (0.3-7.8)	1.74 (0.4-8.4)
0-1 year	3482 (56.7%)	7 (41.2%)	Baseline	Baseline
2 years	561(9.1%)	3 (17.6%)	2.67 (0.7-10.4)	2.92 (0.8-11.4)
3 years	337 (5.5%)	1 (5.9%)	1.48 (0.2-12.0)	1.55 (0.2-12.7)
4-10 years	1141(18.6%)	4 (23.5%)	1.75 (0.5-6.0)	1.94 (0.6-6.7)
Total	4430	17		
Ulcerative Colitis No exposure	616 (10.0%)	2 (15.4%)	1.62 (0.4-7.8)	1.52 (0.3-7.4)
0-1 year	3482 (56.7%)	7 (53.8%)	Baseline	Baseline
2 years	561(9.1%)	1 (7.7%)	0.89 (0.1-7.2)	0.82 (0.1-6.8)
3 years	337 (5.5%)	0	-	-
4-10years	1141(18.6%)	3 (23.1%)	1.31 (0.3-5.1)	1.27 (0.3-5.0)
Total	4430	13		

[$] Adjusted for sex, father's social class and crowding variable

Measles vaccination by 5 years and measles infection by 10 years

Logistic regression analysis was used to assess the relationship between type of exposure to measles (infection, vaccination, both or neither) and subsequent inflammatory bowel disease. Crohn's disease and ulcerative colitis were considered as the dependant variables and type of measles exposure as the independent variable. Those who reported neither measles vaccination nor infection were used as the baseline.

The table below summarises the findings. There was no statistically significant relationship between any of the types of exposure to measles and subsequent IBD. In particular the combination of measles infection and vaccination did not appear to be a significant risk factor for either Crohn's disease or ulcerative colitis, although small numbers in some cells makes interpretation difficult.

Table 54 Unadjusted Relative odds for Crohn's disease and ulcerative colitis in subjects reporting measles vaccination by age 5 and measles infections by age 10 years

	Whole Sample (%)	Crohn's Disease (%)	OR for Crohn's disease (95% CI)	Ulcerative colitis	OR for Ulcerative colitis (95% CI)
Neither measles vaccine or infection	645 (9.9%)	2 (10.0%)	baseline	2 (15.4%)	baseline
Measles vaccine only	2878 (44.2)	8 (40.0%)	0.90 (0.19-4.23)	4 (30.7%)	0.45 (0.08-2.45)
Measles infection only	1920 (29.5%)	8 (40.0%)	1.34 (0.28-6.35)	6 (46.2%)	1.01 (0.20-5.01)
Measles vaccine and infection	1065 (16.4%)	2 (10.0%)	0.60 (0.09-4.30)	1 (7.7%)	0.30 (0.03-3.34)
Total	6508	20		13	
Missing measles vaccine or infection data	3249	10		9	
Total	9757	30		22	

*Data in table only for subjects with complete data for both measles vaccination and infection.

Adverse reactions following vaccinations

Adverse reactions within 48 hours to any vaccination were reported in 2/10 (20%) cases with CD (199/3962, 5% of the whole cohort), both following measles vaccination. In subjects with Crohn's disease, these took the form of a severe measles-like illness in one, and a high fever in the other. Adverse reactions after measles vaccination were associated with CD, unadjusted OR 4.76 (95% CI 1.01 to 22.56), although this did not achieve statistical significance when Fisher's exact test was used to take account the small number in some cells (Fisher's p=0.087). One of 14 cases (7%) with IDDM (unadjusted OR 1.46, 95% CI 0.19 to 11.19), but no cases with UC, reported adverse reactions following measles vaccination. One of 23 cases (4.3%) with IDDM, 1/13 (7.7%) cases with UC and 245/6465 (3.8%) of the whole cohort (unadjusted OR for diabetes 1.16, 95% CI 0.16 to 8.60, for UC 2.12, 95% CI 0.28-16.38), but no cases with CD, reported adverse reactions following diphtheria vaccination. One of 3 subjects with UC (33%) and 48/1415 (3.4%) of the whole cohort reported adverse reaction following smallpox vaccine (OR14.52, 95% CI 1.29-163, Fishers p=0.098). The small number of cases reporting any adverse reactions makes interpretation of these findings difficult.

Contraceptive pill

Data were only available for 2702 girls responding at age 16 and age 26 years. Some 442/2702 (16.4%) girls reported having used the contraceptive pill by age 16 years. There was no statistically significant association between contraceptive pill use and Crohn's disease, UC, IBD combined or diabetes. See Table 55.

Table 55 Relative odds for IBD and diabetes in contraceptive pill users age 16 years

	No reporting use of contraceptive pill (%)	**Unadjusted OR**	**95% CI**	**2-tailed Fisher's p-value**
Whole sample	442/2260 (16.4)	1.00	-	-
Crohn's disease	2/9 (22.2)	1.46	0.30-7.01	0.647
Ulcerative colitis	1/6 (16.7)	1.02	0.12-8.73	1.000
IBD	3/15 (20.0)	1.28	0.36-4.51	0.724
Diabetes	0/8 (0)	-	-	-

Hand, foot and eye preference

Complete data on handedness were available for 8134/9757 (83%) subjects from the BCS70 who responded at age 26-years and 9062/11184 (81%) subjects from the NCDS who responded at age 33-years. For foot preference, data from 7691/9757 (78%) subjects from the BCS70 were available for analysis. Complete data on eye preference were available for 8134/9757 (83%) subjects from the BCS70.

Handedness and sex

Sex was considered to be a potential confounding factor even thought there was no statistically significant association between Crohn's disease, ulcerative colitis or inflammatory bowel disease combined and sex in this study. Left-handedness showed a statistically significant association with male sex in both cohorts combined (χ^2=26.3, Pearson's 2-sided p=0.000.) (Table 56)

Cohort and IBD

There were 31/11184 (0.28%) subjects with IBD in the NCDS and 40/9757 (0.41%) in the BCS70 who had complete data available for analysis. A diagnosis of IBD was more likely in the BCS70 cohort than the NCDS (Unadjusted OR 1.44, 95% CI 0.9-2.37, p=0.109).

Handedness and inflammatory bowel disease

Both cohorts showed increased relative odds for IBD in left-handers. These were statistically significant for the BCS70 (adjusted for sex, OR 2.28, 95% CI 1.08-4.79, Fisher's p=0.031) but not for the NCDS (adjusted for sex, OR 1.94, 95% CI 0.79-4.75, Fisher's p=0.147).

Left-handers had increased relative odds for both CD and UC when analysed as separate diseases in the combined cohorts, although this was not statistically significant. Adjusting for sex and cohort did not alter the significance of the association. (Table 57)

Inflammatory bowel disease was significantly associated with left-handedness when the two cohorts were combined. Again, adjusting for sex and cohort did not alter these findings significantly (Figure 10).

Foot preference and inflammatory bowel disease

Data on foot preference were only available for the BCS70 cohort. Some 980/7691 (12.7%) reported left foot preference overall. There were 2/20 (10.0%) subjects with CD, 5/18 (27.8%) with UC and 7/38 (18.4%) with IBD reporting left foot preference. There was no statistically significant association between left foot preference and Crohn's disease (unadjusted OR 0.76, 95% CI 0.18-3.28, Fisher's p=1.000). For those with ulcerative colitis, there was a non-significant association with left foot preference (unadjusted relative odds 2.64, 95% CI 0.94 to 7.42, Fisher's 2-tailed p=0.069). After adjusting for sex, the relative odds for disease in those reporting left foot preference were 0.79 (95% CI 0.18 to 3.39, p=0.747) 2.59 (95% CI 0.92 to 7.30, p=0.073) and 1.56 (95% CI 0.69 to 3.56, p=0.291) for Crohn's disease, ulcerative colitis and IBD, respectively. (Table 58)

Eye preference and inflammatory bowel disease

Data on eye preference were only available for the BCS70 cohort. There were 2490/8134 (30.6%) cohort members overall who reported left eye preference Of these, some 6/22 (27.3%) with CD, 5/19 (26.3%) with UC, 30/41 (73.2%) with IBD reported left eye preference. There was no statistically significant association between CD (unadjusted OR 0.85, 95% CI 0.33-2.17, p=0.734) UC (unadjusted OR 0.81, 95% CI 0.29-2.25, p=0.684) or IBD (unadjusted OR 0.83, 95% CI 0.42-1.66, p=0.598) and left eye preference.

Table 56 Relative odds for the association between left-handedness and sex in two national birth cohorts

Cohort	Sex	left-handed subjects (%)	Relative Odds (95% CI)	Pearson's 2-tailed p-value
BCS70	Male	487/4000 (12.2%)	1.17 (1.02 to 1.34)	0.025
	Female	438/4134 (10.6%)	-	-
NCDS	Male	558/4379 (12.7%)	1.40 (1.22 to 1.59)	<0.001
	Female	444/4684 (9.5%)	-	-
Combined Cohorts	Male	1045/8379 (12.5%)	1.28 (1.17 to 1.41)	<0.001
	Female	882/8818 (10.0%)	-	-

Table 57 Left-handedness and relative odds for inflammatory bowel disease in two national birth cohorts

Birth Cohort	N Left-handed with Disease (%)	N Left-handed without disease (%)	Unadjusted Relative Odds (95% CI)	Adjusted Relative Odds* (95% CI)
BCS70				
Crohn's disease	4/21 (19%)	921/8113 (11%)	1.84 (0.62 to 5.47) p=0.289	1.86 (0.62 to 5.53) p=0.267
Ulcerative colitis	5/19 (26%)	920/8115 (11%)	2.79 (1.0 to 7.77) p=0.056	2.76 (0.99 to 7.68) p=0.052
IBD combined	9/40 (22%)	916/8094 (11%)	2.28 (1.08 to 4.79) **p=0.040**	2.27 (1.08 to 4.79) **p=0.031**
NCDS				
Crohn's disease	4/17 (23%)	998/9045 (11%)	2.48 (0.81 to 7.62) p=0.110	2.45 (0.80 to 7.55) p=0.118
Ulcerative colitis	2/14 (14%)	1000/9048 (11%)	1.34 (0.30 to 6.00) p=0.662	1.37 (0.30 to 6.13) p=0.683
IBD combined	6/31 (19%)	996/9031 (11%)	1.94 (0.79 to 4.73) p=0.147	1.94 (0.79 to 4.75) p=0.147

*Adjusted for sex

Table 58 **Left-handedness and relative odds for inflammatory bowel disease in the combined birth cohorts**

Birth Cohorts Combined	N Left-handed with disease (%)	N Left-handed without disease (%)	Unadjusted Relative Odds (95% CI) 2-tailed p-value	Adjusted Relative Odds* (95% CI) 2-tailed p-value
Crohn's disease	8/38 (21.1%)	1919/17158 (11.2%)	2.12 *(0.97 - 4.63)* p=0.067	2.12 (0.97 - 4.64) p=0.059
Ulcerative colitis	7/33 (21.2%)	1920/17163 (11.2%)	2.14 (0.93 - 4.93) p=0.089	2.12 (0.92 - 4.90) 0.078
IBD combined	15/71 (21.0%)	1912/17125 (11.o%)	2.13 (1.20 - 3.78) **p=0.008**	2.13 (1.19 - 3.77) **p=0.010**

*Adjusted for sex and cohort

Figure 10 **Relative odds, with 95% CI, of inflammatory bowel diseases in left-handed subjects for BCS70, NCDS and combined cohorts**

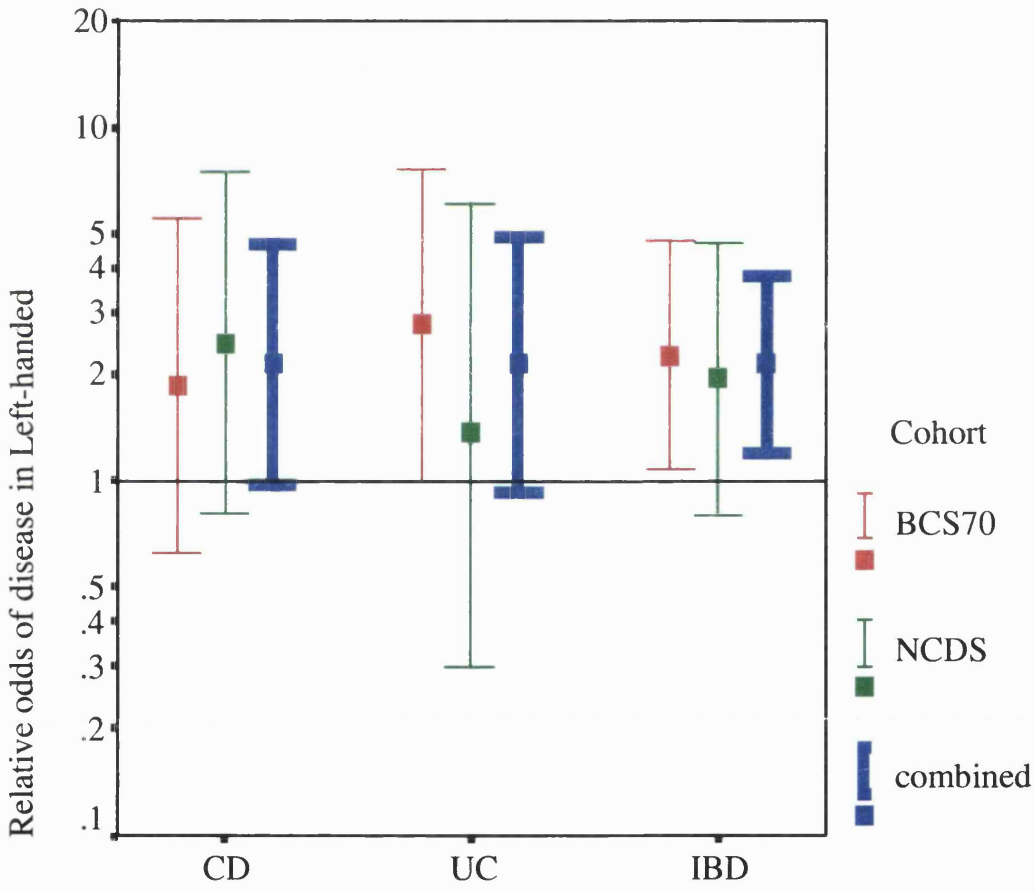


Table 59 Left-foot preference and relative odds for inflammatory bowel disease in the BCS70

BCS70	N preferring Left-foot with Disease (%)	N preferring Left-foot without disease (%)	Unadjusted Relative Odds (95% CI) Fisher's p-value	Adjusted Relative Odds* (95% CI) Fisher's p-value
Crohn's disease	2/20 (10%)	978/7671 (13%)	0.76 (0.18 to 3.28) p=1.000	0.79 (0.18 to 3.40) p=0.747
Ulcerative colitis	5/18 (28%)	975/7673 (13%)	2.64 (0.94 to 7.43) p=0.069	2.59 (0.92 to 7.30) p=0.073
IBD combined	7/38 (18%)	973/7653 (13%)	1.55 (0.68 to 3.53) p=0.324	1.56 (0.68 to 3.56) p=0.291

*Adjusted for sex

Discussion

Study design-advantages and disadvantages

This is one of the largest birth cohort studies with prospectively collected data to examine early risk factors for inflammatory bowel disease. The use of a cohort study has many advantages over retrospective methods in this setting. Firstly, they enable better understanding of the temporal relationship between exposure and disease, because cohort members are free from disease at the start of the study and at the time of exposure to specific proposed risk factors. Secondly, cohort studies are able to examine multiple exposures and outcomes, and rare exposures can be examined. Thirdly, a cohort study in this setting enables calculation of the prevalence (and incidence) of inflammatory bowel disease. The BCS70 is fortunate to have followed members from birth to the present day, thus allowing investigation of possible exposures that may have a long latent period before disease presentation.

Unfortunately one of the disadvantages is that not all the cohort members will have developed inflammatory bowel disease by age 26 years, at the time this study was performed. Indeed it is likely that a second or even third peak (13) in incidence will occur when the cohort are in their eighth decade of life. (6) As the incidence of inflammatory bowel disease is relatively low, compared with other common diseases of modern life such as ischaemic heart disease or asthma, the actual number of cohort members developing IBD, even in such a large birth cohort will be relatively small. This can result in difficulties interpreting results based on small numbers of cases, due to lack of statistical power.

Potential sources of bias must be considered in all study designs. Information bias, which is commonly a problem in case-control studies, is minimised in a birth cohort study such as the BCS70 as exposures to potential risk factors have occurred before onset of IBD in most situations. This will be discussed for each of the exposures we examined. Classification bias is likely to have occurred at the time of data collection, with misclassification of exposure status to specific risk factors inevitable. However, this is likely to be random with regards to outcome measures of IBD status, as in most

situations, the disease status was unknown at the time of data collection. The effect of such non-differential misclassification is to reduce any risk estimate between exposure and outcome, and may obscure any real relationship.

Recall bias may also be relevant to some exposures such as vaccination or infection status as although the data were collected at regular intervals, there may have been difficulty remembering events accurately during these five or ten year periods. Again such bias is likely to be non-differential

In addition it is possible that there may have been some misclassification of inflammatory bowel disease status, both in case ascertainment and in classification of IBD type into Crohn's disease or ulcerative colitis.

Some cohort members with inflammatory bowel disease may not have been acknowledged because they did not wish to identify themselves. The cohort members were asked about several diseases at age 26 years to avoid particular emphasis on IBD, and the reason for the survey was not given in detail in order to avoid such bias. This was especially important with regards to the measles vaccination hypothesis, which they may have been aware of at the time of the survey. Self-reporting of IBD appears to be reliable in this study, as in others (11;45) as only 7/59 cohort members who initially responded saying they had IBD were subsequently refuted. Of these, physicians refuted 3 diagnoses; the remainder were due to errors in filling in the questionnaires. In addition, cohort members with IBD may have been missed because they had not yet been diagnosed with disease or were asymptomatic (28) However, the prevalence of IBD of 33.7 per 10,000 general population (based on physician confirmed diagnoses only) is one of the highest reported in Great Britain suggesting that case ascertainment is likely to have been high and reliable.

Misclassification of disease type between UC and CD is more difficult to evaluate. Where available, in 33/52 (63.5%) subjects with IBD, diagnoses were confirmed from medical notes using fixed criteria. (9) In addition an independent histopathologist also examined histological specimens (see below). It is estimated that 10-15% patients with colonic disease cannot be accurately classified.(6)In view of the problems associated with overlap of these two diseases, where relevant, they have been analysed both separately and combined as IBD.

One of the major sources of bias in this and indeed many cohort studies is selection bias. It is inevitable that in a cohort followed up from birth for many years there will be a degree of non-participation and loss to follow-up. Those lost to follow-up are likely to differ from participants in many important factors. For a birth cohort the size of the BCS70, we were able to trace 13,099 (82%) of the predicted target population of 16,000. There was a good response rate at age 26 years of 77% after excluding invalid and untraced addresses. As some of the important characteristics of the non-participants such as social class, sex, education, ethnic origin and region of residence were recorded at birth, it was possible to compare the responders with non-responders at each subsequent age survey. As expected, non-participants were significantly more likely to be male, British ethnic origin, from the most socially disadvantaged groups, and those whose parents have completed more years of education. None of these factors, except ethnicity, were subsequently found to be significantly associated with IBD. In addition, the cohort responding at age 26 years remained largely representative of the birth cohort, with the proportion of those from the most disadvantaged groups in social class V dropping from 5.8% in the original birth cohort to 4.6% in responders at age 26 years.

It is unlikely that significant observer bias occurred as those interviewing cohort members and their families over the years and those coding and entering the data did not have a special interest in IBD.

Prevalence of IBD, demographic measures and socio-economic status

The prevalence in our study of Crohn's disease (29.8 per 10,000 or 1 in 336) and ulcerative colitis (19.4 per 10,000 or 1 in 515) in 1996 when the cohort were age 26 years, was higher than other studies performed in Britain (31;35) and indeed world-wide. Other studies have reported a prevalence of CD of 1.2 to 9.5 per 10,000 and of UC of 4.0 to 21.0 per 10,000.(6) This may be partly because many previous studies have been hospital based, but as almost all cases are diagnosed in hospital setting, this seems an unlikely explanation. A study of a similar birth cohort born in 1958 (NCDS) showed a prevalence of IBD in 1991 of 28.7 per 10,000 when the cohort was 33years. (45) This increase over time suggests that IBD is becoming more common in Great Britain, with CD now more prevalent than UC. It is unlikely that genetic factors alone could account

for such rapid increases in IBD this century and supports the role of environmental factors in their aetiology.

The mean age at diagnosis for both CD and UC was 20 years, which is likely to increase as the cohort ages and more cases are diagnosed. 5 cohort members had their disease diagnosed before age 16 years (3 with UC and 2 with CD). A high prevalence of paediatric IBD (51, per 100,000 population, 1 in 1953 children under 16 years) is also in keeping with current trends suggested by some groups (18;20), and supports the hypothesis that early environmental factors may be important in the aetiology of IBD. The prevalence reported in this study is much higher than previously reported in Europe (228)

The cohort overall is likely to be representative of the general population as it was conducted nationally, with all births being recorded over a one week interval. Cohort members found to have IBD are likely to be representative of other people with IBD in the general population. The only possible factor in which they may differ is that they were all born during one week of the year in April 1970. However, seasonal variation in the birth of patients with IBD is controversial.(15;47;51)

The findings from this study are in keeping with temporal trends in IBD. They suggest an increase in the incidence of CD over UC in particular since 1960. (12;30;38) As this cohort is relatively young we expect the prevalence to rise further both in the BCS70 and in the general British population.

The prevalence of IBD at age 26 years from this study is now greater than that of insulin dependant diabetes mellitus. The prevalence of diabetes in this study was in keeping with current trends, although further discussion is outside the scope of this thesis.

Histological diagnosis and disease distribution

We used standard criteria according to Riis (9) to classify cohort members into CD or UC groups. This classification was used so as to be comparable to previous work by the department. (11)Whilst there is often overlap both clinically and pathologically between UC and CD, it is useful to make a distinction between the two diseases as they have many differences in epidemiology, which can be masked by combining them

together. It is estimated that 10-15% of patients with colonic disease cannot be classified overall.(6)In our study, review of pathology specimens was made in 27 subjects, adding additional confirmation of the clinical diagnoses. Some 3/27 (11%) and 5/22 (23%) subjects were considered to show non-specific IBD by the initial pathologist and our independent pathologist, respectively. The independent pathologist was unaware of the clinical details of the patient, which may have influenced the decision.

Over half (53%) of the patients with CD who had details on disease distribution available had some involvement of the colon or rectum. This is in keeping with the recent increase in diagnosis of colonic CD that has been described. Similarly, two thirds of the patients with UC who had details on disease distribution available had inflammation confined to the rectum. (6)

Region of Birth

Regional differences in IBD incidence have been described, but there was no difference in disease distribution in our study, perhaps due to the small number of cases per region. (30) (23)

Sex

Sex was not significantly associated with CD or UC, perhaps due to lack of statistical power, but there was an excess of females with CD and an excess of males with UC in keeping with previous studies. Hormonal or lifestyle factors may explain these consistent findings.(6)

Social class, maternal age and parental education

Mother or father's social class at birth as classified by the registrar generals' classification, was not significantly associated with IBD in this study. Whilst this may reflect the small number of cohort members with IBD, rather than any lack of association, there are other explanations for this lack of conformity with previous studies.(22) Younger age at completing education for both parents was significantly associated with UC but not CD. Such traditional measures of affluence may not be useful in today's society, where material circumstances in childhood in this country have improved

compared with the earlier 20th century, and conditions are more homogeneous. Indeed such improvement in circumstances, as indicated by infant mortality, have been suggested to be associated with increased risk of IBD.(77;78)

Maternal age at delivery was similarly unrelated to IBD. Young age at completing education for either parent was significantly associated with UC, however this was based on very small numbers of cases and so is difficult to interpret.

Other proxy measures of social and material circumstances in childhood may be better at distinguishing between conditions in infancy, and will be discussed later.

Household Crowding

Household crowding may be an alternative measure of home circumstances. Increased crowding is associated with increased exposure to infections within the home,(80)and these have been in turn linked with risk of IBD in some studies.(47) In our study crowding showed a significant association with CD only, with those in a less crowded environment being at increased risk of CD compared with those in the most. Again, this was based on small numbers of cases and so is difficult to interpret. However crowding was subsequently considered as a potential confounding factor in subsequent multivariate modelling.

Ethnic origin

This study supports other published literature in finding a statistically significant increased risk of Crohn's disease and ulcerative colitis in children whose parents were born in India, Pakistan or Bangladesh when compared with those whose parents were British. This was independent of family history, sex or household crowding.

The findings are unlikely to be due to any systematic selection bias of excess Asians with IBD due to the uniform methods of tracing used in this study.(224) Asian families may often live in crowded conditions in this country. Such differences in material circumstances in childhood have been proposed as a risk factor for IBD, but the association between Asian ethnic origin and IBD was independent of this potential confounding factor in our study.(47;80) The findings are also unlikely to be due to excess estimation of IBD prevalence, as the risk of IBD in Asians was still significantly increased after excluding those in whom physicians had not confirmed the diagnoses.

Although the number of cohort members is small, the distribution of IBD appears equally divided amongst those of Pakistani and Indian origin, suggesting that grouping them together may be appropriate. Indeed the risk of IBD associated with both Indian and Pakistani groups, when analysed separately, is increased. This is statistically significant for the Indian subgroup and approaches significance at the 5% level for the Pakistani group. Previous studies have shown increased risk of IBD in various Asian ethnic groups. A significantly higher incidence of UC (excluding proctitis) was found in Hindus and Sikhs than Europeans, although incidence of CD was lower in Hindus than Europeans in Leicester. Muslims in the same study had a similar risk of UC and CD to Europeans. (229;230)These differences may be partly explained by smoking habits, although it is difficult to understand how smoking might have influenced the findings of our study as cigarette smoking at age 10 and 16 was not associated with later IBD (see later discussion).

A family history of IBD was also considered to be a potential confounding factor, and was therefore adjusted for in the multivariate model. None of the Asian cohort members, however, reported a family history of IBD. This is similar to other studies. (231) Many of the cohort member's first-degree relatives may have been born and still

resident in Asia where the incidence rates of IBD are increasing but still low. (232) This suggests that environmental factors are important in revealing the genetic predisposition to IBD in this population. This also suggests that cultural factors alone such as diet or betel nut ingestion are unlikely to be responsible for the high incidence of IBD in Asians. Such habits are likely to be maintained in the parents of cohort members resident in the UK as well as in Asia, both groups of who have a low incidence of IBD. (79) Montgomery suggests that poor material circumstances in early childhood, as indicated by higher infant mortality rates, may explain the lower incidence of IBD in those born in Asia. (77;78) (78)This could be due to exposure to an important factor in the aetiology of IBD, which proves fatal in times of high infant mortality. Alternatively those with a genetic predisposition to IBD may be more likely to survive when material conditions in early childhood are improved, such as those born in Great Britain as part of this cohort study. Another explanation may be that as childhood material conditions improve, important factors in the aetiology of IBD may become more prevalent. (79)

Genetic Predisposition and Family History of IBD

Genetic factors are now established as important in the risk of both CD and UC, with recent advances in molecular biology now able to identify susceptibility genes that may also determine phenotype and clinical features of IBD. (233;234)

We were able to investigate the contribution of genetic predisposition to risk of later IBD in the BCS70 by looking at family history of IBD as a marker. The data on family history of disease was obtained when the cohort members were aged 16 years. At this age, 5/38 cohort members themselves had developed IBD, which may have influenced their response. A lower follow-up rate at age 16 years (79% of predicted target population) also reduced the number of cohort members available for analysis. Nevertheless, 2/38 (5%) of the cohort members with IBD reported a first degree relative with IBD, both were parents with concordant disease phenotype. This is in keeping with previous studies. (50)The adjusted relative odds for IBD of 35.3 were highly statistically significant, in spite of the small number of cases and wide confidence intervals. This is

likely to be an underestimate of true risk as it is likely that as the cohort ages, more members and their families will have developed IBD.

The small number of cohort members with IBD who had a family history made it impossible to investigate further the type of relationship with the proband that conferred greatest risk to the child. A recent study has suggested that female siblings (rather than parents or children) were more commonly affected with CD in probands with CD, and that those with multiple first degree relatives affected were more likely to have extensive CD affecting large and small bowel. However, the study was based on a single physicians follow-up which may have led to case ascertainment bias.(235) Future long-term studies may help elucidate this pattern further and may determine whether specific genetic mutations such as the NOD2 genotypes may be responsible.

It is interesting that both cohort members who had a family history had a significantly younger age at diagnosis than the remainder of the responding cohort. Firm conclusions cannot be drawn from this study due to small numbers, but similar findings have been reported elsewhere. (236) The concept of genetic anticipation, where patients with a family history of IBD (particularly CD) develop their disease at a younger age than their relatives, is controversial. Several studies suggest that this may at least in part be explained by ascertainment bias, time trends in incidence of IBD and reduced fertility in patients with early onset disease. (236-238)

Material and cultural circumstances in childhood as proxy measures of pattern of infectious exposure

Patterns of infectious or antigenic exposures in early childhood, that may be important in the pathogenesis of IBD, are difficult to define and quantify. Proxy measures using indicators of material and cultural circumstances that influence such exposures are often used. Early studies identified some important factors for CD, such as the availability of hot water in the home and higher social class (based on fathers occupation).(68) (73) This led to the theory that improved hygienic conditions in childhood may delay exposure to enteric infections in the child, such that later exposure to gut pathogens initiates an abnormal immune response resulting in disease. This

abnormal pattern of exposure to infections has also been suggested as a risk factor for appendicitis.

More recent studies, including this thesis, have failed to find any association between traditional measures of social class, or availability of hot water in the home and IBD. This may reflect the great improvement in home material circumstances over this century, such that crude measures like social class can no longer discriminate people within developed populations. In this thesis, several possible measures of childhood material and social circumstances have been examined. Social class, ethnicity and crowding have already been discussed, but other potential risk factors: hygiene facilities, smoking and passive smoking, appendicectomy and tonsillectomy, birth order, parity and nursery attendance will be discussed further.

Hot water and hygiene facilities

As all the cohort members with IBD and 98% of the whole cohort had access to both hot water and toilet facilities in the home, this is no longer a useful measure of childhood material circumstances in this country.

Birth order and maternal parity

Our findings at both age 5 and age 10 years showed that number of older siblings was associated with later risk of CD or UC. Having 2 or more older siblings was associated with a statistically significant increased risk of UC and appeared non-significantly but consistently protective against CD. No such effect was seen for younger siblings, or total number of siblings overall. Similarly, having older siblings was strongly associated with phenotype of IBD, even though the numbers of cases were small (and confidence intervals wide as a consequence).

These findings are unlikely to be due to confounding factors as adjustment for sex, crowding and social class did not affect these results. Social class was not associated with IBD in this cohort, in comparison to previous studies. (73) This is likely to reflect

improvements in social and material circumstances over the last century so that conditions in the home are now more homogeneous.

The consistency of the findings at age 5 and age 10 years suggests they are robust. In addition, when combined with the NCDS birth cohort study, to increase the power, the same associations are again found, with combined adjusted relative odds for UC of 12.20 (95% CI 2.63-58.68, p for trend 0.001) in those with 2 or more older siblings compared with CD. The adjusted OR in the combined cohorts in those with 2 or more than 2 older siblings compared with those with no older siblings were 2.47 (95%CI 1.01-6.06, p for trend 0.045) and 0.24 (0.07-0.79, p for trend 0.023) for UC and CD respectively. This finding also persisted after excluding those of non-British ethnic origin. (79)

Analysis of maternal parity, using identical grouping gave similar results. Maternal parity gives an indirect measure of number of older siblings, and was recorded at birth so that it is likely to be reliable. Some error due to stillbirths and children dying in childhood may have been introduced but this is unlikely to be differential.

These opposing risks for CD and UC are, like the association between smoking or appendicectomy and subsequent IBD, useful in helping understand the environmental factors that distinguish UC from CD, and the temporal change in incidence of IBD phenotype, with CD now predominating. (3)

It is thought that having older siblings is a marker for exposure to infections at an earlier age and greater dose than those who do not have older siblings. Older siblings will acquire infections from outside the household and bring them home. (80;159;244) If such exposures are protective against developing CD, the reduction in family size, with fewer older siblings may explain why CD rather than UC is becoming more prevalent in developed and developing countries. Such findings are consistent with reports that improved hygiene in childhood (68) and lower antigenic exposure (76) are risks for Crohn's disease.

Nursery attendance

Nursery attendance was considered as a possible indirect measure of exposure to infections outside the home. The age at first attending nursery was also examined to test

the hypothesis that atypical patterns of infectious exposure (at an older or younger age than unaffected cohort members) might be a risk for later IBD. If the hypothesis that CD was associated with delayed pattern of infectious exposure were valid, then an older age or no nursery attendance might be expected. Similarly for UC, earlier infectious exposure was hypothesised and a young age at nursery attendance might be expected. In fact nursery attendance did not prove to be a useful distinguishing factor as only 4% of the cohort and on cohort member with later CD, failed to attend nursery or playgroup by age 5 years. This is similar to findings in previous studies.(47)

Smoking and passive smoking

Active smoking is an established risk factor for Crohn's disease and is thought to be protective against UC. (87) Exposure to passive smoke in childhood and during pregnancy has not been previously been examined in a prospective study, and earlier work is contradictory and inconclusive. (See table 2 in introduction)

The contradiction in the literature may be because passive smoking in early childhood may also be a reflection of childhood material circumstances in the home. Children in smoking environments are prone to increased frequency of infections. If less antigenic stimulation and delayed exposure to childhood infections were important in the aetiology of CD, we might expect smoke exposure in childhood to be protective against CD (and possibly a risk for UC). (239)

We hypothesised that whilst smoking in adult life is known to be a risk factor for CD, passive smoking in early childhood may be more of a reflection of childhood material circumstances in the home. Smoking behaviour in parents is linked to traditional measures of social class (33;227) and predisposes exposed children to respiratory infections and recurrent otitis media. (240) (241) Paternal smoking has also been associated with Helicobacter pylori infection in pre-school children. (242) Helicobacter infection in childhood has also been proposed as a protective factor against IBD (Crohn's disease in particular). (243) Cigarette smoke has also been found to increase anaerobic bacteria and alter bacterial flora in the intestines. (92) If less antigenic stimulation and delayed exposure to childhood infections were important in the aetiology of CD, we

might expect smoke exposure in childhood to be protective against CD (and possibly a risk for UC).

Our study did not find any significant association between maternal smoking in pregnancy and later CD or UC. Active smoking recorded at age 5, 10 and 16 years also did not show any association with later IBD. This was probably due to the young age of the cohort and the small number of cohort members who consequently smoked.

Passive exposure to smoke was consistently associated with a reduction in relative odds for CD when measured by 5, 10 and 16 years, and was statistically significant using Fisher's exact test by age 16 years, even though the number of cases was small. This association was independent of ethnic origin, sex, father's social class or crowding.

Although the number of cohort members with complete data for all the variables was reduced in the multivariate model, those with data available were representative of the original birth cohort in terms of parental social class. The number of children exposed to passive smoking is probably underreported due to loss of non-responders, but this is likely to be non-differential regarding IBD status and would only dilute any significant effect found.

These findings support the hypothesis that passive smoking in childhood, at least up to age 16 years is protective against later Crohn's disease. The mechanism of this is speculative, but may reflect greater exposure to common pathogens (respiratory and possibly enteric) and antigens in the home and subsequent immune stimulation in childhood such that later antigenic challenges are met with appropriately. Further immunological studies are needed to confirm or refute this.

Appendicectomy and Tonsillectomy

In our study there was no statistically significant association between appendicectomy or tonsillectomy and IBD by age 26 years. The well-described protective effect of appendicectomy on ulcerative colitis was not observed in this cohort. (101) This is likely to be because there are as yet insufficient cohort members with ulcerative colitis. In addition, the prevalence of appendicectomy in the whole cohort (5.8%) is likely to increase further. Recent epidemiological studies suggest a lifetime risk of

appendicectomy of 7-9%, with the peak incidence in those ages 13 to 40 years. (101)Appendicectomy by age 26 was associated with a significant 5-fold increase in risk of diabetes, after adjusting for confounding factors, sex, social class, crowding and smoke exposure by age 16 years.

Passive smoking was significantly associated with appendicectomy by age 26, maternal smoking in pregnancy, at age 5 and 10 years and by age 16 years also being a significant risk for appendicectomy by age 26 years. Active smoking has been reported in several studies to be a risk for appendicectomy. The association between passive smoking and appendicectomy has been recently reported in this cohort, and persists even after excluding current smokers at age 26 years. Cohort members who were not exposed to passive smoking in childhood were also found to be at increased risk of appendicectomy after age 10 years, if they started smoking. This suggests that smoke itself may be a risk for appendicitis rather than smoke solely acting as an indicator of social circumstances. Montgomery suggests that appendicectomy may be protective against the development of ulcerative colitis by disabling the immune response associated with UC, and that smoking can act in a similar fashion, additionally leaving the appendix more susceptible to acute appendicitis. (91) Further analysis of the cohort when more have developed ulcerative colitis may help elucidate this association further.

Perinatal events

Birthweight, weight for gestational age and subsequent growth

There was no significant difference between the mean birthweight or weight for gestational age in cohort members who later developed CD or UC compared with the whole cohort. Height, weight and head circumference again did not differ from the remaining unaffected cohort when measured at different ages between birth and age 16 years. By age 16 years' cohort members who later developed IBD tended to be non-significantly shorter and weigh less than the cohort as a whole. This included five cohort members who had already been diagnosed with IBD sine age 10 years, which would have biased these results. Many cultural and material factors could confound these findings, but due to the small number of cases for analysis and the lack of statistical significance at univariate analysis, these were not further evaluated.

Perinatal events-breastfeeding

Some previous studies have suggested that breastfeeding may be protective against the development of IBD, in particular CD, although most have not found a significant association with either disease. (See table in introduction) These were mainly case-control studies of varying sizes and in countries that may have differing practices from those in Great Britain in the 1970's.

Our study is the only published prospective cohort study of breastfeeding and inflammatory bowel disease. It concurs with the majority of previous work in finding no statistically significant association between breastfeeding and later CD or UC. However, examining the relative odds reported it is noticeable that there is a consistent increase in relative odds for CD in those reporting breast-feeding in each of the measures, compared with those who did not breast feed. This increase in relative odds also increased with duration of breast-feeding, although the test for trend was non-significant. In contrast, the patterns of relative odds were reduced for UC in those who were breastfed, again in all of the measures. Adjusting for potential confounding factors did not alter this finding,

except for the association between UC and colostrum on the first day, which increased toward the null on adjustment.

Such observations may be due to chance alone, but the consistency of the findings across several measures of breastfeeding warrant further investigation when the cohort are older, and more cases with IBD are available for analysis.

The possibility that risk factors associated with breastfeeding or protective factors associated with bottle-feeding and later development of CD should be considered. It is possible that bottle-feeding may expose the infant's immature immune system to greater antigenic stimulation and enteric infection, especially once passive immunity from the mother has disappeared, or that breast-feeding may delay such exposure. At present this remains hypothetical, and is contradictory to previous work.(123;124)

Where the neonate spent the first night after birth

Where the infant spent the first night after birth was used as an indirect marker of atypical exposure to low-dose infections in the first 24 hours of life. This was used to test the hypothesis that atypical exposure patterns whilst the immune system is immature may be a risk for developing subsequent IBD.

A non-significant increased risk of inflammatory bowel disease was found in cohort members who spent their first night in the communal nursery, which was unaffected by adjustment for potential confounding factors. Although the number of cases with IBD is relatively small, excluding those with missing data did not greatly affect the results, as univariate analysis with maximum numbers was similar to those in the multivariate model. The cohort responding at age 26 was largely representative of the original birth cohort, as previously described. Adjustment for multiple personal characteristics reduces the risk of systematic bias.

Spending the night in the communal ward nursery, being cared for by nursing staff was compared with those who were not separated from their mother during this period. A third group which was less easy to classify (those born outside hospital or who required special care in a neonatal or surgical unit) were also considered.

Whilst spending the night in the nursery may indicate that the infant or mother were unwell, it is likely that these babies would have been separated both night and day (as in the third group). Individual inspection of the birth records of the cohort members with IBD did not find any evidence of illness in mother or baby in the perinatal period. Separation from the mother at night was common practice in 1970. Since then it has become less popular, with healthy babies being discharged earlier. These factors, coupled with improving material circumstances in the home suggest that newborn babies may be increasingly exposed to low-dose non-familial organisms rather than acute severe infections.

Although the measure is indirect, we believe the variable used identified babies who were in the nursery at night were likely to be exposed to non-familial micro organisms at low dose and for short duration. As this is a very crude measure, any association seen is likely to be conservative due to individual variation in exposure patterns.

Unidentified confounding factors may explain some of the association found between spending the first night in the nursery and subsequent IBD. Such a factor would have to be associated both with spending the first night in the nursery and inflammatory bowel disease. This may be either exposure acting in the neonatal period or a later factor also associated with nocturnal separation. Although efforts to identify potential confounding factors were made, it is impossible to be certain of all the reasons why some babies spent the night in the nursery-many of these are individual factors of preference.

None of the potential confounding factors we identified were significantly associated with later IBD and were not therefore true confounders. There was no significant association between breastfeeding practices either on the first day or as measured by duration of breastfeeding and subsequent IBD. This may indicate that if an infectious exposure is responsible for the association, it is more likely to be airborne. Such infections are likely to be increased in the warm environment of a nursery and by handling by multiple nursing staff. None of the subjects with IBD however developed overt illness in the neonatal period. Of note, however, although not statistically significant overall, lower crowding ratio was associated with increased relative odds of later IBD, as was having one previous pregnancy (but not two). This could reflect

exposures to lower doses of antigen in infancy, that have been suggested to lead to later immune-mediated diseases such as IBD. (245) (246) One explanation for this is that short duration low dose infectious exposures that occur when the infant immune system is immature fail to generate an appropriate immune response, leading to sensitisation. In contrast, children exposed to familial infections or normal gut commensals have infectious exposure to a higher dose and longer duration, with an appropriate immune conditioning resulting. (246) Crowded conditions are associated with a higher dose of antigen exposure (80;159;244)and this may explain why in some studies of family structure have found a protective effect of higher birth order against IBD. (76)

Although there was no statistically significant association between spending the first night in the nursery and later IBD, the increased relative odds, and the consistency in the findings for both CD and UC suggest future studies with larger number of cases be warranted. The crude exposure measure is likely to underestimate any true association measured. The findings are consistent with the hypothesis that pattern of infectious exposure in the first day of life may influence later development of IBD.

A similar finding of a significant increased risk of hay fever in the same cohort in subjects spending the first night in the nursery has been published (246)The adjusted relative odds for hay fever in those separated at night was 1.31 (95% CI 1.08-1.59, p=0.005). Atopic disease (eczema) has previously been identified as a risk factor for later IBD in this cohort (77;78)

Specific Infections in Childhood including measles

Our data did not find any association between a report of measles, mumps, chickenpox or whooping cough by the parent when the child was 10 years and later IBD. This contrasts with one study (171)

None of the cohort members had developed IBD by age 10 and the prospective nature of the data collection makes systematic bias unlikely.

We also examined the reported age of experiencing measles, mumps, chickenpox and whooping cough. The mean age at experiencing measles was non-significantly older for those with later CD than those of the remaining cohort, and non-significantly younger than the remaining cohort for those who later developed UC. A history of measles infection before 1 year was found to be a significant risk factor for UC when maximum numbers of cases for analysis were used but after adjustment for potential confounding factors, this was no longer statistically significant

It is difficult to interpret these findings as they are based on small numbers of cases. However, atypical age of measles infection (<2 years) is known to be a risk factor for persistent measles infection in the brain and SSPE. (80;159;244)If measles infection is associated with later IBD it is likely that an atypical pattern of exposure, such as at an unusual age or in conjunction with other infections is required, as suggested by Montgomery. (48) Such subtle changes in infectious exposures may be impossible to detect in epidemiological studies.

Childhood vaccination including measles vaccination

We have used prospectively collected data from a national population-based birth cohort in order to examine the risk of IBD in relation to prior monovalent measles vaccination by age 5 years. This is one of the largest cohorts in which the hypothesis of the association between measles vaccination and IBD has been examined and the study design had the advantage of reducing many of the biases associated with previous studies. The extremely high prevalence of IBD reported from this study (49.2/10,000, 95% CI 5.3 to 63) (33) suggests that case ascertainment was complete.

Response error, and therefore potential sources of bias, was reduced by using vaccination data collected recently after the childhood vaccination and at least 7 years before the onset of IBD in any of the cohort members.

Although some recall error of vaccination status is evident for all vaccine types, we have shown the responses to the survey at 5 and 10 years for completeness. Recall error did not differ between those with IBD and the remaining cohort, and it is unlikely to have introduced any systematic bias.

We were not able to confirm the vaccination histories from a secondary source, although an average of 3 years (maximum of 5 years) recall for vaccination history is better than other studies.(178) Any misclassification of vaccination status would have been random as the measles vaccination hypothesis had not been proposed at the time of collecting this data and none of the cohort members had developed symptoms of IBD by 10 years.

Social factors were important in determining both response to our surresponses6 years and vaccination status. Those responding (77%) were more likely to have parents with a higher social class and educational level than non-responders. Those responding at age 26 years were also more likely to have been vaccinated than in the original birth cohort. But there was no evidence of systematic bias, and adjustment for the potential confounding factors did not significantly alter the findings.

We chose to look at measles vaccination and measles vaccination age as potential risk factors for IBD. As atypical pattern of infections in childhood, including age, are suggested by Wakefield to be important in the development of CD, age at vaccination may also be important in CD. The age at vaccination against other infectious diseases have been implicated in the aetiology of other chronic diseases. Older age of vaccination with *Haemophilus influenzae* type b vaccine has been associated with type 1 diabetes in children. (183)

The data from age 5 years were likely to be of highest quality as it involved the shortest recall time. However, using the year 5 data did exclude those vaccinated after 5 years of age, which would have consequently underestimated any potential risk of IBD associated with vaccination at a later age.

We did not find any significant excess risk of inflammatory bowel disease following a history of monovalent measles vaccination, or any other vaccine, alone by age 5 or 10 years. Excluding those with a known family history of IBD and those with concurrent mumps and measles infection did not affect these findings either.

Increasing age at measles vaccination was significantly associated with an increased risk of subsequent Crohn's disease. It is difficult to interpret these findings, as the number of patients vaccinated after age 2 years in our study is small. The findings are in keeping with the a priori hypothesis that abnormal patterns of exposure to measles (here, exposure to measles vaccination at an older age: after age 2) are important in the aetiology of Crohn's disease. The relationship between older age of vaccination and Crohn's disease was also independent of the association between concurrent wild-type measles and mumps in the same year of life (another atypical measles exposure) and Crohn's disease reported in an earlier paper from this cohort. The findings are also are in keeping with data reported by Davis et al (180) who found increasing relative odds for CD (although not statistically significant) in those vaccinated with a measles containing vaccine at 12-18 and after 18 months of age respectively, compared with those unvaccinated. Further studies with greater statistical power are required to see if these results are robust.

We also examined the age at first exposure to measles either in the vaccine form or wild type, as this was considered to be another measure of possible atypical exposure to measles virus. No association between age of first exposure to measles and subsequent IBD was found.

The combination of experiencing wild measles infection and measles vaccination by age 10 years was also not found to be a risk for later IBD, compared with experiencing neither measles exposure. This pattern of exposure to measles was only reported in 3 cohort members with IBD. It is also likely that subclinical exposure to measles may have occurred, making interpretation confusing.

The concept of atypical exposure to measles as a risk factor for delayed disease has been previously described in subacute sclerosing pan-encephalitis. Here, atypical age of exposure and concurrent infections, as well as other atypical exposure patterns are known to be risks for this disease. (163;164;247)

There were very few reported adverse reactions following any of the childhood vaccines. As parents reported these at age 10 years, there is likely to be some recall bias, although this is probably non-differential. Although measles vaccination was associated with a four-fold increases risk for CD, this was based on only two cases and is therefore unreliable. Adverse reactions to live attenuated measles vaccine are uncommon, although immediate type hypersensitivity reactions are reported even in the absence of known egg allergy or atopy. (248) More severe reactions were reported when live attenuated virus was given following the previous administration of inactivated virus vaccine, with an atypical measles illness. (249-252)

To conclude, in this study, live attenuated monovalent measles vaccine alone was not associated with an increased risk of inflammatory bowel disease by age 26 years. We did not investigate any relationship with the combined measles, mumps and rubella (MMR) vaccine as the timescale of the study was before this vaccine had been introduced in England. It was also before the introduction of monovalent mumps vaccine.

Just as an atypical pattern of wild measles infection has been suggested to be a risk for IBD, (2) some characteristics of measles vaccination may also prove to be important. The possible association of inflammatory bowel disease with increasing age at vaccination suggested by this study require further examination. Additional modifying factors, including interaction with other infectious agents, may also determine the risk of IBD following measles vaccination. (173) By repeating this research when more cohort members have developed disease, the study power will be improved and may reveal differences between the groups that are not detected in the current study at only 26-years of age. Assuming a confidence level of 90% and a power of 90%, a sample size of 12,377 would be required to detect a 2.5 fold increase in risk ratio for IBD in those receiving measles vaccine if the disease prevalence was 0.3% in the unexposed.

Whilst the benefits of measles vaccination worldwide are undisputed, further specifically designed prospective studies are still required in order to exclude any unexpected long-term sequelae.

Contraceptive pill use

This study did not show any association between contraceptive pill use and IBD. As the data were taken at age 16 years, and only 2702 female cohort members had data available for analysis, this is unlikely to be representative or sufficiently large sample to show any true difference between users and non-users. Further analysis of data extracted from the second survey at age 26 years may be more valuable. The potential confounding role of smoking at this age will also need to be considered.

Hand, foot and eye preference

The results from this study support the original findings of Geschwind and Searleman by demonstrating a statistically significant two-fold increased risk of inflammatory bowel disease in left-handed subjects. The increased relative odds for foot preference observed for UC also endorses these data. (143;145)

The study has the advantage of using data from two population-based national cohort studies, thus avoiding many of the potential biases found in case-control studies. Case-ascertainment in these studies was likely to be complete as they both reported a very high prevalence of IBD. (11;33)In both the cohorts, those responding to the disease surveys at 26 (BCS70) and 33 (NCDS) years were largely representative of the original birth cohorts with some additional loss to follow-up of those whose fathers were Registrar General's social class V at the time of their birth. (225;226)However, social class was not associated with handedness or inflammatory bowel disease in either cohort and therefore is unlikely to be a confounding factor.

Male subjects were significantly more likely to be left-handed than females; a finding that has been previously reported. However sex was not associated with risk of CD, UC or IBD combined in either cohort in this study, and was therefore unlikely to be a confounding factor, as it has been in other studies.(253) Adjusting for sex or cohort did not significantly alter the relationships found between left-handedness and IBD. Cohort members from the BCS70 (born 1970) were more likely to have IBD than those in the NCDS (born 1958) and this follows recent temporal trends in IBD prevalence. (33)

Eleven percent of subjects without IBD reported using their left hand preferentially for writing. This was similar in both cohorts, and is similar to that reported in the control groups of earlier case-control studies. (145;146)We did not assess the degree of handedness, but as we excluded those who responded 'either' or 'mixed right and left' to handedness questions, subjects included in the study will be those with most extreme lateralisation of hand preference. Some misclassification of hand and foot preference will have occurred, but this is not likely to have resulted in systematic bias, as lateralisation was determined at least 2 years (and usually more than 10 years) before onset of symptoms of inflammatory bowel disease was made in any of the subjects.

Left foot preference was increased in those with UC (OR 2.59), although this was not statistically significant, and was based on a small number of cases from one cohort only. However, foot preference is thought to have a less consistent association with cerebral lateralisation than left-handedness. (254) Eye preference also did not show any association with IBD in this study

The association between left-handedness and inflammatory bowel disease is important, as it suggests that the two may share common aetiological influences or may indicate a marker of susceptibility. These could reflect shared genetic traits; environmental factors acting in early life, or a combination of these.

One controversial hypothesis suggests that the influences of testosterone (excess production or increased sensitivity to it) in utero may alter growth of the left cerebral hemisphere and the thymus simultaneously, resulting in an association between left-handedness and certain T-cell dependent immune disorders.(254) Some small immunological studies have supported this theory, by finding different T-cell subsets (255), cytokines (256)and autoantibodies between left and right handers.(257) However, the aetiological processes involved in inflammatory bowel disease, and other immune mediated diseases reported in association with left-handedness, are poorly understood, and the model has received much criticism. (147)

Seasonal differences in the birth of left-handed girls (but not boys) have been reported, (258)suggesting that environmental factors (possibly infectious agents) may be important. Seasonal differences in birth of subjects with inflammatory bowel disease are also described. (51;259) Excess female subjects with IBD, especially Crohn's disease,

have also been reported in some studies. (6) Genetic explanations of the association between left-handedness and autoimmune diseases have been suggested. Different HLA-haplotypes have been described between left- and right-handers that may also be found in some diseases, including ulcerative colitis, (260) although these are inconsistent. (261)

In summary, this study has found an increased risk of inflammatory bowel disease, in particular ulcerative colitis, in left-handed subjects from two national birth cohorts. Such an association may help elucidate the aetiological processes leading to inflammatory bowel disease, although at present the mechanisms remain uncertain.

Conclusions

This study has investigated the association childhood environmental factors and later inflammatory bowel disease using a large, unique, population-based longitudinal cohort study. The study design has the advantage of good quality, prospectively collected data that is largely unbiased compared with previous case-control studies. The major shortcomings of the study were in the small number of cohort members who had developed inflammatory bowel disease by age 26 years, and subsequent loss of statistical power, especially in subgroup analyses. Interpretation of findings in epidemiological studies where there is a long time interval between possible initiating events and the onset of clinical symptoms or diagnosis require caution, especially when causality is being considered. Unidentified confounding must always be considered as an alternative explanation.

The study found an extremely high prevalence of both adult and paediatric inflammatory bowel disease. This is likely to reflect true population prevalence and is in keeping with temporal trends. Crohn's disease in now more common than ulcerative colitis in British 26 year olds, and inflammatory bowel disease overall is indeed more prevalent than insulin dependant diabetes mellitus.

Some risk factors for inflammatory bowel disease proposed from previous studies were not found to be significant in this cohort. Sex, parental social class at birth, perinatal infections, breastfeeding, contraceptive pill use and person per room ratio and infections in childhood were not found to be significantly associated with inflammatory bowel disease.

Asian ethnic origin and a family history of inflammatory bowel disease were found to be the main independent risk factors for both ulcerative colitis and Crohn's disease. Left-handedness was also significantly associated with increased risk of inflammatory bowel disease. Childhood eczema was significantly associated with Crohn's disease and inflammatory bowel disease overall.

The study provided some support for the hypothesis that atypical pattern of infection (such as early or delayed exposures) in childhood and improved hygiene may predispose susceptible individuals to later IBD. Exposure to passive smoke by age 16 was associated with reduced relative odds for later Crohn's disease, suggesting a protective

effect. A larger number of older siblings and increased maternal parity was also associated with increased risk of ulcerative colitis and reduced risk of Crohn's disease. The findings of an increased relative odds for inflammatory bowel disease in those infants spending their first night in the communal nursery also suggests that atypical patterns of infectious exposures in childhood may be important but require further evaluation.

The contrasting findings between ulcerative colitis and Crohn's disease, particularly with reference to sex, birth order, maternal parity and breastfeeding in this study and smoking and appendicectomy from previous studies, may provide useful clues into the aetiology and phenotypic expression of these disorders. The temporal trends showing a recent increase in Crohn's disease over ulcerative colitis are in keeping with the hypothesis that atypical pattern of infectious exposures are a risk for IBD. The reduction in family size, with fewer older siblings and possible delayed exposure to infectious agents may explain why CD rather than UC is becoming more prevalent in developed and developing countries. Further prospective studies to investigate these potential environmental risk factors and the interaction with genetic susceptibility are required, both in adults and children with IBD.

This study did not support the hypothesis that general perinatal or childhood infections, measles infection or monovalent measles vaccination in childhood is a risk factor for inflammatory bowel disease. The association between older age at exposure to either wild measles infection or monovalent measles vaccine and Crohn's disease is based on too few cases to be reliable. The concept of an atypical age or pattern of exposure to measles (such as that described by Montgomery (48) and Wakefield(2))deserves further consideration. By repeating this research when more cohort members have developed disease, the study power will be improved and may reveal differences between the groups that are not detected in the current study at only 26-years of age.

Environmental factors are undoubtedly important in the pathogenesis of inflammatory bowel disease. It is most likely that a combination of factors, such as changing pattern of exposure to infections, increased sanitation and changes in our

society will have influenced the development of our immune system to account for the increased incidence of inflammatory bowel disease and other autoimmune disorders.

Appendix 1 Annual incidence of inflammatory bowel disease in Europe

Country	Author reference	Study Period	Incidence CD /10^6	Incidence UC /10^6	No cases	Design
Belgium						
Liege	(262)	1993-96	4.5	3.6	137CD 111 UC	P
Brussels	(263)	1992-93	4.1 Belgians 6.4 Moroccans	3.7 1.2		P
Czechoslovakia						
Hana	(264)	1994-99	1.5	3.5		P
Nationwide	(265)	1972-79	1.6-2			
Denmark						
Copenhagen	(266)	1961-67	7.3			
Copenhagen	(267)	1991-93	6.6	10.0	61 CD 92 UC	P AS
Copenhagen	(44;268)	1970-78	2.7		909 total	Pop
County		1962-78	0.62	8.1	1161 UC	based
		1979-87	4.1		373 CD	
Nationwide	(269)	1981-92	4.6	13.2	2806 CD 8125 UC	
Faroe islands	(270)	1964-83	1.7	7.5		R
	(271)	1981-88	3.6	20.3	13 CD 66 UC	P
Finland						
Turku	(272)	1950-70	0.3			
Helsinki	(272)	1975-85	1.0-3.0		193 CD	R
France						
Northern	(273)	1988	4.23	2.96	166 CD 116 UC	P
	(274)	1988-90	4.9	3.2	674 CD 466 UC	AS, P
Brittany	(275)	1994-95	2.8	2.9	205 CD 165 UC	P
Brittany	(276)	1994-97	3	2.6	434 CD 314 UC	P

Puy -de-Dome	(277)	1993-94	5.7	1.9	79 CD 29 UC	AS, P
Amiens	(23)	1991-93	8.1	5.6	71 CD 49 UC	AS, P
Germany						
Cologne	(278)	1985-86	5.1		47 CD	P
Essen	(23)	1991-93	3.5	4.3	49 CD 60 UC	P, AS
	(279)	1980-84	4.19		156 CD	R, AS
		1991-95	5.2		132 CD	P, AS
Tubingen	(280)	1970-84	1.2-4	0.5-1.5	828 CD 375 UC	R & P
Greece						
Northwest	(85)	1982-91	0.3 (0.1-0.8)	4.0 (3-5)	5 CD 61 UC	R
Northwest	(272)	1991-93	1.0	8.5	4 CD 35 UC	P, AS
Athens	(281)	1977-83			205 UC	R
Crete	(272)	1991-93	3.9	16.6	14 CD 60 UC	P, AS
Crete	(281)	1990-94	3	8.9 (7.2-10.4)	117 UC	P
Iceland						
Nationwide	(282)	1950-79	0.4-0.9	2.8-7.4	33 CD 318 UC	R
		1980-89	3.1 (2.5-4)	11.7 (10.5-13.2)	75 CD 282 UC	R
Reykjavik	(272)	1991-93	8.2	24.3	32 CD 95 UC	P, AS
Israel						
Jerusalem	(283)	1973-78		6.3		
Kinneret	(284)	1960-90	1.96			R
		1965-94		3.5		R
Tel-aviv	(285)	1970-76	1.28			
Beer-sheva	(286)	1976-80	1.8 Jews			
Beer-sheva	(272)	1991-93	4.3	8.5	20 CD 40 UC	P, AS
Beer-sheva	(287)	1970-78	1.0 (0.6-1.6)	3.2 (2.3-4.2)	66 CD Jews	R & P
		1979-87	2.1 (1.5-4.2)	5.4 (4.5-6.4)	207 UC	AS

		1981-85		5.8		
		1987-92	4.2			R
Galilee	(288)	1967-86		O.88-3.79		R
				6.9 Jews	53 UC	
				0.96 Arabs		
Southern	(289)	1987-97	5.0 Kibbutz		81 CD	R
Central	(290)	1979	3.1			
Italy						
Lombardia	(291)		3.4 (1.6-6.3)	7 (4.3-10.7)	40 CD	P
					82 UC	
Bologna	(292)	1972-93	0.8			
Florence	(293;294)	1978-87	1.5	4.0	96 CD	R
					263 UC	
		1990-92	3.4	9.6		
Florence	(272)	1991-93	2.7	8.1	29 CD	P, AS
					87 UC	
Milan	(272)	19919-3	3.2	10	11CD	P, AS
					34 UC	
Crema	(272)	1991-93	2.7	7.5	14 CD	P, AS
					39 UC	
Reggio Emilia	(272)	1991-93	4.0	7.5	30 CD	P, AS
					56 UC	
Sicily	(295)	1987-89	2.7		103 CD	P, AS
	(272)	1991-93	5.8	8.5	13 CD	P, AS
					19 UC	
Palermo	(296)	1987-88	2.7		51 CD	P
Nationwide	(292)	1989-92	2.8	6.8	222 CD	P, AS
					509 UC	
Netherlands						
South Limberg	(297)	1991-95	6.9 (5.9-7.9)	10 (8.7-11.2)		P, AS
Leiden	(272)	1979-83	3.9	6.8		R
Maastricht	(272)	1991-93	7.7	13.1	82 CD	P, AS
					140 UC	
Norway						
Nationwide	(298)	1956-63	2.6			
	(8)	1964-69	1			
North	(299)	1983-85	5.8			P

		1983-86		12.8		
West	(300)	1984-85	5.3	14.8	86 CD 239 UC	
Southeast	(301)	1990-93	5.8	13.6	225 CD 525 UC	P
Oslo	(272)	1991-93	6.9	15.6	112 CD 251 UC	P, AS
Portugal						
North	(272)	1991-93	3.7	5.5	15 CD 22 UC	
South	(272)	1991-93	2.3	1.7	11 CD 8 UC	
Oporto	(302)	1975-88			195 CD 180 UC	P
Spain						
Galicia	(303)	1966-75	0.14		39 CD	R
	(303)	1976-82	0.8		152 CD	R
Granada	(304)	1979-88	0.9	2	79 CD 167 UC	R
Central	(304)	1981-88	1.61	3.16	57 CD 111 UC	R
Northeast	(272)	1991-93	4.9	9	28 CD 52 UC	P, AS
Northwest	(272)	1991-93	4.8	7	40 CD 58 UC	P, AS
Castellon	(305)	1992-96	1.9	6.8	133 Total	R
Aragon	(306)	1992-95	3.9 (3.1-4.7)	7.2 (6.1-8.3)	104 CD 204 UC	R
Sagunto	(307)	1990-98	3.56	6.42	72 UC 39 CD	P, AS
Nationwide	(308)	1991-93	5.5 (4.1-6.9)	8 (6.3-9.7)	135 CD 191 UC	P, AS
Sweden						
Central	(309)	1956-59	1.4			
	(310)	1968-73	2.6-5			
	(310)	1965-73	4-5.1			
Gothenberg	(311)	1951-70	1.2-6.3			
Stockholm	(37)	1955-79	1.5-4.1			

	(312)	1955-79		1.7-4.3	1274 UC	R
	(37)	1955-89	1.4-4.9		1936	R, AS
Northern	(313)	1974-81	4.9		199 CD	R
Malmo	(116)	1958-73	3.5-6		191 CD	P
	(314)	1958-82		4.2-9.4	354 UC	R
Orebro	(52;314)	1963-87	4.3-6.6	3.3-14.9		R
Orebro	(26)	1983-87	6.7			
Uppsala	(29)	1965-83	5-7	7-12	1469 CD 2509 UC	R, AS
Nationwide	(26)	1963-87	4.3 –6.7		246 CD	R, AS
Switzerland						
Basle	(315)	1960-68	1.1-2.6			
Yugoslavia						
Zagreb	(316)	1980-89	0.7	1.5	77 CD 173 UC	P

R=retrospective p=prospective AS=Age Standardised Hosp=hospital based
pop=population based GP=general practice

Appendix 2 Worldwide incidence of inflammatory bowel disease

Country	Ref	Study Period	Incidence CD/10^6	Incidence UC/10^6	No Cases	Design
South Africa						
Durban	(317)	1987	0.7			
	(318)	1983-87		2.7 Indians		
Capetown	(319)	1980-84	2.6 whites	7.5 whites	134 CD	R
			1.8 coloureds	1.9 coloureds	197 UC	
			0.3 blacks	0.6 blacks		
North America						
Baltimore	(16)	1960-63	1.2	3		
		1973	2.2	3.8		
		1977-79	3.1	2.2		AS
Olmstead	(320)	1935-54	1.9			AS
County						
		1955-64	4			
		1965-75	6.6			
		1935-75				
	(321)	1943-82	4		103 CD	AS
	(38;322)	1940-93	5.8	8.3 (6.5-10.1)	225 CD	AS,R
					278 UC	
	(38)	1970-93	7 (5.9-8.1)	7.3 (6.1-8.4)	163 CD	AS
					158 UC	
Rochester	(323)	1935-64	6.6	2-4		
	(14)	1930-39	0	.06	864 CD	Hosp
		1940-49	0.12	0.07	574 UC	
		1950-59	0.39	0.34		
		1960-69	0.92	0.8		
		1970-79	2.81	1.74		
		1980-89	5.0	3.5		
		1930-89	3.9	2.3		
	(324)	1960-79		15	138 UC	AS
15 regions	(13)	1973	2.4	3.5		Hosp R
Washington	(325)	1981-85	8.8			
Argentina	(24)	1987-93	2.2	2.17	1 CD	R

					38 UC	
Australia	(326)	1967-91	2.1		130 CD	
Canada						
Ontario	(327)	1969-71	0.7			
Manitoba	(328)	1989-94	14.6	14.3	997 CD 977 UC	R, AS
Fiji	(329)	1985-6	0.14	1.7 Indians 0.15 Melanesians		R
Iran	(330)	1989-99			122 CD	P
Japan						
	(331)	1979	0.08			
Nationwide	(332)	1991	0.51		4243 CD 12559 UC	R
Korea	(27)	1986-97		0.68 (0.54-0.82)	94 UC	R, AS
Kuwait	(333)	1976-82			91 UC 17 CD	P
New Zealand	(334)	1954-58		5-6 Maoris		
Oman	(335)	1987-94		1.35	108 UC	P
Panama	(24)	1987-93	0	1.2	0 CD 15 UC	R

ppendix 3 The Incidence of Crohn's Disease in the United Kingdom

Country	Author	Study Period	Incidence CD /10^6	Prevalence CD /10^6	No cases	Design
Vales						
lid	(336)	1961-70	1.97		23	R
lamorgan		1971-80	4.34	55.5	56	
ardiff	(337)	1934-77	0.18 to 4.8	56	232	R
	(338)	1981-85	8.3 (7-10.1)		117	R
	(36;339)	1986-90	5.9 (4.7-7.3)		329	R
ationwide	(339)	1967-76		40	1098	
cotland						
ortheast	(10;30;340)	1955-57	1.3		17	P
		1958-60	2		27	
		1961-63	2.9		39	
		1964-66	4.2		56	
		1967-69	4.9		66	
		1970-72	6.4		85	
		1973-75	5.4		82	
		1976-78	6.2		94	
		1979-81	7.3		110	
		1982-84	7.6		115	
		1985-87	9.8	147	148	
lydesdale	(341)	1961-70	1.5		357	R
outheast	(18)	1975-79	4.5			
ationwide	(18)	1981-83	1.91			AS
aediatric)			(1.64-2.59)			R
		1990-92	2.91 (2.4-3.62)			
othian	(18)	1981-85	2.57		61	AS
aediatric)		1986-90	2.42			R
		1991-95	3.52			

orthern Ireland						
orthern Ireland	(342)	1966-73	1.3		159	R
	(343)	1973-81	2.34			
elfast	(343)	1966-73	3.5			R
ounty own	(343)	1966-73	0.3			R
ire						
ublin	(267)	1991-93	5.2 (3.2-7.2)		46	AS P

ngland						
ondon	Wright			13		
ower Hamlets	(229)	1972-79	3.8 Europeans		99	AS
			1.2 Bangladeshis			R
			4.6 W. Indians			
		1980-89	4.1 Europeans			
			2.3 Bangladeshis			
			5.4 W. Indians			
orth Tees	(344)	1971-77	5.3	35	73	R
	(32)	1995	7.36	156	212	R
loucester	(345)	1966-70	1.5			
lackpool	(35)	1971-75	3.3		185 total	R
		1976-80	6.1	47		
		1981-83	6.5			
ottingham	(346)	1958-73	3.6	26.5	144	R
xford	(31)	1951-60	0.8	9	34	R
erby	(34)	1951-55	0.7		225	R
		1981-85	6.67	85		AS

eicestershire	(230)	1981-89	3.4-4.7 Europeans 2.4 Hindus 3.4 Sikhs 5.4 Muslims		582 28 Asians	R AS
eicester on-immigrants	(23)	1991-93	3.8 (0.7-6.9)		10	AS
eicester mmigrants	(23)	1991-93	5.6 (0-12.5)		5	AS
Volverhampton	(347)	1978-85	3.78 (1.22-6.34)		74	AS
alisbury	(347)	1978-85	5.5 (1.17-9.83)		45	AS
windon	(347)	1978-85	7.07 (2.56-11.58)		77	AS
ottingham	(348)	1999		84	6	GP
ationwide 6 yr olds)	(33)	1996		298 (190-406)	30	R
ationwide (GP)	(349)	1991-92	10.1-11.1	54.6-59.8	291	R GP
ationwide 3 yr olds)	(11)	1991		254 (UC & CD)		R

ppendix 4 Incidence and prevalence of ulcerative colitis in the United Kingdom

ountry	Author	Study Period	Incidence UC /10^6	Prevalence UC /10^6	No cases	Design
Vales						
ardiff	Srivastava	1968-77	6.4		357	AS
		1978-87				R
			6.3			
Glamorgan	(350)	1968-77	7.2		277	R
ngland						
eicester	(120)	1972-89	5.3 (4.3-6.3)		573	AS
	(excludes		Europeans		Europeans	R
	proctitis)		10.8 (7.4-14.1)		115	
			Hindus		S. Asians	
			16.5 (7.9-25.2)			
			Sikhs			
			6.2 (1.6-10.9)			
			Muslims			
	(119)	1991-94	7.0 (5-9.5)		41	P
			Europeans			
			17.2		33	
			(11.8-24.3)			
			S Asians			
eicester	(23)	1991-93	10 (4.7-15.3)		24	AS
			Non-immigrants			P
			15.3 (4.6-26)		15	
			Immigrants			
olverhampton	(347)	1978-86	11.59		222	AS
			(7.1-16.0)			P
alisbury	(347)	1978-86	8.70		71	AS
			(3.1-13.3)			P
windon	(347)	1978-86	6.0		65	AS
			(1.9-10.1)			P
xford	(31)	1951-60	5.2	79.9	180	R
orth Tees	(344)	1971-77	15.1	99	212	R
	(32)	1995	22.1	268	364	R
ottingham	(348)	1999		157	11	GP

ationwide	(33)	1995-96		194 (105-281)	22 at 26 years	pop
cotland						
ortheast	(351)	1967-76	11.3		537	R
outheast	(352)	1975-79	6.5			
ire						
ublin	(23)	1991-93	15.2 (11.5-18.9)		120	AS P

Appendix 5 Study Questionnaires

Serial Number: xxxxxxxx

THE 1970 BRITISH COHORT STUDY
1995/96 SURVEY

CONFIDENTIAL

Please help us to find the causes of some illnesses that affect many people in Great Britain, by filling in this questionnaire.

We would like you to complete and return the questionnaire, *even if you haven't had any of the illnesses listed below.*

Please answer all of the questions.

1 Just to check our records are accurate: what is your full date of birth? _____

2 Have you **ever** had, or were you ever told by a doctor that you had, any of these illness?

Please tick one box for each illness

Crohn's disease	Yes ☐	No ☐
Ulcerative colitis	Yes ☐	No ☐
Appendicitis - that required surgical removal of your appendix	Yes ☐	No ☐
Diabetes requiring insulin injections	Yes ☐	No ☐

3 Has a doctor ever said that you had pneumonia? Yes ☐ No ☐

If yes, did you spend one or more nights in hospital because of this pneumonia? Yes ☐ No ☐

Please return this questionnaire to City University in the enclosed FREEPOST envelope - you do not need a stamp. If you have any questions, please contact Scott Montgomery at City University - telephone 0171 477 8492.

The information that you supply will be treated in confidence.

Appendix 5 Study Questionnaires (cont)

BCS70 serial number:

The 1970 British Cohort Study

Crohn's Disease and Ulcerative Colitis Research Project

PRIVATE AND CONFIDENTIAL

Please fill in this questionnaire to help us find the causes of Crohn's disease and ulcerative colitis.

1. Do you give us permission to look at your medical records, to help us with our research into the causes of ulcerative colitis? Yes ☐ No ☐ *(Please tick one box)*

2. What is the full name and address of the *last* hospital that you visited because of ulcerative colitis?

Hospital Name: _____

Hospital Address: _____

_____

_____

_____

_____

3. What is the name of the doctor that you saw at the above hospital?

Doctor's Name: _____

4. What age were you when you were first told that you had ulcerative colitis?

Age: _____ years

5. Please sign here if we have your permission to consult your medical records

Signature: _____ Date: _____

THANK YOU FOR YOUR HELP - PLEASE RETURN THIS QUESTIONNAIRE IN THE ENVELOPE PROVIDED TO: Scott Montgomery, SSRU, City University, Northampton Square, London EC1V 0HB (Tel 0171 477 8492)

Published work and contribution to conjoint work associated with this thesis

1. **Morris DL**, Montgomery SM,Galloway ML, Pounder RE, Wakefield AJ.Inflammatory bowel disease and laterality: is left-handedness a risk? Gut 2001 49:199-202.

Data collection (part), statistical analysis, interpretation and writing of paper.

2. **Morris DL**, Montgomery SM, Thompson NT, Ebrahim S, Pounder RE, Wakefield AJ. Measles vaccination and inflammatory bowel disease: A national British cohort study. Am J Gastroenterol 2000 95:3507-3512.

Data collection (part), statistical analysis, interpretation and writing of paper.

3. Montgomery SM, Wakefield AJ, **Morris DL**, Pounder RE, Murch SH. The initial care of newborn infants and subsequent hayfever. Allergy 2000 55(10):916-22

Assist with data collection.

4. Montgomery SM, **Morris DL**, Pounder RE, Wakefield AJ. Paramyxovirus infections in childhood and subsequent inflammatory bowel disease. Gastroenterology 1999;116:4 796-803.

Assist with data collection.

5. Montgomery SM, **Morris DL**,. Pounder RE, Wakefield AJ. Ethnic origin and the risk of inflammatory bowel disease in Great Britain. European Journal of Gastroenterology and Hepatology 1999; 11(5):543-546.

Assist with data collection.

6. Montgomery SM, **Morris DL**, Thompson NP, Subhani J, Pounder RE, Wakefield AJ. Prevalence of inflammatory bowel disease in British 26 year olds: national longitudinal birth cohort. BMJ 1998;316:1056-9.

Assist with data collection

7. Is passive smoking in childhood associated with inflammatory bowel disease?

Morris DL, Montgomery SM, Pounder RE, Wakefield AJ. Gut 2001:(SuppI) 48:A86:323.

Data collection (part), statistical analysis, interpretation and writing of paper.

8. Montgomery SM, Wakefield AJ, **Morris DL**, Pounder RE, Murch SH. Do inflammatory bowel disease and atopy share similar aetiological origins in early life?. Digestion 1998;59:117

Assist with data collection and literature review

9. **Morris DL**, Montgomery SM, Wakefield AJ. Pounder RE. Does a Family History usefully predict Inflammatory Bowel Disease by 26 years? Gastroenterology 1998:114,No4 Pt2:A1044

Data collection (part), statistical analysis, interpretation and writing of paper.

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