A contribution to knowledge of the aetiology and indirect impact of inflammatory bowel diseases.

(Based upon analysis of routinely and semi-routinely available data.)

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Thesis submitted to the University of Nottingham for the degree of Doctor of Philosophy

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Abstract

The incidence of the idiopathic inflammatory bowel diseases ulcerative colitis and Crohn's disease appears to have risen markedly during the 20th century. These diseases now account for a considerable proportion of the workload of gastroenterologists in the developed world, and may affect as much as 1% of the population at some point in their lives.

The aetiology of these diseases has been subject of much research over a number of decades and it is clear that both genetic and environmental factors are involved. The certain knowledge of environmental risk factors however remains scant. Similarly although inflammatory bowel diseases cause considerable morbidity and a small amount of mortality for their sufferers directly there is little agreement as to their overall impact once indirect effects are accounted for.

This thesis contains studies contributing to the knowledge of both these areas using routinely or semi-routinely collected data. It examines two hypotheses relating to the aetiology of IBD (that risk is related to the season of birth, and that it is related to antibiotic use), and two areas of the impact of the diseases (overall mortality and fracture risk).

With regard to aetiology the studies described show no variation in the risk of IBD with season of birth. They do show an increase in risk associated with the use of antibiotics, but since this is not specific (it is seen to occur with other groups of drugs also) it is far from clear that the association is causal. With regard to the indirect impact of the diseases a significant excess in overall mortality is demonstrated which is greater in Crohn's disease than in ulcerative colitis, and is greatest in relative terms in the young but in absolute terms in the elderly. An excess is also shown for hip fractures in those with inflammatory bowel diseases, which is only partially explained by the use of corticosteroids.

Abbreviations

IBD	Inflammatory bowel disease
GPRD	General Practice Research Database
BMI	Body mass index
GI	Gastrointestinal
UC	Ulcerative colitis
SMR	Standardised mortality ratio
HRT	hormone replacement therapy
CD	Crohn's disease
UK	United Kingdom
BSG	British Society of Gastroenterology
BPSU	British Paediatric Surveillance Unit
BSGRU	British Society of Gastroenterology Research Unit
RCPCH	Royal Society of Paediatrics and Child Health
OG	Orofacial Granulomatosis
IC	Indeterminate colitis
VAMP	Value added medical products
OXMIS	Oxford Medical Information System
GP	General practitioner
IBS	Irritable bowel syndrome
BNF	British national formulary
PAF	Population attributable fraction
OR	Odds ratio
CI	Confidence interval
SE	Standard error

HR	Hazard ratio

Acknowledgements

The work in this thesis was supervised by Professor Richard Logan and was funded by grants from the Wellcome Trust and from the National Association of Colitis and Crohn's disease.

In addition to these people I would also like to thank

Joe West with whom I shared an office. He was a great source of encouragement and enthusiasm throughout. I would like to apologise for the bruising of his psyche that must inevitably have occurred with our continual bouncing of ideas around our office.

Richard Hubbard who was also a great source of encouragement and whose experience of and expertise in the use of the GPRD was invaluable.

Jerry Wheeler, and Laura Rodrigues who helped me to conduct the study of antibiotic use and through it introduced me to the GPRD without which I could not have completed this thesis.

My wife Fatima who has encouraged me despite suffering more as a result of this work than anyone else.

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Chapter 1. Introduction

1.1. A brief introduction to idiopathic inflammatory bowel disease.

1.1.1. Definition

The idiopathic inflammatory bowel diseases are in general thought of as comprising 2 major subtypes, ulcerative colitis and Crohn's disease. These diseases are defined by their clinical and pathological features. Those features have themselves varied somewhat over the years to the extent that Crohn's name is now associated with a chronic transmural inflammation which can affect any part of the gut although he originally described with Ginzburg and Oppenheimer a disease limited to the ileum [1]. To allow uniformity of diagnosis a number of standardised criteria have therefore been produced, the best known of which perhaps are those of Lennard-Jones [2]. To summarize these ulcerative colitis can be thought of as a chronic inflammation of the colon with no identifiable cause which extends a variable distance continuously from the anus. Crohn's disease in contrast is a discontinuous chronic inflammation of any part of the GI tract, for which no cause is identifiable and which is characteristically although not always transmural and granulomatous. Despite the availability of such criteria the diagnosis of and between these conditions remains unclear in many cases. For practical purposes when studying large populations whose disease cannot be individually verified I shall

therefore use a working definition that UC and Crohn's disease are the conditions that attract these diagnoses in clinical practice.

1.1.2. Descriptive epidemiology

It is unclear whether inflammatory bowel diseases have occurred throughout human history. The earliest references to them may be as early as 1859 for ulcerative colitis and 1761 for Crohn's disease [3], but even if these sources are accepted as describing the diseases we now accord these names they can only set the latest and not the earliest possible advent of the diseases. What is rather clearer is that inflammatory bowel diseases have become far more commonly diagnosed over the last century [4]. Based upon recent publications it is likely that in the UK the incidence of Crohn's disease is about $8/10^6$ per year and of UC about $14/10^6$ per year with prevalence of around $145/10^6$ and $244/10^6$ respectively [5]. These diseases each have their peak onset in early adulthood, but can occur at any age, and there is some evidence to suggest that the incidence of Crohn's disease is growing still among children[6, 7], which if the incidence has stabilised in adults[8] may suggest a shift towards a younger age distribution.

1.1.3. Aetiology

The aetiology of inflammatory bowel disease remains largely unknown. In recent years much attention has focussed on genetic factors due to their well demonstrated familial aggregation (in

particular of Crohn's disease) first shown in 1963 [9], and the subsequent demonstration of heritability via twin studies[10] and genetic linkages first with areas of the genome and more recently with specific genes[11]. Nevertheless, while genetic factors clearly play an important role they cannot account for the rise in incidence of the disease over the last century[4]. Many environmental factors have been proposed as potential aetiological factors including increasing levels of hygiene [12, 13], the oral contraceptive pill [14], non-steroidal anti-inflammatory drugs [15, 16] and a wide variety of factors associated with a western lifestyle [17]. Of these smoking[18] is the only one which is well established to date, but it is not sufficient to explain the entire environmental component of the causation of Crohn's disease[10].

1.2. The role of micro-organisms in the aetiology of IBD

1.2.1. Background

One aspect of the environment which is increasingly accepted as being associated with the aetiology of Crohn's disease, is the intestinal microflora [19]. If as is suggested by animal models such as the IL-10 deficient mouse [20] , and the emerging evidence regarding probiotics [21], inflammatory bowel diseases may depend upon the relationship between the gut and it's microflora, then anything

interfering with this relationship such as antibiotics or delivery by caesarean section might contribute to their aetiology.

1.2.2. The role of season

Prenatal or perinatal environmental exposures have been postulated to alter the risk of a number of diseases manifest later in life over recent years [22]. Such early exposures have also been the subject of some study in inflammatory bowel disease (IBD) [23]. One manifestation of such effects which has been proposed to exist is an association between the month of birth and risk of developing IBD latter in life [24-26]. Such an association has been hyopthesised to arise in other diseases for a number of reasons. In childhood psychiatric illness in general it has been hypothesised that an excess of psychiatric disorders among the youngest members in a school year (those born in the summer in England and Wales) might be due to stresses associated with being the youngest in the class[27]. This is likely to be related closely to those factors which cause the same group of children to be overrepresented among groups with “learning difficulties”[28]. Another proposed mechanism for a relationship with season of birth is the suggestion that an excess of birth defects among those conceived in spring in one area of Minnesota might be explained by the use of herbicides applied at that time of year[29]. In the case of Crohn’s disease however as for Coeliac disease, multiple sclerosis, type I diabetes and schizophrenia the suggested mechanism is that the disease is the

result of an infection that occurs seasonally[24-26, 30-32]. In the cases of multiple sclerosis and schizophrenia it is suggested that this is via a direct neurological effect of Borelliosis[30], whereas in Coeliac disease the mechanism is suggested to be the induction of an immunological cross reaction with Gliadin[32]. In the case of Crohn's disease the proponents of a seasonal association have in general not specified the mechanism by which they thought an infection might act although in at least one study the possibility of persistence of virus causing a direct effect upon the gut has been raised[25].

Two recent publications, one from the UK [25], and the other from Denmark [26] have examined cohorts of Crohn's patients for such seasonality of birth. The findings of these two studies as well as their interpretations differ markedly. The British study was of adult patients diagnosed between 1972 to1989 by four regional IBD registers in which a weak association was found between Crohn's disease and birth in the first half of the year. The second (Danish) study examined national computerised hospital discharge records of children and young people aged less than 20 years coded between 1977-1992 for Crohn's disease. This latter study found an apparently stronger association with month of birth with the peak risk being for those born during August with a 'sine-wave' variation in risk between those born in different months of the year. The authors suggest that the differences compared to the British study might be explained by differences in age mix and nationality of the

subjects, and further suggested that their findings give support to the importance of in utero and early childhood events in the aetiology of Crohn's disease.

1.2.3. The role of antibiotics

Antibiotics can clearly alter at least temporarily the bacterial microflora and are therefore worth considering as a potential risk factor for IBD. The first evidence of the possibility that alterations in intestinal microflora, occasioned by antibiotics, might contribute to the aetiology of Crohn's disease was from two case control studies [33, 34] which showed an association between increased antibiotic use and diagnosis of Crohn's disease in children. Both studies relied on recall of use of antibiotics, assessed many years after the initial diagnosis. Such recall of exposures is known to be susceptible to bias in studies where the onset of disease could influence recall. In both studies the authors consider the finding an artefact, and not causal. Demling in 1994[35] hypothesised on the basis of a subjective assessment of the trends in Crohn's disease and antibiotic use over time that a causal link may exist. Since antibiotic use is common it might make a large contribution to the risk of Crohn's disease in the population if the association these studies have described is causal.

1.3. The impact of IBD

1.3.1. Mortality in IBD

The mortality associated with diseases is studied for a number of reasons. Clearly if mortality is high this will render the disease more important and hence direct therapeutic and research effort towards it. It is therefore important for policy makers to have information regarding a disease's mortality. Knowledge of the prognosis of diseases is also of immense importance both to people suffering from them and to their physicians since patients have an understandable wish to know the implications of any diagnosis they receive. Both of these reasons for wishing to know the mortality associated with a disease apply to inflammatory bowel diseases. One other group also greatly interested in mortality risk are life insurance companies who load their premiums (increase them) to balance any perceived higher risk associated with having a known diagnosis. This has led to criticism of what has been perceived as unfair loading of policies for IBD patients[36].

At the present time there is considerable uncertainty as to what if any increase in mortality is associated with IBD. Current estimates range from a 40% decrease to a 70% increase in mortality with ulcerative colitis (UC),[37, 38] and from no increase to doubling in mortality with Crohn's disease (CD).[39, 40] (Table 1-1, Table 1-2). These inconsistencies may be due in part to the selected nature of

cases studied, a failure to control for important confounders such as smoking and weight, and differences in the time periods studied. To address these issues statistically powerful general population based studies of contemporary mortality risk in IBD patients are clearly required.

First author / Year	Area	Period	Cohort	Deaths	Standardised Mortality Ratio *(95% CI)*
Langholz et al 1992[41]	Copenhagen	1962-1987	1,104	121	107
Farrokhyar et al 2001[39]	3 English districts in Midlands	1978-1986	356	41	103 *(79-140)*
Persson et al 1996[42]	Stockholm	1955 -1984	1,547	255	137 *(120-154)*
Ekbom et al 1992[43]	Uppsala, Sweden	1965-1983	2,509	505	140 *(120-150)*
Palli et al 1998[37]	Florence	1978-1992	689	47	62 *(40-80)*
Davoli et al 1997[44]	Rome	1970-1989	508	27	98 *(64-142)*
Viscido et al 2001[45]	Italy	1964-1989	2,066	93	100 *(80-120)*
Gyde et al 1982[38]	Birmingham	1940-1976	676	141	170

Table 1-1 Previous large studies of all-cause mortality in UC patients

First author / Year	Area	Period	Cohort	Deaths	Standardised Mortality Ratio *(95% CI)*
Cottone et al 1996[46]	Sicily, Italy	1973-1993	531	9	97 *(40-180)*
Farrokhyar et al 2001[39]	3 English districts in Midlands	1978-1986	196	23	94 *(59-140)*
Persson et al 1996[42]	Stockholm	1955-1984	1,251		151 *(129-175)*
Weterman et al 1990[40]	Leiden, Holland	1934-1984	659	64	223 (*175-285)*
Ekbom et al 1992[43]	Uppsala, Sweden	1963-1986	1,469	179	160 *(140-190)*
Palli et al 1998[37]	Florence	1978-1992	231	23	136 *(90-200)*
Jess et al 2002[47]	Copenhagen followed	1967-1987	374	84	130 *(101-150)*
Mayberry et al 1980[48]	Cardiff, UK	1930s-1970s	219	40	216

Table 1-2 Previous large studies of all-cause mortality in CD patients

1.3.2. Fractures in IBD

Although many studies have shown that IBD patients are at increased risk of osteoporosis [49-53] there is relatively little data as to the extent of the increased risk of fracture in these patients relative to the general population. A small number of case series have suggested high levels of osteoporotic fracture[54, 55], but data from the available controlled studies are inconsistent, with one study showing a rise in fracture risk both for UC and Crohn's [56], two an increase in risk in Crohn's but not in UC [57, 58] and one no increase in risk in either[59]. Since corticosteroids are a risk factor for osteoporosis[60], and are widely used in IBD they might explain the associated osteoporosis. However the size of the contribution from corticosteroids is unclear [49, 61-64].

Of the controlled studies of fractures to date only one has addressed the role of corticosteroid use [57], and in this study the use of corticosteroids was a risk factor for fracture in Crohn's disease but not in UC. Important limitations of this study however included the use of retrospective data derived from questionnaires, and the ability only to examine cumulative duration of steroid use which might underestimate the role of these drugs if as has recently been suggested their effect is reversible[65].

1.4. Aims and studies

The overall aim of this thesis is to examine factors relating to both the aetiology and impact of IBD in those areas of uncertainty identified above using available data. Within this wide brief specific objectives are addressed by individual studies which are outlined below.

1.4.1. Chapter 2

This chapter examines the possibility that the season in which one is born affects the risk of IBD

1.4.2. Chapter 4

This chapter examines the hypothesis that antibiotic use might predispose to Crohn's disease.

1.4.3. Chapter 6

This chapter examines all cause mortality rates in IBD patients.

1.4.4. Chapter 7

This chapter examines the risk of hip fracture in IBD patients and its relationship to the use of corticosteroids.

In addition to these studies describing specific studies Chapter 3 and Chapter 5 give background information on the data used in Chapter 1, Chapter 6 and Chapter 7. The final chapter (Chapter 8) summarises the findings of the studies, and draws some conclusions.

Chapter 2. Month of birth and the risk of Crohn's disease

2.1. Introduction

The study presented in this chapter addresses the inconsistencies in the methodologies and results between previous examinations of the possible association between birth at certain times of the year and subsequent diagnosis of IBD. It is not based upon any single hypothesis as to the mechanism by which such association might occur, but rather examines for any seasonality by whatever mechanism it might arise.

2.2. Methods

2.2.1. IBD case data used in this study.

This study utilises data originally collected for a survey of childhood Inflammatory Bowel Disease (IBD) in the British Isles by the British Paediatric Surveillance Unit (BPSU), and the British Society of Gastroenterology Research Unit (BSGRU). This survey as published is a record of a 13 month programme of prospective reporting of new diagnoses of IBD under age 16 encountered by paediatricians, gastroenterologists, surgeons and pathologists who were members of the British Society of Gastroenterology (BSG) or the Royal College of Paediatrics and Child Health (RCPCH) in the UK and the Faculty of Paediatrics of the Royal College of Physicians of Ireland. Participating members of these organisations received once a month a card on which they were to record whether they had

encountered any new diagnoses of IBD under the age of 20 during the month. This card was to be returned whether or not there were any cases to report. In order to confirm the initial clinical diagnosis from the reporter of the case, a follow up questionnaire was sent. This allowed confirmation that the initial diagnosis remained valid, as well as ascertaining date of birth and of presentation. From the previously published data we removed notifications from the Republic of Ireland, and to it we added notifications of patients aged 16-20 years from the BSGRU survey.

2.2.2. Population data used in this study

The monthly numbers of live births during the period when children reported above were born (1978-1998) were obtained for England and Wales [66, 67], Scotland (from General Register Office for Scotland: personal communication) , and Northern Ireland (from Northern Ireland Statistics and Research Agency: personal communication). These numbers are given in Appendix 1. From them was calculated the number of live births per month from 1978 to 1998 for the whole of the UK Table 2-1.

	January	February	March	April	May	June	July	August	September	October	November	December
1978	54374	51269	58906	55841	58721	57360	58467	58898	60236	60347	55620	56995
1979	60080	55666	64283	61772	65246	62457	64332	61858	60278	62436	58631	57605
1980	62957	59028	64115	64160	66037	62827	66513	62579	63707	64216	57741	59694
1981	61158	55794	63508	60813	62575	61587	64820	62187	61530	61689	57837	57358
1982	59325	55084	62532	60010	61568	58732	62438	61535	61874	61470	57112	58209
1983	59108	54575	61611	60065	62470	62174	63137	62092	62241	59344	57017	57699
1984	58979	55913	60947	57597	61890	61134	64022	63932	63017	63771	60403	57329
1985	62986	56692	63513	61517	65561	61906	66754	65124	64862	64563	59291	57842
1986	61832	56524	63974	63843	66270	63633	65042	64785	64711	64298	58131	61921
1987	62677	57763	65448	64142	67609	67389	68159	65884	66717	65884	60944	63190
1988	65270	62885	69227	65689	68394	66153	68045	67935	67104	63315	61065	62397
1989	63674	59069	66670	64114	68559	66830	67700	66810	64099	64592	62183	62960
1990	64835	59791	66639	64659	69408	68367	70795	69208	67547	68617	65186	63620
1991	67472	61088	65902	64755	68019	66419	70486	68369	67105	67036	62532	63306
1992	66672	62481	66643	65324	66752	66626	69151	66203	66171	64147	60394	60397
1993	62924	57329	64169	62215	64552	65336	66699	65384	66546	64327	59905	62360
1994	63055	57414	65481	62517	65287	64683	64392	62949	63347	62770	59165	59485
1995	61059	56127	62691	58671	64036	63049	63611	62918	62149	62406	58391	57003
1996	61381	56957	59705	57469	60705	60045	64969	63299	63204	64240	60641	60763
1997	62215	55917	60311	61771	62337	60931	63849	61623	60851	60349	56897	59766
1998	60473	54944	60537	59250	59396	60145	63655	61073	62347	60755	56350	57762

Table 2-1 Numbers of live births by month in the UK 1978-1998

Statistical analysis

The expected number of cases for each month was obtained by dividing the observed cases born in each year between the year's months in the ratio of the total births within the months of that year. The monthly expected cases were then summed for each month over all 20 years. Total numbers of observed cases by calendar month of birth were similarly summed across the 20 year period. The numbers of cases expected were then compared to the number observed using a Chi-Square test. This was repeated examining for six-month periods (January to June and July to December) instead of months. (The same division of the months which demonstrated a weak association between birth in the first half of the year and subsequent Crohn's disease in the study by Haslam and colleagues [25].)

The monthly observed 'risk' of births joining this incident cohort was calculated as the proportion of those born in a given calendar month between 1978 and 1998 diagnosed with IBD in the study period per 100,000. Expected risks were calculated both as a constant rate model across the calendar months, and as a periodic model.

In the constant risk model, risk was calculated as the proportion of all births between 1978 and 1998 that were diagnosed with IBD during the study period also per 100,000.

For periodic regression models methodology similar to that previously used to show a suggested link between the season of birth and risk of IBD [26] was used. I.e. linear regression models incorporating as covariates in a linear regression, sine and cosine terms were used to model the relationship between 'risk' and month, and also between observed and expected numbers of cases by month.

These constant rate and periodic models were then compared and likelihood ratio tests were used to assess whether the inclusion of the periodic term significantly improved the fit of the model.

The equations of the models used were

$$\text{Risk} = \text{const.} \times B^{1}\sin(\text{month } 30\ \text{Pi}/180) \times \beta^{2}\cos(\text{month } 30\ \text{Pi}/180)$$

(*For modelling risk with a periodic component*.)

$$\text{Risk} = \text{const.}$$

(*For modelling risk without a periodic component*.)

$$\text{N observed} = \text{const.} \times \beta^{1}\ \text{N expected} \times \beta^{3}\sin(\text{month } 30\ \text{Pi}/180) \times \beta^{4}\cos(\text{month } 30\ \text{Pi}/180)$$

(*For modelling numbers of diagnoses with a periodic component*.)

$$\text{N observed} = \text{const.} \times \beta^{1}\ \text{N expected}$$

(*For modelling numbers of diagnoses without a periodic component*.)

Since a single sine cosine pair constrains the model to have only one maximum and one minimum within the year, models were refitted with 2 and then 3 sine cosine pairs to permit a closer fit between model and data. Again the contribution of the periodic element of the models was assessed using likelihood ratio tests.

Analyses were repeated for all IBD cases, and for both UC and CD separately.

2.3. Results

2.3.1. Description of cases observed.

In total there were 1040 incident cases of IBD diagnosed in those aged 0-20 years in the UK during the study period of June 1998 to June 1999. There were 634 cases of Crohn's disease (CD), 277 cases of ulcerative colitis (UC), 12 cases of Orofacial Granulomatosis (OG), and 117 cases of indeterminate colitis (IC) Table 2-2. The median year of birth of these cases was 1984 with a mode in 1983. The interquartile range ran from 1982 to1987. Diagnoses for each month of birth during the years 1978-1998 are given in Table 2-3.

	Month of birth												
IBD type	January	February	March	April	May	June	July	August	September	October	November	December	Total
Crohn's Disease	69	45	44	59	49	58	59	56	61	43	52	39	634
Indeterminate Colitis	6	9	12	12	10	13	8	9	8	12	9	9	117
Orofacial Granulomatosis	2	1	1				1	2		1	1	3	12
Ulcerative Colitis	26	26	23	17	29	20	20	25	20	24	20	27	277
Total	103	81	80	88	88	91	88	92	89	80	82	78	1040

Table 2-2 Counts of IBD diagnoses by calendar month of birth and IBD type

	January	February	March	April	May	June	July	August	September	October	November	December	Total
1978	1		1		1	1	1		2			2	9
1979	3	3	1	4	2	2	2	1	2	4	4	4	32
1980	2	5	5	5	4	4	5	5	6	7	7	3	58
1981	7	6	8	8	10	8	10	6	11	5	5	8	92
1982	12	2	10	5	8	11	11	13	8	6	12	15	113
1983	12	11	6	11	13	11	10	14	14	7	13	7	129
1984	12	14	7	9	7	12	12	10	5	8	8	9	113
1985	12	7	11	14	14	9	8	9	6	7	4	5	106
1986	12	7	7	7	7	10	7	7	9	8	6	6	93
1987	7	5	6	8	4	9	4	10	5	8	6	5	77
1988	6	7	9	7	6	4	7	5	5	2	4	3	65
1989	5	3	3	6	5	3	4	5	5	2	5	5	51
1990	4	3	3	1	1	2	2		2	3	2	2	25
1991		2	1	2	2	2			2	4	2		17
1992	1	3		1	2	1	3	1	2	3		2	19
1993	2	2	1		1		1	1	1	1	2		12
1994					1			2	2			2	7
1995	2	1	1				1	1	1		1		8
1996	2					1		1	1	2	1		8
1997	1					1		1		1			4
1998										2			2
	103	81	80	88	88	91	88	92	89	80	82	78	1040

Table 2-3 IBD cases born by month 1978-1999. (The number given is the total of Crohn's disease (CD), ulcerative colitis (UC), Orofacial Granulomatosis (OG), and indeterminate colitis (IC))

2.3.2. Observed and expected numbers of IBD diagnoses compared using the Chi squared test.

Calculated numbers of observed and expected diagnoses of IBD, CD and UC by calendar month are given in Table 2-4.

There was no statistically significant difference between the observed and expected numbers for IBD (P = 0.88 by chi squared test), CD (P = 0.17) or UC (P = 0.77). These differences remained non-significant when the data were analysed by half year (January to June and July to December) as opposed to month (P = 0.40 for IBD, P = 0.50 for CD and P = 0.70 for UC).

	Jan	Feb	Mar	Apr	May	June	July	Aug	Sept	Oct	Nov	Dec
CD observed	69	45	44	59	49	58	59	56	61	43	52	39
CD expected	52.11	48.22	54.01	52.30	54.74	53.29	55.40	54.27	54.02	53.51	50.08	50.37
UC observed	26	26	23	17	29	20	20	25	20	24	20	27
UC expected	22.78	21.07	23.56	22.83	23.91	23.28	24.21	23.69	23.61	23.41	21.87	22.03
IBD observed	103	81	80	88	88	91	88	92	89	80	82	78
IBD expected	85.49	79.13	88.56	85.76	89.79	87.42	90.88	89.00	88.61	87.80	82.13	82.67

Table 2-4 Observed and expected numbers of diagnoses of IBD by calendar month. CD Crohn's disease, UC ulcerative colitis, IBD the total CD, UC, Orofacial Granulomatosis (OG), and indeterminate colitis (IC))

2.3.3. Observed and expected risks of IBD diagnoses compared using the Chi squared test.

Table 2-5 shows the monthly observed risk of IBD diagnosis during the study period for UK live born infants from 1978-98. Also shown is the risk that would be expected if risk were constant throughout the year irrespective of calendar month of birth. The application of a chi squared test to these figures shows no significant difference between observed and expected rates (P =1.00 each of all IBD, UC and CD.

	Jan	Feb	Mar	Apr	May	June	July	Aug	Sept	Oct	Nov	Dec
UK births 1978-98	1,303	1,202	1,337	1,296	1,355	1,328	1,377	1,345	1,340	1,331	1,245	1,258
No. CD diagnoses	69	45	44	59	49	58	59	56	61	43	52	39
Observed Risk CD	5.30	3.74	3.29	4.55	3.62	4.37	4.28	4.16	4.55	3.23	4.18	3.10
Expected Risk CD	4.03	4.03	4.03	4.03	4.03	4.03	4.03	4.03	4.03	4.03	4.03	4.03
No. UC diagnoses	26	26	23	17	29	20	20	25	20	24	20	27
Observed Risk UC	2.00	2.16	1.72	1.31	2.14	1.51	1.45	1.86	1.49	1.80	1.61	2.15
Expected Risk UC	1.77	1.77	1.77	1.77	1.77	1.77	1.77	1.77	1.77	1.77	1.77	1.77
No. IBD diagnoses	103	81	80	88	88	91	88	92	89	80	82	78
Observed Risk IBD	7.91	6.74	5.98	6.79	6.49	6.85	6.39	6.84	6.64	6.01	6.58	6.20
Expected Risk IBD	6.62	6.62	6.62	6.62	6.62	6.62	6.62	6.62	6.62	6.62	6.62	6.62

Table 2-5 Observed and expected risks of diagnosis of IBD during the study period among UK births from 1978-98. CD Crohn's disease, UC ulcerative colitis, IBD the total CD, UC, Orofacial Granulomatosis (OG), and indeterminate colitis (IC))

2.3.4. Periodic models of risk with one sine cosine pair.

The fitted periodic models of risk using models with one sine cosine pair are shown in figures Figure 2-1 for ulcerative colitis, Figure 2-2 for Crohn's disease and Figure 2-3 for all IBD. Also plotted are the observed levels of risk and a model assuming constant risk across the twelve months of birth.

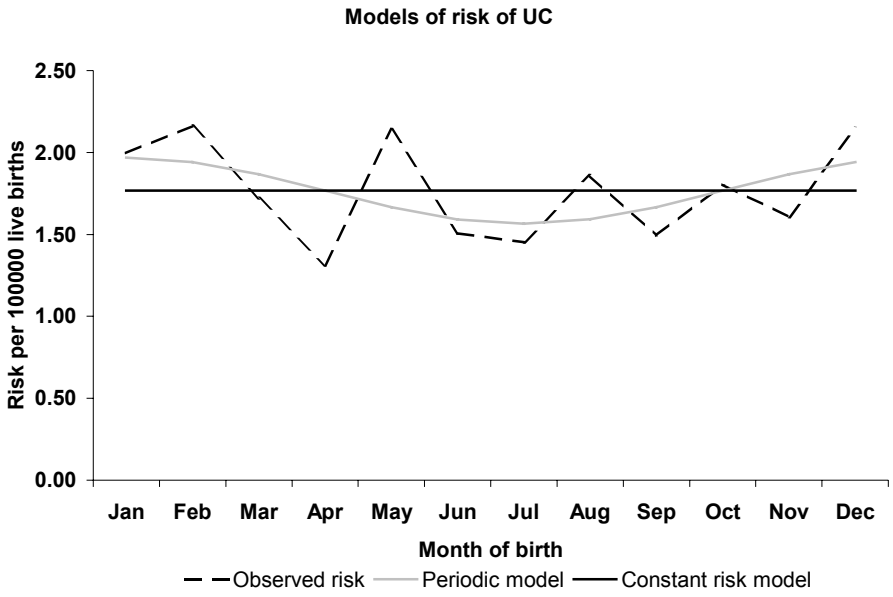

Figure 2-1 Models of risk for Ulcerative colitis.

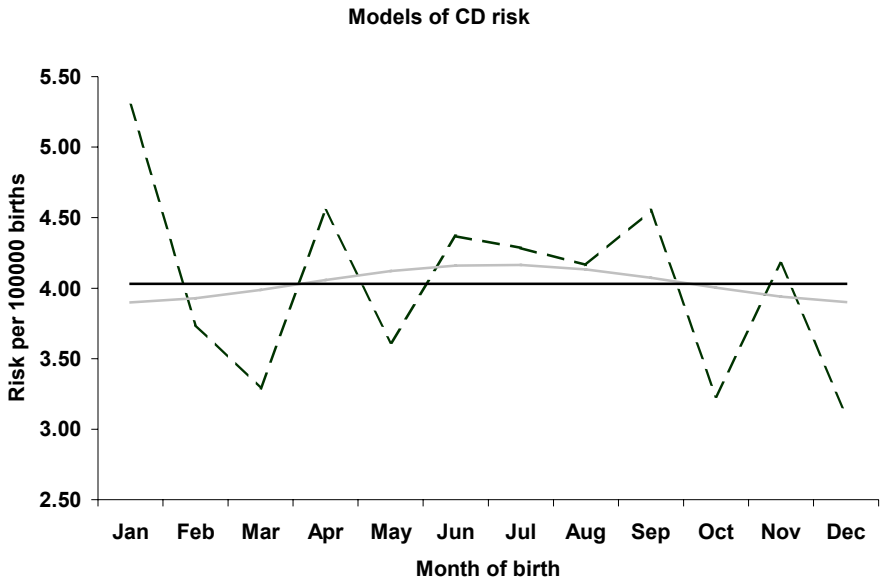

Figure 2-2 Models of risk for Crohn's disease.

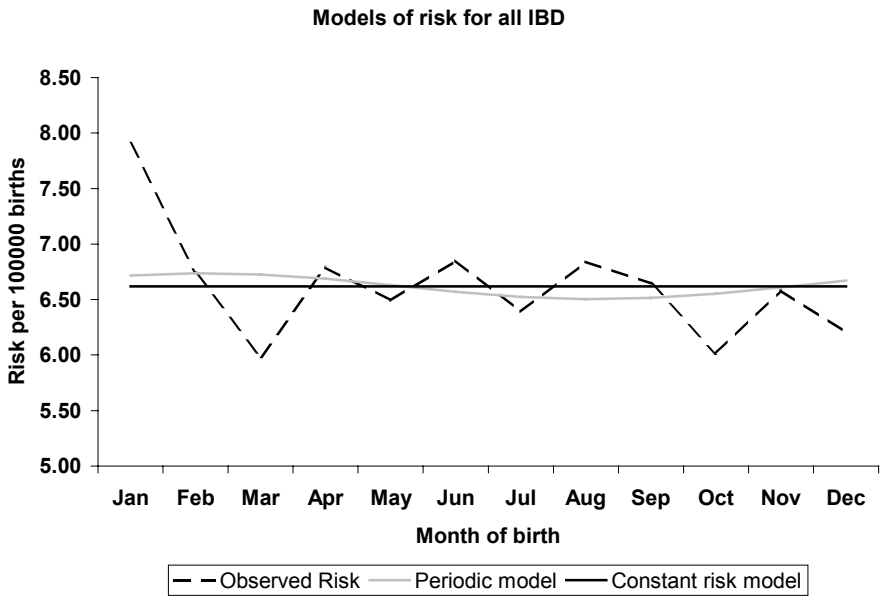

Figure 2-3 Models of risk for all IBD (the total of CD, UC, Orofacial Granulomatosis (OG), and indeterminate colitis (IC) cases).

A comparison between these periodic models and constant risk models using a likelihood ratio test showed that any improvement in fit as a result of the inclusion of periodic terms was not significant (P = 0.84 for all IBD, P = 0.87 for CD and P = 0.18 for UC).

2.3.5. Periodic modelling of expected numbers of cases with one sine cosine pair.

Similarly comparing models examining the relationship between observed and expected numbers, the likelihood ratio test showed that models incorporating periodic terms did not fit significantly better than those without (P = 0.95 for all IBD, P = 0.90 for CD and P = 0.42 for UC).

2.3.6. Periodic modelling of risk with more than one sine cosine pair.

Models with two and three sine cosine pairs showed a visibly better fit (Figure 2-4, Figure 2-5, Figure 2-6, Figure 2-7, Figure 2-8, Figure 2-9), but none of them were significantly better than the non-periodic model when taking the increase in model saturation into account.

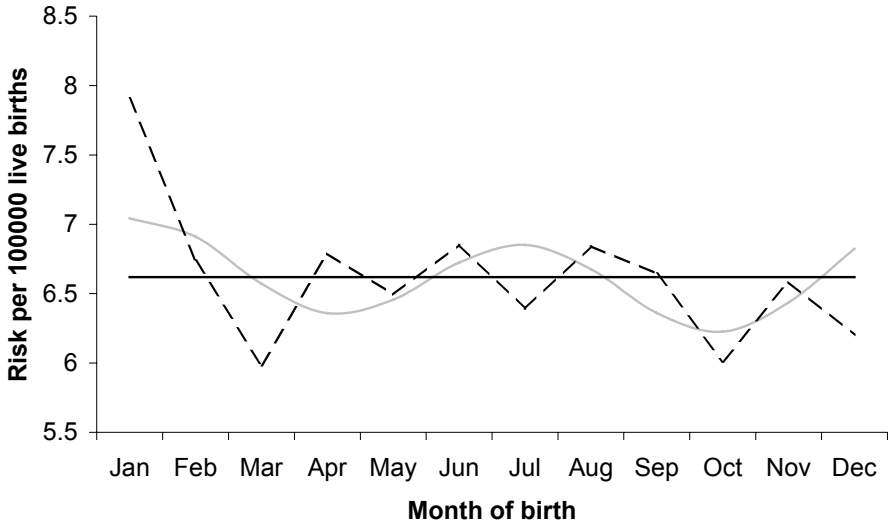

Figure 2-4 Models of risk of all IBD using 2 sine cosine pairs

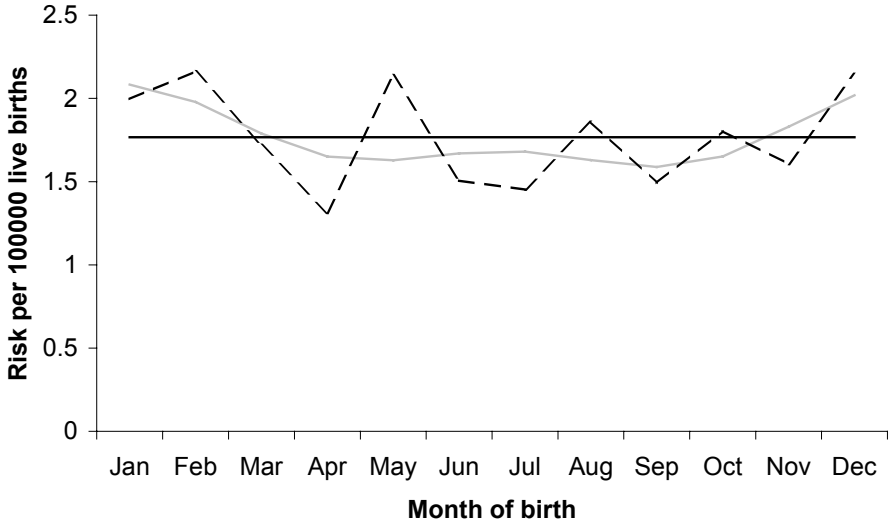

Figure 2-5 Models of risk of UC using 2 sine cosine pairs

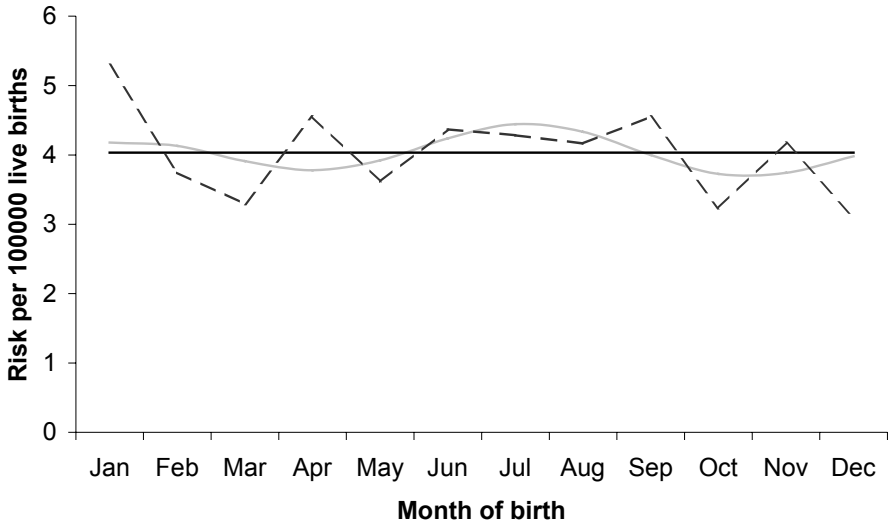

Figure 2-6 Models of risk of CD using 2 sine cosine pairs

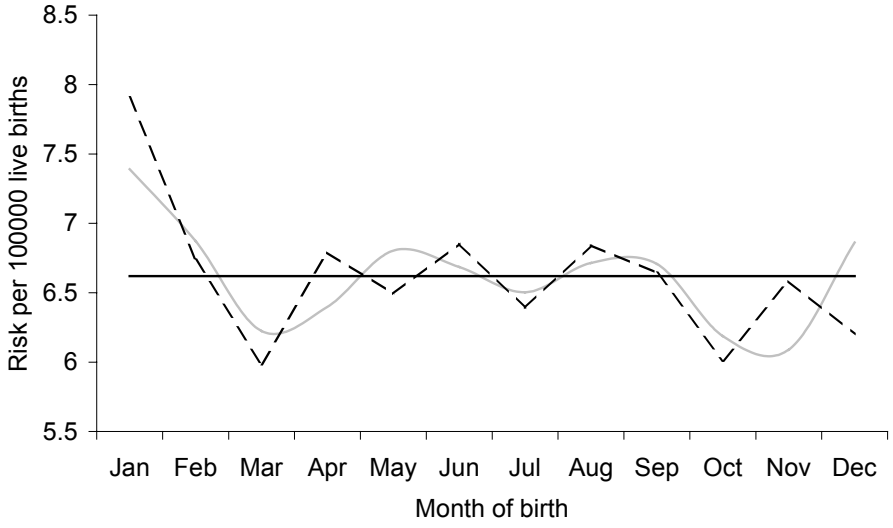

Figure 2-7 Models of risk of all IBD using 3 sine cosine pairs

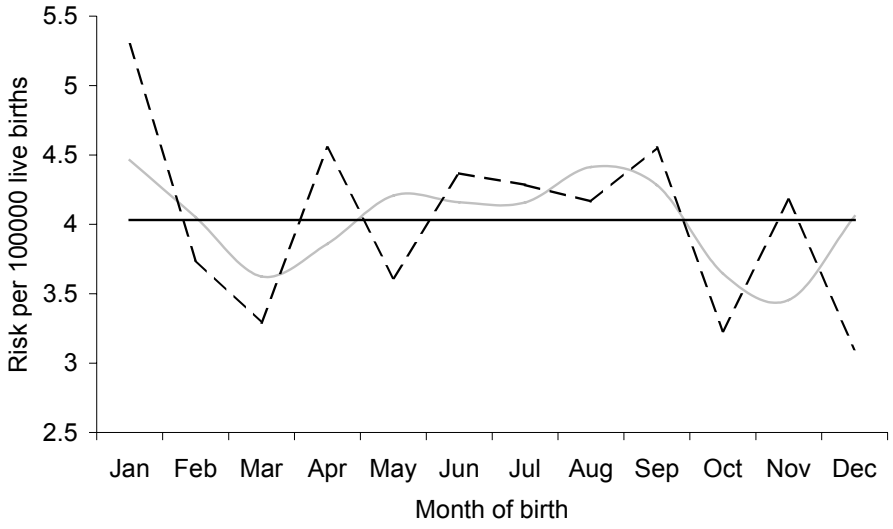

Figure 2-8 Models of risk of CD using 3 sine cosine pairs

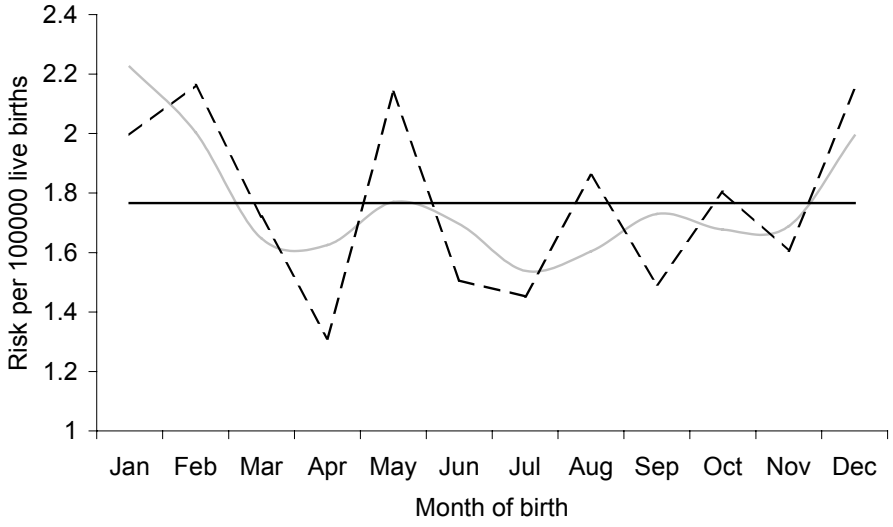

Figure 2-9 Models of risk of UC using 3 sine cosine pairs

2.4. Discussion

2.4.1. Findings

This study found no statistically significant relationship between month of birth and the risk of developing inflammatory bowel diseases in the early years of life. This remained true whether the relationship was examined using a chi squared test or periodic regression. In the case of chi squared testing this was true both comparing between months and between the halves of the year. Similarly for periodic modelling the addition of further periodic components did not reveal any relationship.

2.4.2. Comparison with other studies

These findings are consistent with the previous British study of older Crohn's disease patients [25] but are at odds with the published interpretation of a series of cases of similar age from Denmark [26]. The similarity in the age structure between our study and the recent Danish one demonstrate that age cannot explain the difference between these and the Danish findings (as was suggested by the authors of this study as a possible explanation of the difference between their findings and previous studies). There are however differences between the studies which may explain the difference in findings. These differences include methods of case ascertainment, time-period of case diagnosis and statistical technique. The ascertainment of cases in the data used for this study is without

doubt incomplete. It is however extremely unlikely that this has in any way biased our results since to do so it would be necessary for the probability of ascertainment to be related to the calendar month of birth. Similarly although the data used here relate only to diagnoses in one 13 month period (compared to all from 1957 to 1992 in the Danish study), it seems unlikely that seasonality of this nature occurred until but not after the early 1990s. Finally with respect to statistical technique, although we have used methodology similar to that previously described one important difference is that we have quoted a significance test for the periodic regression models.

2.4.3. Limitations of this study

One major problem of methodology in all of the studies of this issue to date that we have been unable to overcome is the necessity of summing observed births within a calendar period over the years. Although this is necessary to obtain enough births in each month for a reasonably stable estimate, it imposes a limit of 12 data points that ensures that statistical models unless they are kept parsimonious will become rapidly saturated. This may explain the apparently good fit that can be seen from graphical representations of models for which periodic components give no significant benefit. For this reason unless any true periodicity had a form which approximated fairly well to a sine wave it might be hard to detect by this methodology. However to overcome this problem a truly massive

study examining the incidence in a huge population over many years would be necessary (to allow each separate month of chronological time to be counted as an independent period within the analysis), and such a study is at present not feasible. In fact given that seasonal factors may vary to some extent geographically it may never be feasible.

With respect to this study specifically there are some limitations to the data used. Although the birth, data being derived from national statistics are likely to be highly valid, the data on IBD diagnoses are perhaps less reliable in two respects. Firstly it is possible that some of the IBD cases notified did not have IBD. This possibility was guarded against by rechecking the clinician's opinion of the diagnosis by questionnaire. Nonetheless it is possible that there was some error in the diagnosis. Since such error is unlikely to have been differential between months of birth it's only effect would be to slightly reduce the power of the study (i.e. to impart a null bias). Secondly since return of reporting cards for the surveillance was incomplete it is possible that some cases were not reported. One indication perhaps of this under reporting is the age distribution of our cases. As can be seen in Table 2-3 the numbers of cases born in the late 1990s is low which one would expect since these children would have been young at the time of data collection and Crohn's disease is very rare in young children. What one would not expect is the fall off in numbers diagnosed with birth before 1983 since the

incidence would be expected to be higher among 20 year olds than 16 year olds. It is likely that this reflects poorer levels of response and of reporting among adult physicians (who would be likely to care for these older groups) than among Paediatricians. It is unlikely however that such non-reporting varied in a manner related to month of birth, and hence this should not affect the validity of the results. A further potential cause for concern is the apparent excess of births in January among cases in this study. This might lead one to question whether some subjects with unknown date of birth have been assigned the 1st of January of their year of birth. In fact this is not the case since a specific date of birth was obtained for each case, and inspection of the data confirms that cases were born throughout January without undue numbers concentrated on the first of the month. It is likely therefore that this is a chance finding which would be in line with the lack of significant variation from a constant risk of IBD across the months of the year which we have shown.

2.4.4. Conclusions

Although the lack of evidence of any variation in risk of Crohn's disease by month of birth in this or previous studies does not prove that no such variation exists, it seems unlikely that future studies in the UK at least will find such evidence. This does not by any means exclude the possibility that factors acting specifically at or around the time of birth may be important in the aetiology of this disease, but it does suggest that such aetiological factors may be unlikely to be found among exposures varying by season.

Chapter 3. The General Practice Research Database

3.1. Introduction

This chapter will first give a brief description of the General Practice Research Database (GPRD). It will then describe the subsets of this database used in the studies presented subsequently.

3.2. The nature of the GPRD

The General Practice Research Database (GPRD) is a collection of anonymous computerised patient records from over 500 British general practices. It is the world's largest longitudinal, primary care database and contains approximately 50 million patient years of data. Collection began in 1987 as a commercial enterprise by VAMP (Value Added Medical Products), the ownership and running of the database subsequently passed to Reuter's who in turn gave it to the Department of Health of the UK government[68].

Throughout these changes in ownership and management the GPRD's data collection has remained uniform. Data are downloaded periodically from practice computer systems that were initially uniform, but subsequently have varied. The data collected has remained constant, and is reformatted from differing practice computer systems for uniform presentation. To ensure data quality, contributing practices receive data quality training, and are audited to ensure that at least 95% of prescribing and morbidity events are

included[69]. Practices are considered to contribute data which is "up to standard" when this as well as a variety of other criteria are met and for this reason studies are in general based upon such "up to standard data"[70].

3.3. Data collected

Data collected by GPRD are presented in four basic tables. These are:

- The patient records table.

This contains on one line per subject a practice identifier, a patient identifier, date of birth, sex, the dates during which the patient contributed up to standard data and information on the registration status of the patient with the practice (permanent, temporary, dead etc.).

- The medical records table.

This contains on many lines per subject, practice and patient identifiers to precisely identify the subject as well as the date of the recorded event, a code identifying what event is being recorded and codes showing where the consultation took place and what follow up or referral was organised if any. The coding of events utilises a modification of the Oxford Medical Information System (OXMIS) classification as well as the Read codes so that a very wide variety

of signs, symptoms, risk factors, diagnoses and medical interventions can be identified.

- The therapy table

This contains on many lines per subject data detailing the date and nature of prescriptions. These are coded using a coded drug dictionary based on the Prescription Pricing Authority's dictionary. In addition fields are available for the entry of data on the quantity prescribed and the duration over which it is to be taken. (These last data are far from complete.)

- The prevention table

This contains on many lines per subject data detailing findings and activities related to disease prevention. This includes vaccinations and also records of height, weight, blood pressure, allergies and smoking and drinking behaviour.

The format of these tables is given in full in Appendix II

3.4. Strengths and weaknesses of the GPRD.

(With specific reference to epidemiological studies of IBD.)

The GPRD is a remarkable resource for epidemiology with a number of important strengths, but as with any data source it has limitations. The following paragraphs will address some of these strengths and weaknesses, and their consideration to some extent

underpins the design of the studies presented in the following chapters.

3.4.1. Size

For studies of IBD one of the greatest strengths of GPRD is its size. As shown in Table 1-1 the relative rarity of these conditions has led to large numbers of small studies and rather fewer large ones. Small studies have been adequate to make some progress in the study of IBD but they will inevitably provide less precision and less power than can be achieved using GPRD when it contains the necessary data.

3.4.2. Representativeness.

Although the practices in GPRD are self-selected they are from a wide variety of different areas of the UK, and have been shown to have levels of morbidity that mirror national estimates [68]. It is therefore reasonable to generalise results form the GPRD to the population of the UK as a whole.

3.4.3. Prospectively gathered.

The identification of each subject's entry date to the dataset ensures that it is easy to ascertain which data are prospectively, and which retrospectively recorded. This is of particular importance for studies where exposure recall may be likely to be biased. Perhaps the best example of such an exposure and the GPRD's strength in this

respect is the use of medication. Since almost all prescriptions in GPRD practices are electronically produced and added to the database by the same process that produces them, there is very little opportunity for error in recording, and almost none for bias.

3.4.4. Contemporary

Although it seems likely that the aetiology of IBDs (assuming that they are distinct entities rather than a final common pathway for a large number of disease processes) remains essentially unchanged over decades, the same may not be true of their outcome. There is good reason to think that the mortality directly attributable to IBD at least in the USA and UK may have changed over the years[71]. Since corticosteroids, amminosalicylates and immunomodulators (the mainstays of medical therapy for IBD) have all been introduced or more widely adopted over a relatively small number of decades it is quite likely that other measures of outcome will also have altered as a result. Hence the fact that GPRD can provide many thousands of patient years of recent data encourages the belief that any results should be generalisable to current rather than historical clinical settings.

3.4.5. Validatable

Although as outlined above strict data standards are maintained for the GPRD it is of great importance that systems also exist for the independent validation of the data by third parties. The mechanism

for this is via the requesting of anonymised copies of paper records, or the completion of questionnaires by GPs. This system although it is sufficiently expensive (£100-200 approximately per validated subject) to prevent its application to very large numbers does permit validation of samples. By this means a number of diagnoses and outcomes have been validated in GPRD [70, 72-76] and IBD is one of these. In a study of the validity of diagnoses of IBD within the GPRD [77] 92% of diagnoses recorded found to be accurate (the diagnoses of Crohn's disease (94% accurate) and UC (93% accurate) were noted to be more reliable than those for indeterminate IBD (80% accurate)).

3.4.6. Short duration of follow-up

The flip side of having contemporary data is that since there are no prospective records prior to 1987, no subject can have very prolonged follow up. In fact the situation is somewhat weaker even than this would suggest since the turnover of participating practices in addition to the mobility of the UK population has ensured that many subjects have even less follow up. This means that the power available for the following of incident case series is greatly limited.

3.4.7. Incomplete recording

One problem with the use of any routinely collected data (which is in effect what GPRD is) is that what is recorded is determined not by

the needs of the research, but by what is felt relevant to the primary purpose of the data recording. This means that recording is determined by the GP's assessment of what is relevant to the ongoing primary medical care of subjects. Hence not only is data incomplete, but it is likely that there is bias as to which data are missing. For example it is likely that a GP will record that a patient drinks heavily if they know this as it may adversely affect health, it perhaps less likely that they would record the knowledge that the patient was teetotal unless they suffered from a condition which might be attributable to alcohol.

Chapter 4. Antibiotic use and the risk of Crohn's disease.

4.1. Introduction

This chapter presents a study carried out in order to examine the hypothesis that antibiotic use is associated with the subsequent development of Crohn's disease without the potential for recall bias.

4.2. Methods

4.2.1. Subjects

All data used in this study were derived from a subset of the GPRD prepared for a different study (funded by the Department of the Environment, Transport and the Regions to investigate a possible relationship between exposure to Mycobacterium paratuberculosis via drinking water and Crohns disease).

The subset contained data from all subjects for whom a new diagnosis of Crohn's disease was recorded whilst they were contributing "up to standard" data to the GPRD. In addition, for each case two individually age and sex matched controls with no previous diagnosis of Crohn's disease or ulcerative colitis, were available.

Cases with five or more years of prospectively gathered data prior to first diagnosis of Crohn's disease were extracted. Cases for whom a diagnosis of ulcerative colitis had also been recorded were

discarded. The controls used here were a randomly selected sample of the full set of the controls who also had over five years of prospectively gathered data.

4.2.2. Overview of Exposures

Information on exposures extracted from the GPRD included age at index date (grouped in 20 year age bands), gender, smoking (classified as current smoking, non-smoking or unknown based upon the last relevant record in the dataset prior to the index date), and all drugs prescribed, and reason for consultations (usually a symptom or diagnosis) and the dates on which these occurred.

4.2.3. Symptoms

All events recorded as gastrointestinal (GI) infections, perianal sepsis, anaemia, irritable bowel syndrome (IBS), abdominal pain or diarrhoea were identified among cases using a combination of Oxmis and Read codes[78, 79] (Table IV-1Table IV-2Table IV-3Table IV-4Table IV-5). These are referred to hereafter as GI events. Each of these events was assigned to the six-month period in which it occurred working back from an index date which was the date of Crohn's disease diagnosis for cases and the date of the end of data for controls. (i.e. events were coded as occurring in the 1^{st}, 2^{nd}, 3^{rd} ---- n^{th} six-month period prior to the index date.) In order to assess whether symptoms were consistent with undiagnosed Crohn's

disease, the number of GI events for each subject during each six-month block was plotted (Figure 4-1). The figure shows an excess of events consistent with undiagnosed Crohn's disease among cases which was most marked in the last two years prior to diagnosis. Based on this finding we limited our primary analyses of antibiotic exposure to the period from the third to the fifth year prior to index date, to reduce the possibility that the antibiotic exposure followed the onset of any symptom or illness due to Crohn's disease. To further assess the possibility that any association between antibiotics and Crohn's disease might be due to prescriptions for the symptoms of undiagnosed Crohn's disease (i.e., of reverse causality) we divided cases and controls according to whether, during the studied period (the third to fifth year prior to diagnosis), they had any record of GI events, or had any drugs for GI disease prescribed (GI drugs).

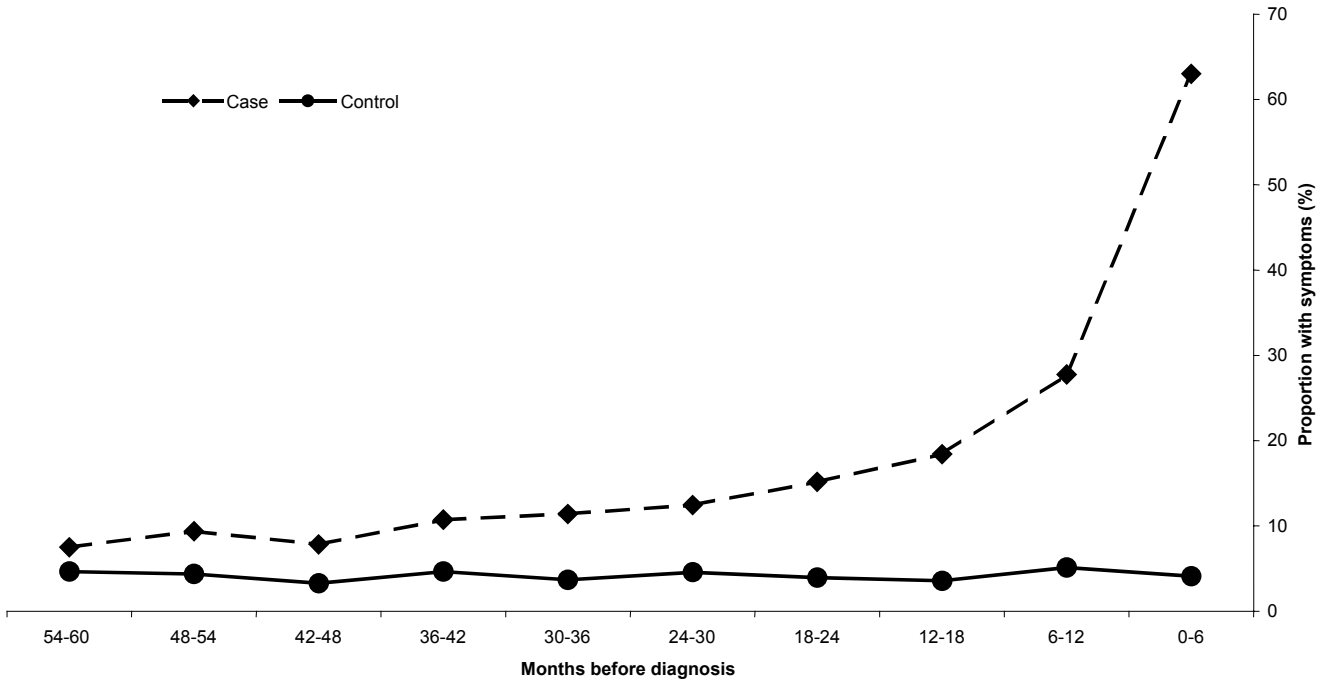

Figure 4-1 Symptoms consistent with undiagnosed Crohn's disease recorded before the index date.

The proportion of cases and controls with these symptoms is shown within 6 month periods prior to the index date.

4.2.4. Drugs

Drugs prescribed were classified according to sections of the British National Formulary (BNF), which groups drugs by indication and by pharmacological types. For example drugs used for infections are in chapter 5, antibacterials in section 5.1 and Penicillins in section 5.1.1. Prescriptions were assigned to six-month periods as described for symptoms and diagnoses above. In this way we counted the prescription of antibiotics both in total and in subgroups defined based upon the subheadings in BNF section 5.1. We also counted all prescriptions, prescriptions of drugs for gastrointestinal disease (BNF chapter 1) as GI drugs, oral contraceptive pills (BNF section 7.3.1 and 7.3.2)(previously described as associated with Crohn's disease[80, 81]), drugs used for cardiovascular disease (BNF chapter 2), and drugs for disorders of the central nervous system (BNF chapter 4) (as "control drugs", not expected to be associated with Crohn's).

4.2.5. Analyses

All analyses were conducted using Stata 7. We calculated odds ratios (OR) for developing Crohn's disease according to our main suspected exposure, usage of antibiotics 2 to 5 years before diagnosis, and other exposures. Logistic regression was used to assess exposures and to control for potential confounders, i.e. age, sex, and smoking. To correct for the effect of an individual's

tendency to receive prescriptions in general (rather than those specifically for antibiotics) we included within the regression analyses a measure of the prescription of other drugs, as the total number of prescriptions minus the number for antibiotics. This was coded into quartiles. These analyses were repeated for cases with GI symptoms and prescriptions in the 2 to 5 years before diagnosis (indicating possible undiagnosed Crohn's disease), and those subjects with no symptoms or GI drugs during that period. Additionally, separate estimates were made for different groups of antibiotics, and for the effect of receiving different numbers of antibiotics prescriptions. To assess whether any association was specific to antibiotics as opposed to other drug groups we repeated our analyses for oral contraceptive pills, drugs used for cardiovascular disease, and drugs for disorders of the central nervous system. Finally to assess the potential importance of any association found if it were causal we calculated the population attributable fraction (PAF) using appropriate methodology for multivariate analyses[82].

4.3. Results

4.3.1. Univariate analyses.

A total of 587 cases of Crohn's disease and 1460 controls were available for analysis. Cases had a median of 8.1 years of data available (range 5.1-11.6) of which 6.4 years (range 5.0-10.5) occurred before diagnosis. Controls had a median of 8.2 years of data (range 5.0-11.6). Cases and controls were of similar sex distribution (43% male for cases and 44% for controls), but cases were slightly older having a mean age at the index date 2.5 years greater than that of controls Table 4-1. A greater proportion of cases were recorded as being current smokers (28% versus 20%). Antibiotics were prescribed on at least one occasion between 2 and 5 years before the index date for 71% of cases and 58% of controls ($P<0.001$), and cases received on average a greater total number of antibiotic prescriptions (median 2 compared to 1 for controls).

Table 4-1 Age, gender, antibiotic use, date of entry to study and smoking in cases and controls.

	Case N = 587		Control N =1460		
	n (%)		n (%)		
Age					
0-20	79	*(13)*	76	*(5)*	
20-40	207	*(35)*	569	*(39)*	P<0.001
40-60	156	*(27)*	445	*(30)*	
60-80	145	*(25)*	370	*(25)*	
Median	41.64		43.76		P=0.003
Sex					
Male	253	*(43)*	642	*(44)*	P=0.7
Female	334	*(57)*	818	*(56)*	
Entry to study					
Median	1/10/90		1/03/90		P<0.001
Range	*1/06/87-23/08/93*		*1/06/87-8/10/93*		
Smoking					
Smoker	165	*(28)*	297	*(20)*	P=0.001
Non-smoker	291	*(50)*	796	*(55)*	
Unknown	131	*(22)*	367	*(25)*	
Antibiotic courses *					
At least one	418	*(71)*	843	*(58)*	P<0.001
Median	2		1		P<0.001

(P values derived by chi squared tests for categorical variables and by the Kruskal-Wallis Test for comparison of continuous variables.)

4.3.2. Multivariate analysis of the role of antibiotics

In the multiple logistic regression analysis of all cases, there were statistically significant associations between Crohn's disease and prescription of antibiotics 2 to 5 years before the index date (OR 1.32, 95%CI 1.05-1.65), other drugs (OR 1.54, 95% CI 1.38-1.70) and smoking (OR 1.55, 95%CI 1.22-1.98 compared to non-smokers) after adjusting for age and gender Table 4-2. Although gender and smoking were included in this model on an a-priori basis they did not appreciably confound the relationship between antibiotics and Crohn's disease (their omission from the model leaving the odds ratio for antibiotic use unchanged at 1.32). Restricting the analysis to the cases with no symptoms or GI drugs, suggestive of undiagnosed Crohn's disease between 2 and 5 years before diagnosis (252 cases and 1022 controls), the association with antibiotic prescriptions was slightly stronger (OR 1.53, 95%CI 1.12-2.07), and was weaker with other drugs prescribed (OR 1.19, 95%CI 1.03-1.08). Repetition of the analysis limited only to those coded as current smokers gave a slightly greater estimate of the effect of antibiotics. The confidence intervals for this estimate was wide however.

Table 4-2 Multivariate logistic regression models[1] of the association between antibiotic use and subsequent diagnosis of Crohns disease.

	Odds Ratio	95% CI
All subjects		
Smoker	1.55	1.22 to 1.98
Smoking status unknown	0.86	0.64 to 1.16
Drugs other than antibiotics[2]	1.54	1.38 to 1.70
Antibiotics[3]	1.32	1.05 to 1.65
Subjects without symptoms or GI drugs in 3rd to 5th yrs pre diagnosis		
Smoker	1.55	1.08 to 2.20
Smoking status unknown	0.79	0.52 to 1.18
Drugs other than antibiotics	1.19	1.03 to 1.38
Antibiotics	1.53	1.12 to 2.07
Analysis limited to current smokers only		
Drugs other than antibiotics[2]	1.48	1.21 to 1.81
Antibiotics[3]	1.70	1.08 to 2.70

[1]All models include age and sex as co-factors in addition to those listed.

[2]Drugs other than antibiotics represents prescriptions for all other drugs with the exception of antibiotics, and the odds ratio is for moving from one quartile of prescription density to the next.

[3]For antibiotics the odds ratio is for a comparison of any prescription for that group against none.

4.3.3. Examination of specificity between antibiotic groups

Examination of the associations between Crohn's and different groups of antibiotics and with differing levels of exposure gave odds ratios ranging between 0.95 and 1.71 (Table 4-3). For two groups the odds ratio was significantly greater than one (tetracyclines (OR 1.33, 95%CI 1.01-1.77) and metronidazole and tinidazole (OR 1.71, 95%CI 1.05-2.76)). Restriction of the analysis to subjects who had had no symptoms suggestive of undiagnosed Crohn's disease and no prescriptions for GI drugs recorded between 2 and 5 years before the index date rendered the association with metronidazole and tinidazole non-significant (OR 1.08, 95%CI 0.39-2.99), although the association with tetracycline strengthened (Table 4-4).

Group	Number exposed (%)		OR	95% CI		
	Cases = 587	Controls = 1460				
Ben pen, penicillinase resistant pens	128 (22)	286 (20)	0.94	0.74	to	1.21
Broad spectrum and anti pseudomonal penicillins	271 (46)	531 (36)	1.10	0.90	to	1.36
Cephalosporins	91 (16)	153 (10)	1.18	0.88	to	1.58
Tetracyclines	98 (17)	172 (12)	1.34	1.01	to	1.77
Macrolides	87 (15)	188 (13)	0.96	0.72	to	1.27
Sulphonamides and Trimethoprim	87 (15)	160 (11)	1.16	0.86	to	1.57
Metronidazole and tinidazole	33 (6)	45 (3)	1.70	1.05	to	2.75
Quinolones	31 (5)	55 (4)	1.15	0.72	to	1.83
Others	8 (1)	17 (1)	1.09	0.46	to	2.57

Table 4-3 The effect of different groups of antibiotics in all subjects.

(All ORs are corrected for age, sex, smoking and prescriptions of all non-antibacterial drugs)

Group	Number exposed		OR	95% CI		
	Cases =252	Controls= 1022				
Ben pen, penicillinase resistant pens	47 (19)	169 (17)	0.93	0.64	to	1.36
Broad spectrum and anti pseudomonal penicillins	96 (38)	317 (31)	1.04	0.77	to	1.42
Cephalosporins	29 (12)	78 (8)	1.30	0.81	to	2.09
Tetracyclines	36 (14)	91 (9)	1.72	1.12	to	2.64
Macrolides	32 (13)	95 (9)	1.12	0.71	to	1.75
Sulphonamides and Trimethoprim	21 (8)	68 (7)	1.21	0.71	to	2.05
Metronidazole and tinidazole	5 (2)	19 (2)	1.08	0.39	to	2.99
Quinolones	4 (2)	19 (2)	0.67	0.22	to	2.03
Others	2 (1)	5 (0)	1.66	0.31	to	8.76

Table 4-4 The effect of different groups of antibiotics in subjects with no symptoms or GI drugs.

(Symptoms suggestive of undiagnosed Crohn's disease or prescriptions for GI drugs between 2 and 5 years before the index date.)

4.3.4. Examination for a dose response relationship

There was also no evidence of a dose response relationship between frequency of any antibiotic prescription and Crohn's disease, with similar ORs for 1, 2 to 5, or more than 5 courses between 2 and 5 years prior to the index date (Table 4-5).

	Number courses	Number exposed					
		Cases (N=252)	Controls (N=1022)	OR	95% CI		
All antibiotics	1	62	192	1.57	1.07	to	2.29
	2 to 5	81	258	1.50	1.05	to	2.14
	Over 5	20	50	1.51	0.82	to	2.78

Table 4-5 Adjusted odds ratios for the relationships between different numbers of courses of antibiotics and Crohn's disease in subjects with no symptoms or GI drugs.

4.3.5. Examination of specificity to antibiotics.

When our analysis was repeated to examine drug groups other than antibiotics, we found similar associations between other drugs and Crohn's disease (Table 4-6). Among all cases the odds ratios of 1.34 (1.08-1.66), 1.25 (0.95-1.66) and 1.48 (1.00-2.17) were found respectively for neurological drugs, cardiovascular drugs and oral contraceptives in multivariate analyses analogous to those presented in Table 4-2. These associations however did not remain significant in the subset analysis looking at subjects without possible symptoms of Crohn's disease or GI drugs (Table 4-7).

Group	All subjects					
	Number exposed		OR	95% CI		
	Cases (N=587)	Controls (N=1460)				
Antibacterials	418	843	1.32	1.05	to	1.65
Drugs for cardiovascular disease	127	260	1.26	0.95	to	1.66
Drugs for nervous system disease	275	520	1.34	1.08	to	1.66
Oral contraceptive pills	94	198	1.48	1.00	to	2.17

Table 4-6 Multivariate regression models of different drug groups in all subjects.

	All subjects					
Group	Number exposed		OR	95% CI		
	Cases (N=252)	Controls (N=1022)				
Antibacterials	163	500	1.53	1.12	to	2.07
Drugs for cardiovascular disease	41	139	1.49	0.97	to	2.29
Drugs for nervous system disease	70	274	0.93	0.67	to	1.29
Oral contraceptive pills	37	121	1.42	0.81	to	2.47

Table 4-7 Multivariate regression models of different drug groups in subjects with no symptoms or GI drugs.

4.3.6. Attributable risk

Based on the observed OR of 1.32 for any antibiotic exposure and the observed 81% of the cases using antibiotics over the period between 2 and 5 years prior to diagnosis the calculated PAF was 17%. The equivalent figure for current smoking was 10%.

4.4. Discussion

This study is the first to examine in detail antibiotic use as a risk factor for Crohn's disease and the first to examine it in adults. It provides evidence of an association between antibiotic use and the subsequent diagnosis of Crohn's disease. A variety of factors suggest that this association is real but a lack of specificity suggests that its causality is uncertain. The study also throws some light upon the previously described association between Crohn's disease and the use of the oral contraceptive pill since although we have replicated this result similar questions are raised as to whether this association is causal.

The use of the GPRD to carry out this study confers a number of benefits. Firstly unlike the two previous studies in which antibiotic use was ascertained after the diagnosis of Crohn's disease[33, 34], this study utilizes data on antibiotic use which was collected before the diagnosis was made. This establishes clearly that the associations found in previous studies are unlikely to have resulted solely from bias with respect to recall of antibiotic use. Recall bias cannot explain any of the associations found in this study. In addition the use of a complete cohort of eligible patients from a large, representative database, and an appropriate group of controls makes selection bias unlikely.

So if the association was not the result of bias, could it be due to confounding? There are few known risk factors for Crohn's disease, with age, sex, smoking and family history being the most important. Of these we have data on all but family history and have therefore been able to construct a multivariate model correcting for the effects of age, sex and smoking. We have been unable to adjust for possible confounding by family history although for this to be a confounder it would need to be associated with antibiotic use, which seems unlikely. The data available on smoking are incomplete and it is possible that some confounding remains. However as the effect of adjusting for smoking classified as smoker/non-smoker was so small it seems highly unlikely that the associations demonstrated are explained by residual confounding by smoking. As well as being incomplete the smoking data within GPRD is likely to suffer from some degree of misclassification. There is reason to believe that some ex-smokers are coded as non-smokers in GPRD, but that current smokers may be more accurately coded[73]. For this reason we conducted an analysis limited to current smokers as a further check for confounding by smoking status. The results of this analysis showed that the association we report remained present in this subgroup with the point estimate for the Odds ratio being slightly greater. The small numbers of subjects involved however led to a lack of precision in this estimate.

We considered two other potential artifacts: reverse causation and a possible “tendency to receive prescriptions”. A challenge for any study examining the aetiology of a chronic disease is to define date of onset accurately, and hence to establish whether exposures preceded the onset of symptoms. This is necessary to exclude reverse causation, the situation when an exposure is in fact a response to symptoms of the still undiagnosed disease. Although the date of diagnosis of inflammatory bowel diseases has been validated within GPRD and found to be accurate to within a few weeks [77], it is likely that for a proportion of patients the time between onset of symptoms and diagnosis can be long, as shown by the analysis in Figure 4-1. Also the age distribution of our cases is rather older than would be expected of inident cases of Crohn’s disease. Although this might be explained by the catchment population for GPRD having an age distribution different to the UK population, the possibility must be considered that a proportion of these cases might not truly be incident. Thus it remains possible that the association seen may at least in part be due to antibiotics prescribed as treatment for the symptoms of undiagnosed Crohn's disease or of Crohn’s disease which has been previously diagnosed but not recorded in the GPRD record. We corrected for this by *firstly* excluding from our multivariate analyses the two year period before diagnosis in which symptoms were common; and *secondly* by repeating all analyses in the subgroup of cases with no gastrointestinal symptoms or prescription of gastrointestinal drugs

within the period from 2-5 years prior to diagnosis. The fact that the association between antibiotics and Crohn's disease remains, and is of the same magnitude in the subgroup analysis, gives some evidence against the association being a result of reverse causation.

To try to correct for the tendency of subjects to receive prescriptions we explored whether the association between diagnosis of Crohn's disease and prescription of antibiotics was specific in three ways. Firstly we examined whether the association was limited to specific groups of antibiotics. Although the power available for this analysis was limited, we were unable to demonstrate a clear specificity with any antibiotic group since although only tetracyclines were found to have a significant odds ratio as a subgroup, the confidence interval for this odds ratio overlapped those of all other groups. Secondly we examined whether the association was specific to antibiotics as opposed to other drug groups. We found an association similar to that for antibiotics with the oral contraceptive pill (this association is of similar magnitude to that previously described [80, 81]), but also found similar associations with cardiovascular and neurological drug prescribing. In each of these cases the association was close to the same magnitude but statistically non-significant (in contrast to the significant association with antibiotic use). This to some extent reflects the frequency of antibiotic use and hence the greater power to find associations for this drug group. Finally we included in the multivariate model as a factor the number of prescriptions for drugs

other than antibiotics, and from this there was evidence of some degree of confounding: the association between antibiotic use and Crohn's decreased from 1.56 to 1.32 when prescriptions for other drugs were included in the model. This adjustment however did not remove all of the association between antibiotic use and the subsequent diagnosis of Crohn's disease.

Both the lack of specificity and the lack of a dose response relationship provide some evidence that the association between Crohn's disease and prior antibiotic use may not be causal. This begs the question of what alternative explanations there might be. Clearly it is possible that despite our best efforts to exclude reverse causality our findings might be explained if Crohn's disease does indeed have a longer than generally recognised prodrome, which presents non-specifically to clinicians and hence causes a wide variety of prescriptions. Equally it may be that only a proportion of cases of Crohn's disease are diagnosed, and that the probability of being diagnosed is related to the degree of contact the sufferer has with medical services (and hence the number of prescriptions which they receive). Finally it is possible that some prescribed drug does indeed have a causal relationship with Crohn's disease, and that since the prescription of one drug is associated with the prescription of others the association we have seen with each drug group is in effect a proxy for the association with this causally related drug.

Although caution needs to be exercised before accepting the hypothesis that there is a causal association between antibiotic use and Crohn's disease it is equally important to guard against the premature rejection of the hypothesis. Despite its advantages the dataset we have used for this study has allowed us only to examine the effect of recent use of antibiotics. There were very few subjects for whom much more than 5 years of data prior to diagnosis were available, and almost none with complete data from birth to diagnosis. We were therefore unable to examine the possibility that a greater and perhaps more specific effect would be seen from antibiotic use extending over a longer or earlier period or at a particular period of life. One potentially important period would be early childhood to which the previous studies of this association relate[33, 34].

As a by-product of this study we have been able to examine the relationship between Crohn's disease and prior use of oral contraceptives. This is an exposure which has been claimed to exert a causal influence on Crohn's Disease[80, 83, 84]. The evidence to support this from several previous studies is far from entirely supportive of this contention however. Firstly those studies previously carried out have had quite varied results reporting odds ratios from 0.7 to 2.5[14]. A selective meta-analysis gave a pooled OR corrected for confounding by smoking of 1.44 (1.12-1.86) [14]. There has also been evidence to suggest that there is no dose response in

this relationship[14, 80], that it is not reversible[85], and that unlike the relationship with smoking it is not specific to Crohn's disease but is found with ulcerative colitis also[80, 83]. The published studies have in general like previous antibiotic studies been based upon patient recall of exposure and hence liable to recall bias, and none have looked as we have at exposure to other drugs. Our finding of an OR of 1.48 in our corrected model for oral contraceptive use is consistent with previous findings, but the lack of specificity that we have shown is yet one further factor which casts doubt on its causality in our study and in the previous studies.

In conclusion we have demonstrated a significant association between antibiotic use and diagnosis of Crohn's disease 2 to 5 years later in prospectively collected data. That we have not demonstrated a specific association does not disprove the hypothesis that antibiotics can contribute to the causation of Crohn's. In view of the potential importance of the association with antibiotics (that if causal it might account for 17% of Crohn's disease), and the possibility that the time period available for study may not be the most appropriate further study of this question is clearly required.

Chapter 5. The dataset used for subsequent chapters

5.1. Introduction

This chapter will briefly describe the selection of the cohorts of subjects used in the subsequently described studies ("Mortality in Inflammatory Bowel Disease" and "The risk of fracture in patients with IBD"). It will then go on to detail those aspects of the data abstraction and analysis common to both studies as well as giving descriptive statistics of the cohorts. For the sake of brevity full code lists are in general not included within this or subsequent chapters but in Appendix IV. Since the purpose of this chapter is merely to set out those elements of the two subsequent studies that are common the results presented are not discussed here.

5.2. Selection of subjects

5.2.1. Criteria for selection of cases

The object in selecting this cohort was to permit studies of the impact of IBD generalisable to contemporary clinical practice in the UK. For this reason the only criterion applied for the selection of IBD cases was that they should have a coded diagnosis of Inflammatory bowel disease at least once in up to standard data. This criterion has been previously validated as defining IBD cases with a validity of 94% for CD 94% for UC and 80% for indeterminate IBD as judged against a gold standard of the diagnosis of the condition being made

based upon barium radiology, endoscopic examination, the opinion of a gastroenterologist or a combination of these [77]. Our list of codes to define cases was similar to that used in this validation study (Table 5-1, Table 5-2, Table 5-3). Hereafter the date of the first coded episode of IBD for each case is referred to as their index date.

Code	Description
0092LR	Regional Iletis
5630C	Regional Colitis
5630CR	Crohn's Disease
5630ER	Enteritis Regional
J08z900	Orofacial Crohn's Disease
J40..00	Regional Enteritis - Crohn's Disease
J40..11	Crohn's Disease
J400.00	Regional Enteritis Of The Small Bowel
J400000	Regional Enteritis Of The Duodenum
J400100	Regional Enteritis Of The Jejunum
J400200	Crohn's Disease Of The Terminal Ileum
J400300	Crohn's Disease Of The Ileum Unspecified
J400400	Crohn's Disease Of The Ileum Nos
J400z00	Crohn's Disease Of The Small Bowel Nos
J401.00	Regional Enteritis Of The Large Bowel
J401000	Regional Enteritis Of The Colon
J401100	Regional Enteritis Of The Rectum
J401z00	Crohn's Disease Of The Large Bowel Nos
J401z11	Crohn's Colitis
J402.00	Regional Ileocolitis
J40z.00	Regional Enteritis Nos
Jyu4000	[X]Other Crohn's Disease
N031100	Arthropathy In Crohn's Disease
N045300	Juvenile Arthritis In Crohn's Disease

Table 5-1 Codes used to define Crohn’s disease

Code	Description
5631	Ulcerative Colitis
14C4.11	H/O: Ulcerative Colitis
J41..12	Ulcerative Colitis And/Or Proctitis
J410.00	Ulcerative Proctocolitis
J410100	Ulcerative Colitis
J410200	Ulcerative Rectosigmoiditis
J410300	Ulcerative Proctitis
J410z00	Ulcerative Proctocolitis Nos
Jyu4100	[X]Other Ulcerative Colitis
N031000	Arthropathy In Ulcerative Colitis
N045400	Juvenile Arthritis In Ulcerative Colitis

Table 5-2 Codes used to define Ulcerative colitis

Code	Description
92N	Inflammatory Bowel Disease
J4...12	Inflammatory Bowel Disease
J41z.00	Idiopathic Proctocolitis Nos

Table 5-3 Codes used to define indeterminate IBD

5.2.2. Criteria for selection of controls

Controls were matched and chosen by the following criteria

- Same sex as their matched case.
- Age within 5 years of the case.
- Registered at the same General practice as the case.
- Alive and contributing data to GPRD on the index date of the case (the date of the first coded episode of IBD in up to standard data). (This date hence is also the index date for the control hereafter.)
- No record of IBD at any time in their GPRD record.

Among those meeting these criteria 5 were chosen randomly (or all were taken if 5 or less were available).

5.3. Importation of data and basic error checking of selection.

All data manipulation and analysis within for these studies were conducted in Stata 7 SE (Stata Corporation, 4905 Lakeway Drive, College Station, Texas 77845, USA). On importation to this program it was found that some dates did not fit the correct data format having only year indicated, these were dealt with by ascribing a date of 1st July of the indicated year. Cases and controls were checked to ensure that no subjects belonged to both sets. Further error checking and exclusions were carried out when extracting specific data. Data entered more than once identically were counted

only once when extracting data, and impossible data (such as events or prescriptions prior to birth or after death) were ignored.

5.4. Basic data extracted

5.4.1. Defining subtypes of IBD

IBD type was classified based on the codes listed above. Where a subject had codes related to only one form of IBD they were considered to have this form of disease. Subjects were classified as having *indeterminate* IBD if they had codes for both UC and CD, as having UC if codes both for non-specific IBD and UC were present and as having CD if codes for both this and for non-specific IBD were found.

5.4.2. Diagnosis date of IBD

The diagnosis date of IBD was defined as being the earliest event date for an episode coded with any of the IBD codes listed above. Each control was assigned a pseudo-diagnosis date identical to the diagnosis date of their case.

5.4.3. Incident and prevalent cases

Subjects having a diagnosis of IBD coded as occurring first at least two years after their collection of prospective data in GPRD began were considered to be incident cases. All other subjects were considered prevalent.

5.4.4. Age and sex

Since sex and date of birth are both recorded for all GPRD subjects directly, it was necessary to determine only the point in time at which age should be measured in order to define these data. For the purposes of the studies presented below age when used as a covariate in analyses is defined as the age at the index date for each subject.

5.4.5. Smoking

Subjects' smoking status was classified based upon the coding during up to standard data in both the medical and prevention tables of GPRD as unknown, never a smoker, ex smoker or current smoker. Where smoking was referred to by Oxmis or Read codes this coding of behaviour was based upon the codes listed in Table IV-6, and where it was referred to as a number of cigarettes smoked in the prevention table subjects smoking 1 or more were considered smokers and those smoking none non-smokers. Subjects who appeared in more than one of these categories at differing times were coded in the category suggesting greatest smoking experience.

5.4.6. BMI

All data coding height and weight during up to standard data recording were identified from the prevention table. Since BMI is a measure of questionable validity in children data recorded when subjects were aged under 18 was ignored. Inspection of the data showed large numbers of outliers that recorded impossible or highly unlikely figures (weights or heights of zero for example as well as heights of as much as 4 metres). Records of height over 2.5 metres or under 1 metre were therefore ignored as being probable errors as well as records coding a weight under 30kg. In each of these cases the excluded data were mostly at least an order of magnitude different to these limits which since data are entered as 1000 times the weight in kilos or the height in metres might suggest that an incorrect number of zeros had been entered. BMI was calculated as the median of an individuals weight records in kg divided by the square of the median of their height records in metres.

5.4.7. Systolic Blood Pressure

Systolic blood pressure is recorded in the prevention table of GPRD and was extracted directly from this source. As for height and weight some very unlikely values were found in the data. Values above 300mm of Hg or below 50 were therefore ignored as being likely to be either errors or indicative of current acute ill health (as opposed to being a long term indicator of risk for future ill health). The final

blood pressure value used in analyses is the median of all recorded values for a subject during the up to standard data recording period.

5.5. Results of basic data extraction

5.5.1. Numbers in the cohorts

In total there were 16,550 people with IBD and 82,917 appropriately matched controls. Within the IBD cohort 5,960 (36%) people had Crohn's disease, 8,301 (50%) had ulcerative colitis and 2,289 (14%)had *indeterminate* IBD. Table 5-4

5.5.2. Age and sex

The average age at entry to the study was 46 years for both IBD cases and controls, and 46% of each cohort were male. Table 5-4

5.5.3. Incident and prevalent status

Among the IBD cases 5631 (34%) were incident, and 10919 (66%) were prevalent. The age at diagnosis was lower among the prevalent cases with a mean of 40 years compared to 47 years in incident cases. Table 5-4

IBDtype		All IBD		UC		Crohns		indeterminate	
		case	control	Case	control	case	control	case	control
Number	N	16551	82917	8301	41589	5961	29843	2289	11485
Female	%	53.6	53.7	48.9	48.9	58.7	58.8	57.2	57.3
Male	%	46.4	46.3	51.1	51.1	41.3	41.2	42.8	42.7
Age at entry									
under 20	%	5.4	5.4	3.2	3.2	8.2	8.2	5.9	5.9
20-39	%	38.7	38.6	34.4	34.3	44.5	44.4	39.3	39.0
40-59	%	32.2	32.1	35.4	35.3	28.2	28.2	30.8	30.5
60-79	%	19.8	20.0	22.8	23.0	15.7	15.9	19.8	20.0
80 or over	%	3.9	4.0	4.1	4.3	3.3	3.4	4.3	4.6
Mean		46.2	46.3	48.6	48.7	42.8	42.9	46.1	46.3
SE		0.1	0.1	0.2	0.1	0.2	0.1	0.4	0.2
% incident		34		33		31		46	
mean age at diagnosis		47.3		50.0		43.0		47.5	
% prevalent		66		67		69		54	
mean age at diagnosis		39.7		41.8		36.6		41.1	

Table 5-4 Demographic details of cases and controls subdivided by disease type

5.5.4. Smoking

Smoking was more common amongst Crohn's cases than among the control cohort (28% smokers versus 21% of their matched controls) and less common among UC cases (12% versus 20%), *indeterminate* cases had intermediate levels of smoking (22% versus 21%). There was less missing data for cases. These results are summarised in Table 5-5.

5.5.5. BMI

The IBD cohort had a slightly lower BMI than did controls. Overall the mean of their BMIs was 24.72 as opposed to 25.48 for the control cohort, and they were more likely to have a BMI under 25 (36% versus 29%) Table 5-6. These differences were most marked among the Crohn's cases for whom the comparison between mean BMIs was 24.02 for cases versus 25.25 for controls. Likewise between the Crohn's cases and their controls their was a greater disparity between the proportions of low or high BMI with 40% of the Crohn's cases having a BMI below 25 compared to 29% of their controls. Again there was less missing data for cases.

		Case		Control	
		Number	%	Number	%
ALL IBD	never smoker	477	3	2189	3
	non smoker	6983	42	30680	37
	ex smoker	887	5	3289	4
	current smoker	3209	19	17110	21
	Unknown	4995	30	29649	36
UC	never smoker	259	3	1094	3
	non smoker	3945	48	15511	37
	ex smoker	541	7	1770	4
	current smoker	1027	12	8442	20
	Unknown	2529	31	14772	36
CD	never smoker	144	2	773	3
	non smoker	2107	35	10888	37
	ex smoker	226	4	1051	4
	current smoker	1682	28	6265	21
	Unknown	1802	30	10866	36
Indeterminate	never smoker	74	3	322	3
	non smoker	931	41	4281	37
	ex smoker	120	5	468	4
	current smoker	500	22	2403	21
	Unknown	664	29	4011	35

Table 5-5 Smoking behaviour by IBD type and case status

	BMI	Case		Control	
		Number	%	Number	%
ALL IBD	<19	544	3	1570	2
	19-24	5454	33	21948	26
	25-29	2990	18	15371	19
	30-34	848	5	4657	6
	>35	263	2	1657	2
	Unknown	6452	39	37714	45
	Mean (SE)	24.72	0.04	25.48	0.02
UC	<19	167	2	698	2
	19-24	2626	32	10722	26
	25-29	1703	21	8263	20
	30-34	490	6	2395	6
	>35	147	2	838	2
	Unknown	3168	38	18673	45
	Mean (SE)	25.22	0.06	25.63	0.03
CD	<19	301	5	647	2
	19-24	2067	35	8124	27
	25-29	863	14	4952	17
	30-34	236	4	1595	5
	>35	87	1	580	2
	Unknown	2407	40	13945	47
	Mean (SE)	24.02	0.03	25.25	0.04
Indeterminate	<19	76	3	225	2
	19-24	761	33	3102	27
	25-29	424	19	2156	19
	30-34	122	5	667	6
	>35	29	1	239	2
	Unknown	877	38	5096	44
	Mean (SE)	24.69	0.12	25.49	0.06

Table 5-6 Body mass index by case status and IBD type.

5.5.6. Blood Pressure

The recorded blood pressures of the IBD cohort were lower than those of controls with a mean systolic BP of 130 for cases and 133 for controls. The difference in mean values between cases and controls was similar for each IBD type, but the difference in the proportion of cases and controls with a systolic BP below 120 was greater for Crohn's disease.

		Case		Control	
		Number	%	Number	%
ALL IBD	Under 100	239	1	710	1
	100-119	3250	20	12914	16
	120-139	4885	30	22335	27
	140-159	2979	18	14702	18
	over 160	1293	8	7402	9
	Unknown	3905	24	24854	30
	Mean (SE)	130	(0.18)	133	(0.08)
UC	under 100	82	1	328	1
	100-119	1346	16	5665	14
	120-139	2552	31	11158	27
	140-159	1728	21	8159	20
	over 160	718	9	4155	10
	Unknown	1875	23	12124	29
	Mean (SE)	132	(0.24)	134	(0.12)
CD	under 100	127	2	283	1
	100-119	1402	24	5346	18
	120-139	1649	28	7994	27
	140-159	854	14	4533	15
	over 160	392	7	2200	7
	Unknown	1537	26	9487	32
	Mean (SE)	127	(0.30)	130	(0.14)
Indeterminate	under 100	30	1	99	1
	100-119	502	22	1903	17
	120-139	684	30	3183	28
	140-159	397	17	2010	18
	over 160	183	8	1047	9
	Unknown	493	22	3243	28
	Mean (SE)	129	(0.46)	132	(0.22)

Table 5-7 Systolic blood pressure by case status and IBD type.

Chapter 6. Mortality in Inflammatory Bowel Disease

6.1. Introduction

This chapter presents a study of the mortality associated with IBD that uses the GPRD cohorts described in Chapter 5.

6.2. Methods

6.2.1. Identifying deaths.

For each subject we used a combination of Oxmis and Read coding (Table IV-7) and the subject's registration status within GPRD to assess whether they had died. Where a subject was multiply recorded as having died we used the earliest recorded date to define the date of death.

6.2.2. Co morbidity measures

To allow adjustment for the effect of co-morbidities we used two approaches. Firstly we used the Charlson index [86] (Table 6-1) as a composite measure of co-morbidity for use as a confounder in multivariate analyses. For this subjects were scored based upon co morbidities coded prior to entry to the study before calculation of the score. Secondly we formed "healthy" cohorts both of IBD cases and controls by excluding subjects with ischaemic heart disease, heart failure, hypertension, COPD, asthma, renal disease, any malignancy and diabetes. The presence of these conditions was assessed using

a combination of Oxmis and Read codes, with analysis again limited to disease recorded before entry to the study. (The codes used for this analysis were identical to those used for the relevant co morbidities in the Charlson index with the exception of hypertension codes for which are given in Table IV-28). We then carried out analyses in these restricted cohorts. As well as stratifying for co-morbidity these cohorts approximately illustrate the risks of subjects not loaded for life insurance for reasons other than IBD.

Score	Condition
1	Myocardial infarct Congestive heart failure Peripheral vascular disease Cerebrovascular disease Dementia Chronic pulmonary disease Connective tissue disease Ulcer disease Mild liver disease Diabetes
2	Hemiplegia Moderate or severe renal disease Diabetes with end organ damage Any tumour Leukaemia Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumour AIDS

Table 6-1 The Charlson index

A subject gains the score of each of the conditions listed from which he/she suffers. The overall score is the sum of all of these individual comorbidity scores.

(Codes used for this scoring are given in Table IV-8 to Table IV-26.)

6.2.3. Univariate analysis

Univariate analysis of mortality using the matched cohort design was conducted by the production of crude mortality rates (for which 95% confidence intervals were calculated based upon the Poisson distribution), survival plots and log rank tests. In each case the origin of the time axis and the entry of the subject to the study were both set as the date of the first prospectively recorded IBD code (the matched case's relevant date was used for controls). Additionally life tables were created based upon the crude mortality rates calculated to allow the comparison of life expectancy for cases and controls. Finally as a check upon the likely validity of the GPRD database for studies of this sort we calculated standardised mortality ratios (standardised to annual age and sex specific national mortality figures for England and Wales), for both cases and controls. Because national statistics were available only until 1999 it was necessary to truncate the data at that point.

6.2.4. Multivariate analysis

Multivariate analyses were conducted using a Cox regression model, and the validity of the assumption of proportional hazards was assessed using Log Log plots. As age, sex, and smoking are all known to be associated with both the risk of IBD and the risk of death they were all included within our models on an a priori basis. Other potential confounding factors added to this base model were retained only if they resulted in a 10% or greater change in the hazard ratio. For BMI, and blood pressure as for smoking the confounding variable was included in the analysis as a categorical variable with a category representing missing data. The multivariate analyses were repeated stratifying both for disease type and age group at entry. Tests for interaction by these groups were carried out. In addition restriction analyses were carried out to examine the risks among incident cases of IBD, prevalent cases and those with a recorded date of first diagnosis at least five years prior to entry to the study (i.e. prevalent cases with at least a five year history). A further restriction analysis was carried out after exclusion of all subjects with the chronic diseases specified above.

To check the robustness of our results we attempted to increase diagnostic specificity by limiting our analyses to cases with at least two episodes coded as IBD. To examine the reliability of death recording within GPRD and the possibility of bias within it (due to the possibility that controls may be more likely to move away without their GP knowing, and therefore more likely to die without it being

recorded) we repeated the analysis excluding all subjects with no recorded medical data dated within the last year of their data. Since a diagnosis is more likely to be recorded at a time when it is causing ill health (even if it is a longstanding condition) we examined the effect of censoring data for one or two years from the date of entry to the study. Lastly to investigate whether misclassification of ex-smokers as non-smokers may have affected our results we carried out an analysis limited to current smokers.

All analyses were conducted using Stata version 7.

6.3. Results

6.3.1. Univariate analysis of mortality

The IBD cohort contributed 61,215 years of follow up and 1,047 deaths and controls 306,183 years of follow up and 3,758 deaths. These corresponded to crude mortality rates of 17.1 per thousand person years for cases and 12.3 per thousand patient years for controls (Table 6-2).

	Deaths	Follow up	Mortality Rate	95% CI	Rate difference
Case	1047	61.2	17.1	16 18	
Control	3758	306.2	12.3	12 13	4.8

Table 6-2 Crude mortality rates for all cases and all controls. (Follow up is quoted as thousands of person years: Mortality rate and Rate difference are quoted per 10^3 person years)

A breakdown of deaths, follow up available and crude rates by disease and age at entry to the study are given in Table 6-4. The absolute mortality rate difference between cases and controls was higher in the older age groups (rate differences in the over 80s of 39.2 deaths per 1000 person years for UC and 55.9 deaths per thousand person years for Crohn's disease) than among the young (rate differences in the under 20s of 0.5 deaths per 1000 person years for UC and 1.0 death per thousand person years for Crohn's

disease). Overall the mortality rate difference was higher for Crohn's disease (6.2 deaths per 1000 person years) than for UC (3.7 deaths per 1000 person years) or indeterminate IBD (5.3 deaths per 1000 person years). These small excesses of mortality are shown graphically by Kaplan Meier plots in Figure 6-1, Figure 6-2, Figure 6-3 and Figure 6-4. Expressing these results as hazard ratios via a univariate Cox regression model showed hazard ratios of 1.39 for all IBD, 1.27 for UC, 1.62 for CD, and 1.40 for indeterminate IBD (Table 6-3).

	HR	95 % confidence interval
All IBD	1.39	1.30 to 1.49
UC	1.27	1.16 to 1.40
CD	1.62	1.44 to 1.83
Indeterminate IBD	1.40	1.17 to 1.66

Table 6-3 Univariate Cox regression models

		Case					Control					
IBD type	Age group	Deaths	Follow up (/10^3 years)	Mortality Rate	95% CI		Deaths	Follow up (/10^3 years)	Mortality Rate	95% CI		Rate difference /10^3 person yrs
UC	under 20	0	0.9	0.0	.	.	0	4.3	0.0	.	.	0.0
	20-39	15	10.6	1.4	0.9	2.4	46	51.3	0.9	0.7	1.2	0.5
	40-59	95	12.0	7.9	6.5	9.7	297	59.1	5.0	4.5	5.6	2.9
	60-79	290	6.8	42.6	38.0	47.8	1167	35.3	33.0	31.2	35.0	9.6
	80 or over	136	0.8	161.8	136.8	191.4	586	4.8	122.6	113.1	132.9	39.2
	Total	536	31.1	17.3	15.9	18.8	2096	154.8	13.5	13.0	14.1	3.7
Crohn's	under 20	2	1.6	1.2	0.3	4.9	2	8.0	0.3	0.1	1.0	1.0
	20-39	22	9.4	2.3	1.5	3.6	27	46.2	0.6	0.4	0.9	1.8
	40-59	58	6.6	8.7	6.8	11.3	163	33.3	4.9	4.2	5.7	3.8
	60-79	187	3.4	55.1	47.7	63.6	591	18.6	31.8	29.3	34.5	23.3
	80 or over	82	0.5	160.0	128.8	198.6	312	3.0	104.0	93.1	116.3	55.9
	Total	351	21.6	16.3	14.6	18.0	1095	109.2	10.0	9.5	10.6	6.2
Indeterminate	under 20	0	0.5	0.0	.	.	1	2.5	0.4	0.1	2.8	-0.4
	20-39	4	3.4	1.2	0.5	3.2	16	15.9	1.0	0.6	1.6	0.2
	40-59	28	2.8	10.2	7.0	14.7	59	13.8	4.3	3.3	5.5	5.9
	60-79	87	1.7	51.5	41.7	63.6	316	8.6	36.7	32.8	40.9	14.9
	80 or over	41	0.2	198.9	146.5	270.1	175	1.4	129.6	111.7	150.3	69.3
	Total	160	8.5	18.8	16.1	21.9	567	42.2	13.5	12.4	14.6	5.3

Table 6-4 Deaths, follow up time, crude mortality rates and rate differences between cases and controls by IBD type and age band.

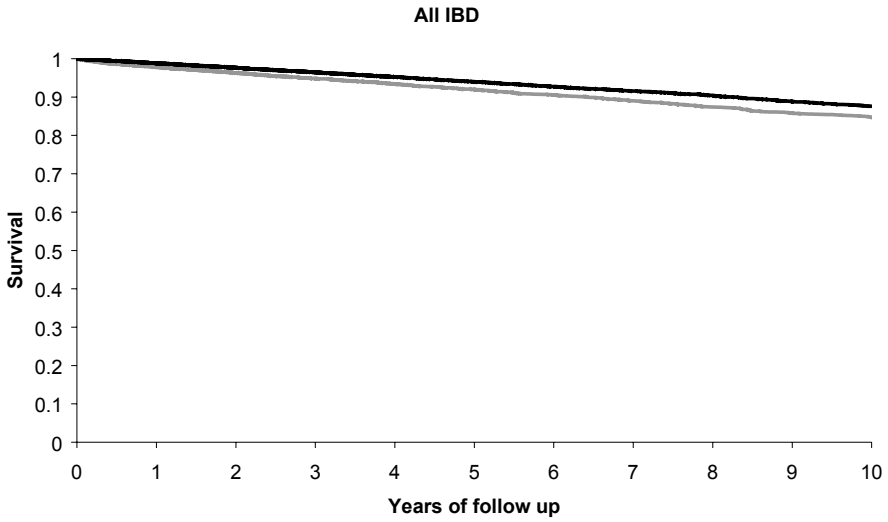

Figure 6-1 Kaplan Meier plot of all cause mortality for all IBD patients versus controls

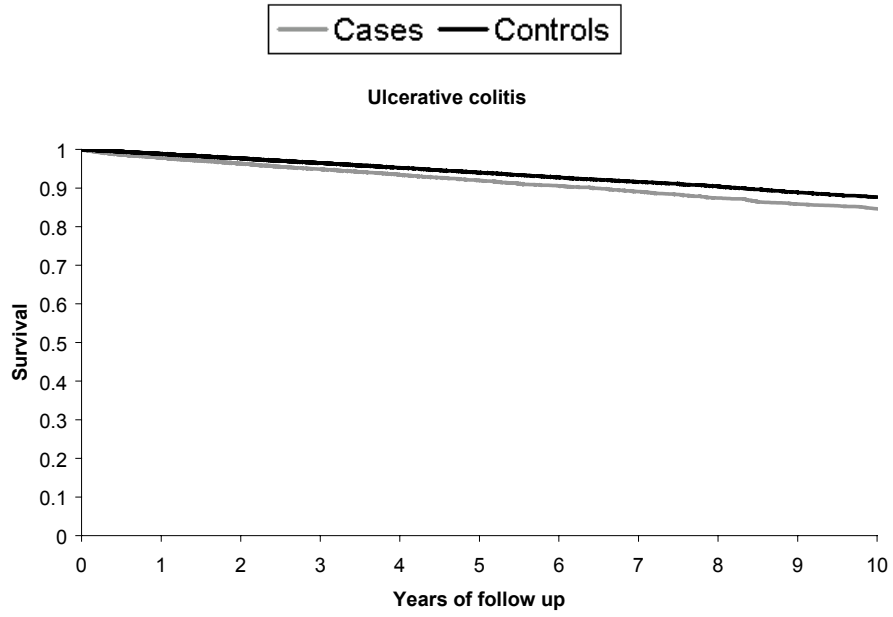

Figure 6-2 Kaplan Meier plot of all cause mortality for UC patients versus controls

Figure 6-3 Kaplan Meier plot of all cause mortality for Crohn's disease versus controls

Figure 6-4 Kaplan Meier plot of all cause mortality for indeterminate IBD versus controls.

6.3.2. Life table analysis

The life tables (Table 6-5, Table 6-6, Table 6-7, Table 6-8, Table 6-9, Table 6-10) demonstrate that the IBD cases overall have a roughly 3.5 year lower life expectancy than their controls on average. With advancing age this difference diminishes so that by the age of 60 the life expectancy of an IBD case is only about 1.5 years lower than that of a control.

These differences are more marked for cases with Crohn's disease (who have on average an 5 year lower life expectancy than their controls) but less for those with UC (who have on average an 2.3 year lower life expectancy than their controls).

Age group	Deaths observed	Years observed	Mortality Rate	Qx	Px	lx	dx	Lx	Tx	ex
0	0	99	0.0000	0.000	1.000	1000	0.00	5000	75024	75.02
5	0	574	0.0000	0.000	1.000	1000	0.00	5000	70024	70.02
10	0	2304	0.0000	0.000	1.000	1000	0.00	5000	65024	65.02
15	2	5174	0.0004	0.002	0.998	1000	1.93	4995	60024	60.02
20	3	12620	0.0002	0.001	0.999	998	1.19	4987	55029	55.14
25	12	22978	0.0005	0.003	0.997	997	2.60	4978	50041	50.20
30	19	29667	0.0006	0.003	0.997	994	3.18	4963	45063	45.32
35	26	30572	0.0009	0.004	0.996	991	4.21	4945	40100	40.46
40	37	30871	0.0012	0.006	0.994	987	5.90	4920	35155	35.62
45	82	32488	0.0025	0.013	0.987	981	12.30	4874	30235	30.82
50	99	27977	0.0035	0.018	0.982	969	16.99	4801	25361	26.18
55	159	22253	0.0071	0.035	0.965	952	33.40	4675	20560	21.60
60	211	21412	0.0099	0.048	0.952	918	44.16	4481	15885	17.30
65	395	20285	0.0195	0.093	0.907	874	81.16	4168	11404	13.05
70	560	18227	0.0307	0.143	0.857	793	113.13	3682	7236	9.12
75	696	14059	0.0495	0.220	0.780	680	149.75	3025	3554	5.23
80	1457	14623	0.0996	0.399	0.601	530	211.43	529	529	1.00

Table 6-5 Life table for controls of all IBD

Age group	Deaths observed	Years observed	Mortality Rate	Qx	Px	lx	dx	Lx	Tx	ex
0	0	20	0.0000	0.000	1.000	1000	0.00	5000	71531	71.53
5	0	109	0.0000	0.000	1.000	1000	0.00	5000	66531	66.53
10	0	450	0.0000	0.000	1.000	1000	0.00	5000	61531	61.53
15	1	1043	0.0010	0.005	0.995	1000	4.78	4988	56531	56.53
20	3	2626	0.0011	0.006	0.994	995	5.67	4962	51543	51.79
25	6	4751	0.0013	0.006	0.994	990	6.23	4932	46581	47.07
30	10	6183	0.0016	0.008	0.992	983	7.92	4897	41649	42.36
35	13	6213	0.0021	0.010	0.990	975	10.15	4852	36753	37.68
40	18	6332	0.0028	0.014	0.986	965	13.62	4792	31901	33.05
45	29	6621	0.0044	0.022	0.978	952	20.61	4707	27109	28.49
50	46	5607	0.0082	0.040	0.960	931	37.42	4561	22402	24.06
55	42	4441	0.0095	0.046	0.954	894	41.28	4365	17841	19.97
60	70	4261	0.0164	0.079	0.921	852	67.25	4093	13476	15.81
65	124	3977	0.0312	0.145	0.855	785	113.53	3641	9383	11.95
70	167	3461	0.0482	0.215	0.785	672	144.56	2996	5741	8.55
75	169	2569	0.0658	0.282	0.718	527	148.84	2263	2745	5.21
80	349	2549	0.1369	0.510	0.490	378	192.84	482	482	1.27

Table 6-6 Life table for all IBD cases

Age group	Deaths observed	Years observed	Mortality Rate	Qx	Px	lx	dx	Lx	Tx	ex
0	0	31	0.0000	0.000	1.000	1000	0.00	5000	75212	75.21
5	0	159	0.0000	0.000	1.000	1000	0.00	5000	70212	70.21
10	0	1034	0.0000	0.000	1.000	1000	0.00	5000	65212	65.21
15	1	2978	0.0003	0.002	0.998	1000	1.68	4996	60212	60.21
20	1	6836	0.0001	0.001	0.999	998	0.73	4990	55216	55.31
25	5	10501	0.0005	0.002	0.998	998	2.37	4982	50227	50.35
30	7	12839	0.0005	0.003	0.997	995	2.71	4969	45245	45.46
35	8	11678	0.0007	0.003	0.997	993	3.39	4954	40275	40.58
40	9	10466	0.0009	0.004	0.996	989	4.24	4935	35321	35.71
45	28	10217	0.0027	0.014	0.986	985	13.40	4891	30386	30.85
50	36	8624	0.0042	0.021	0.979	971	20.07	4807	25495	26.24
55	49	6902	0.0071	0.035	0.965	951	33.18	4674	20688	21.74
60	58	6586	0.0088	0.043	0.957	918	39.56	4492	16014	17.44
65	109	6050	0.0180	0.086	0.914	879	75.74	4204	11522	13.11
70	157	5429	0.0289	0.135	0.865	803	108.27	3744	7318	9.11
75	210	4156	0.0505	0.224	0.776	695	155.80	3084	3574	5.14
80	417	4687	0.0890	0.364	0.636	539	196.09	490	490	0.91

Table 6-7 Life table for Crohn’s disease controls

Age group	Deaths observed	Years observed	Mortality Rate	Qx	Px	lx	dx	Lx	Tx	ex
0	0	6	0.0000	0.000	1.000	1000	0.00	5000	70207	70.21
5	0	31	0.0000	0.000	1.000	1000	0.00	5000	65207	65.21
10	0	195	0.0000	0.000	1.000	1000	0.00	5000	60207	60.21
15	1	588	0.0017	0.008	0.992	1000	8.46	4979	55207	55.21
20	2	1435	0.0014	0.007	0.993	992	6.89	4940	50228	50.66
25	4	2177	0.0018	0.009	0.991	985	9.01	4901	45287	45.99
30	4	2644	0.0015	0.008	0.992	976	7.35	4860	40387	41.39
35	8	2341	0.0034	0.017	0.983	968	16.41	4800	35527	36.69
40	5	2081	0.0024	0.012	0.988	952	11.37	4731	30726	32.28
45	11	2048	0.0054	0.026	0.974	941	24.92	4640	25995	27.64
50	20	1706	0.0117	0.057	0.943	916	52.16	4448	21355	23.32
55	12	1373	0.0087	0.043	0.957	863	36.92	4225	16907	19.58
60	21	1317	0.0159	0.077	0.923	827	63.37	3974	12682	15.34
65	38	1197	0.0318	0.147	0.853	763	112.27	3535	8708	11.41
70	67	957	0.0700	0.298	0.702	651	193.97	2770	5173	7.95
75	46	720	0.0639	0.275	0.725	457	125.82	1970	2404	5.26
80	112	789	0.1419	0.524	0.476	331	173.38	433	433	1.31

Table 6-8 Life table for Crohn’s disease cases

Age group	Deaths observed	Years observed	Mortality Rate	Qx	Px	lx	dx	Lx	Tx	ex
0	0	19	0.0000	0.000	1.000	1000	0.00	5000	75081	75.08
5	0	265	0.0000	0.000	1.000	1000	0.00	5000	70081	70.08
10	0	869	0.0000	0.000	1.000	1000	0.00	5000	65081	65.08
15	0	1379	0.0000	0.000	1.000	1000	0.00	5000	60081	60.08
20	1	3819	0.0003	0.001	0.999	1000	1.31	4997	55081	55.08
25	5	9099	0.0005	0.003	0.997	999	2.74	4987	50084	50.15
30	7	12483	0.0006	0.003	0.997	996	2.79	4973	45097	45.28
35	13	14912	0.0009	0.004	0.996	993	4.32	4955	40125	40.40
40	22	16228	0.0014	0.007	0.993	989	6.68	4928	35170	35.57
45	43	17852	0.0024	0.012	0.988	982	11.76	4881	30242	30.79
50	58	15647	0.0037	0.018	0.982	970	17.82	4807	25361	26.13
55	91	12702	0.0072	0.035	0.965	953	33.52	4679	20553	21.58
60	125	12185	0.0103	0.050	0.950	919	45.96	4480	15874	17.27
65	229	11860	0.0193	0.092	0.908	873	80.41	4164	11394	13.05
70	317	10078	0.0315	0.146	0.854	793	115.58	3674	7229	9.12
75	392	7845	0.0500	0.222	0.778	677	150.39	3010	3555	5.25
80	793	7596	0.1044	0.414	0.586	527	218.04	545	545	1.03

Table 6-9 Life table for UC controls

Age group	Deaths observed	Years observed	Mortality Rate	Qx	Px	lx	dx	Lx	Tx	ex
0	0	4	0.0000	0.000	1.000	1000	0.00	5000	72748	72.75
5	0	50	0.0000	0.000	1.000	1000	0.00	5000	67748	67.75
10	0	174	0.0000	0.000	1.000	1000	0.00	5000	62748	62.75
15	0	283	0.0000	0.000	1.000	1000	0.00	5000	57748	57.75
20	0	776	0.0000	0.000	1.000	1000	0.00	5000	52748	52.75
25	2	1880	0.0011	0.005	0.995	1000	5.31	4987	47748	47.75
30	4	2618	0.0015	0.008	0.992	995	7.57	4955	42761	42.99
35	4	3042	0.0013	0.007	0.993	987	6.47	4919	37807	38.30
40	11	3355	0.0033	0.016	0.984	981	15.95	4863	32887	33.54
45	14	3652	0.0038	0.019	0.981	965	18.32	4778	28024	29.05
50	18	3150	0.0057	0.028	0.972	946	26.66	4665	23246	24.56
55	24	2557	0.0094	0.046	0.954	920	42.17	4493	18581	20.20
60	39	2439	0.0160	0.077	0.923	878	67.46	4219	14087	16.05
65	74	2310	0.0320	0.148	0.852	810	120.16	3750	9868	12.18
70	71	1961	0.0362	0.166	0.834	690	114.52	3163	6118	8.87
75	100	1468	0.0681	0.291	0.709	575	167.48	2458	2955	5.13
80	175	1361	0.1286	0.487	0.513	408	198.51	496	496	1.22

Table 6-10 Life table for UC cases

6.3.3. SMR analysis

The standardised mortality ratios for all IBD cases and all controls (against national figures for England and Wales in appropriate years) are set out in Table 6-11. Controls are at significantly reduced risk of death when compared to the whole UK population (SMR 0.91 (95% CI 0.88-0.94)).

	Observed	Expected	SMR	95% CI	
Cases	981	730	1.34	1.26	1.43
Controls	3612	3977	0.91	0.88	0.94

Table 6-11 SMRs for all IBD cases and controls.

6.3.4. Multivariate analysis

In the multivariate Cox regression analysis we included age at entry to the study, sex and smoking as confounders on an a priori basis. No appreciable further confounding either by Charlson index score, BMI or systolic blood pressure was found and hence these were not included in the final model. Overall we found a hazard ratio for death among subjects with IBD of 1.54 (1.44-1.65) when corrected for age, sex, and smoking habits. Within this model the hazard ratio for death associated with male sex was 1.41 (1.33-1.50) and for being a current smoker (compared to a never smoker) was 1.96 (1.57-2.45). Subdividing IBD cases by disease type showed that the hazard ratio was greater for Crohn's disease at 1.73 (1.54-1.96) and that it was lower for ulcerative colitis (1.44 (1.31-1.58)). There was no statistically significant evidence of interaction between the effects of sex or smoking behaviour and IBD but such interaction was detected for age group. The hazard ratio for death associated with inflammatory bowel diseases was in general larger among younger age groups although there were few deaths available for study in the youngest age groups. These results are set out in table Table 6-12. Log-log plots for these models an example of which is shown in Figure 6-5 showed no gross violation of the proportional hazards assumptions.

Age at entry (years)	Deaths among cases	Hazard Ratio	95% CI	
UC				
All ages	536	1.44	1.31	1.58
under 20	0	1.00	-	-
20-39	15	1.68	0.94	3.02
40-59	95	1.79	1.42	2.27
60-79	290	1.37	1.20	1.56
80 or over	136	1.37	1.20	1.56
Crohn's				
All ages	351	1.73	1.54	1.96
under 20	2	5.30	0.74	37.87
20-39	22	3.82	2.17	6.75
40-59	58	1.80	1.33	2.43
60-79	187	1.73	1.47	2.04
80 or over	82	1.49	1.17	1.90
Indeterminate				
All ages	160	1.56	1.31	1.86
under 20	0	0.00	-	-
20-39	4	1.31	0.44	3.94
40-59	28	2.49	1.59	3.91
60-79	87	1.46	1.15	1.86
80 or over	41	1.46	1.03	2.05

Table 6-12 Hazard ratios for death by age group and type of IBD derived from Cox regression models corrected for the effects of sex and smoking

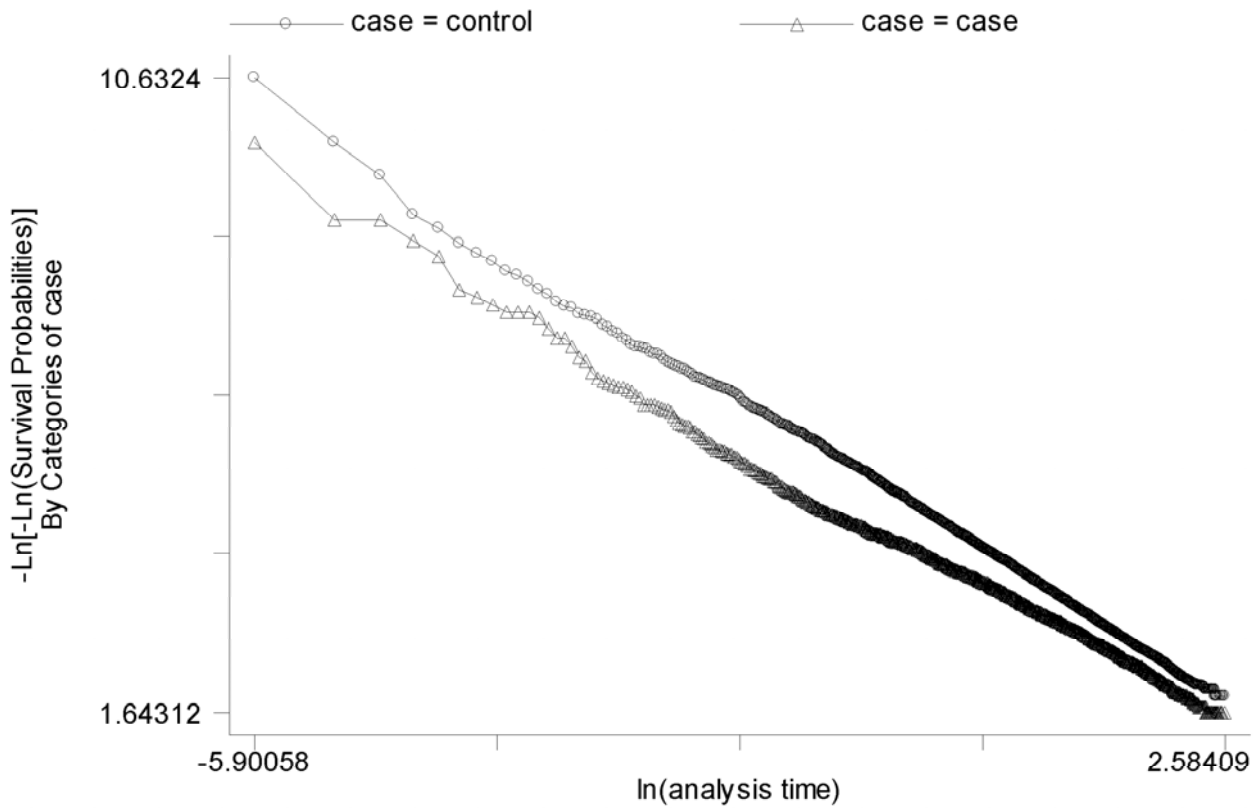

Figure 6-5 Log log plot for multivariate analysis of mortality for all IBD

6.3.5. Restriction analyses

Table **6-13** shows a series of analyses limited to subsets of the available data. The hazard ratios were reduced slightly when the analysis was limited to subjects with 2 or more coded episodes of IBD (hazard ratio 1.37 for UC, 1.53 for CD, and 1.31 for indeterminate disease), and are similarly reduced when subjects having no medical codes entered in the final year for which they contributed were excluded or when the first year of each subject's data after entry was censored (censoring of 2 rather than one year made no appreciable additional difference). The limitation of the analysis to prevalent cases diagnosed at least 5 years before entry to the study slightly reduced the hazard ratio for CD (1.58), but increased it for UC (1.49). Further restricting analysis to cases diagnosed at least 5 years before entry to the study accentuates this change in UC. When only subjects without previously diagnosed heart, lung or renal disease malignancy, hypertension or diabetes are included a rather larger increase in hazard is seen (hazard ratios 1.83 for UC and 2.33 for CD). Finally analysis limited to current smokers slightly increased the hazard ratio for CD (1.90).

	UC			CD			Indeterminate		
	HR	95% CI		HR	95% CI		HR	95% CI	
All subjects	1.44	1.31	1.58	1.73	1.54	1.96	1.56	1.31	1.86
2 or more episodes of IBD coded	1.37	1.22	1.53	1.53	1.33	1.76	1.31	1.01	1.69
First year of data censored	1.37	1.22	1.53	1.58	1.37	1.82	1.21	0.97	1.52
2 or more episodes and one year censored	1.36	1.20	1.55	1.50	1.28	1.75	1.16	0.86	1.57
Incident cases only	1.32	1.10	1.58	2.21	1.77	2.77	1.87	1.42	2.45
Prevalent cases only	1.49	1.33	1.66	1.58	1.37	1.82	1.38	1.09	1.73
Cases > 5 years post diagnosis (at entry)	1.69	1.42	2.01	1.58	1.26	1.98	1.27	0.76	2.1
Subjects without specified morbidity [1]	1.83	1.54	2.17	2.33	1.89	2.88	1.97	1.43	2.72
Excluding subjects with PSC [2]	1.41	1.28	1.55	1.74	1.54	1.96	1.54	1.29	1.84
Excluding subjects with no medical data coded in their last year	1.32	1.20	1.45	1.61	1.43	1.82	1.45	1.22	1.73

Table 6-13 Cox regression models corrected for age sex and smoking for subgroups of cases and their matched controls.

([1]Specified morbidities are any record of ischaemic heart disease, heart failure, hypertension, COPD, asthma, renal disease, any malignancy and diabetes. [2] Codes defining PSC are given in Table IV-27)

6.4. Discussion

This study of 1,047 deaths in over 16,000 IBD patients is the largest of IBD mortality published to date. It has shown that in contemporary clinical practice IBD patients do have a small increase in mortality rate of about 0.5% per annum greater than an age and sex matched general population. This excess mortality is not removed by correction for confounding by smoking in a multivariate Cox regression. Nor is it limited to the initial period after diagnosis of the condition since subjects with at least 5 years of disease before entry to the study have an only slightly lower hazard than does the entire IBD cohort. Overall the hazard associated with Crohn's disease (HR 1.73) is greater than is that of Ulcerative colitis (HR 1.44). The effect of the excess mortality in terms of life expectancy (uncorrected for any confounding) is to reduce this by 3.5 years in IBD patients (2.3 in UC and 5 in Crohn's disease).

This study is the first to compare IBD patients to both a healthy and a general population. After exclusion of subjects with a history of malignancy or of a number of common chronic diseases associated with increased mortality we have demonstrated a hazard ratio of around 2 for death among IBD patients. The size of this study also allows examination of the effect of age in greater detail than has previously been possible, and in this respect it is important to note that although the hazard ratios are greatest for these diseases

among young people, the absolute risk difference is higher among older age groups.

Aside from the benefits that it derives from greater power, and the correction of confounding by smoking, our study has some other advantages. Firstly it is likely to better represent the national (as opposed to regional or even centre based) mortality experience of IBD patients than are previous studies, which have been limited to specific areas within a nation. Also because in contrast to most other population based studies we have included both prevalent and incident cases it is better able to reflect the mortality due to late complications of IBD (such as malignancy) than are previous studies. Finally since our study is based upon data purely from 1987 to 2001 it is more representative of current rather than historical levels of risk, which is of importance in view of the fall in mortality certified as caused by IBD over recent decades[71] despite the rise in incidence of these diseases.

There are however some limitations to our study. Firstly we were unable to individually validate the diagnoses of all the cases. Nonetheless the diagnosis of IBD has previously been validated within the GPRD and been found to be valid in over 90% of cases[77]. Furthermore when we limited our analyses to cases with at least two coded episodes of IBD (for whom greater validity might be expected) we did not see appreciable changes in the hazard ratios

calculated. The other side of this problem is of course that since IBD may remain quiescent for long periods it is likely that some cases will not have been recorded by their GPs' during the time window of our data. It has been shown by validation studies utilising hospital letters that the vast majority of diagnoses relevant to hospital care are recorded in GPRD [70, 76], and hence we can expect to have detected patient's under follow-up. Any non-recording therefore may be greatest among those with inactive disease who are not under hospital follow-up. The results therefore may be generalisable to those under follow-up for IBD rather than to all individuals who have ever received a diagnosis of IBD.

Secondly there may be a chance that control deaths might be underreported if controls are more likely than cases to move without informing their GP (a chronic disease might well keep one in greater touch with ones doctor). Such under-reporting might be suggested by the fact that controls appeared based on the SMR results to have lower than expected mortality, although this cannot directly address the question of whether it is differential between cases and controls. Against this when we excluded subjects with no events recorded in their last year of data there was little change and so this potential bias is unlikely to be important. In fact it may even be that the low SMR of the controls is an indication that IBD patients come from a section of the population at lower than average risk of death. (This could easily be so if for example those sleeping rough who are

unlikely to register for healthcare in the normal way do not contribute cases since they are at markedly increased risk of death.)

The data on confounders such as smoking is clearly incomplete. It is possible that this has resulted in some uncorrected residual confounding, but this should be considerably less than in previous studies without data on these factors. It is also important to note that there is potential for bias with respect to which subjects have missing data (which has been shown to occur in a validation of smoking data within GPRD[73]), our analysis strategy by including a category for missing data rather than ignoring affected subjects will have minimised the potential influence of this. To investigate whether this was a problem specifically with respect to smoking we carried out an analysis limited to current smokers (for whom there is reason to believe the data is most valid[73]) and found that this did not greatly alter our results. As for all studies of this type since cases present preferentially when they are most unwell, and therefore at greatest risk of death, the earliest part of the follow up may carry a higher risk of death. In contrast to most other studies we have been able to demonstrate that this effect though real is not great since the censoring of the first year of follow up only slightly reduces the hazard ratios found.

The use of prevalent as well as incident cases within the study has potential to cause bias since those prevalent subjects not detected

and therefore not included may differ from those who are included. Within this dataset since patients do not in general choose a GP for reasons related to illness, this is most likely to occur if those susceptible to death due to IBD die early in the course of their disease (leading to a bias towards a healthier cohort), or if those with mild or quiescent disease among the prevalent cases cease to consult their GP and are therefore at increased chance of being missed (leading to a bias towards a less healthy cohort). The analyses restricted to incident cases and to prevalent cases show that there is some difference between the mortality experienced by these groups with incident cases experiencing in general greater mortality for CD and lower for UC, however the confidence intervals for these restricted analyses do not exclude the findings from the total cohort.

Finally we should note that in the life table analysis there is no correction made for the confounding factors addressed in the Cox regression. This clearly implies that we should not attribute the whole of the 5-year reduction in life expectancy seen in Crohn's disease to the disease itself since at least a part of this can be expected to be due to smoking. Equally however one might argue that this method will underestimate the impact of UC on mortality and hence it is likely that the true reduction in life expectancy due to IBD does indeed lie somewhere between the figures for UC and Crohn's. This difficulty is an inevitable consequence of such a life

table analysis. Such analysis although it must be interpreted with some care has however we believe value in the communication of results to non-epidemiologists. This belief is due to the fact that during the review process for a paper produced from this study[87] it became clear that much of the likely readership might have difficulty interpreting the magnitude of the results presented in the form of harazrad ratios. In particular it seemed that they might overestimate the likely effect of IBD upon life expectancy.

Our results are consistent with some other population based studies of IBD mortality reported in the last decade which have shown SMRs from 1.3 to 1.6 for CD[43, 47] and of 1.4 for UC[42, 43] although these studies included data from as early as the early 1960s. Other studies from Britain[39, 88] and Italy[44, 46] based upon more recent data have failed to demonstrate any significant excess mortality. The studies finding no excess mortality have in general however been small (none of the cited examples containing more than 100 deaths), and have also been largely limited to the early years of incident disease. Among the differences between our results and those of previous studies of particular interest is the fact that hazard ratios for death for UC are greater among those with a long disease history (at least five years of disease). This is in contrast to the early descriptions of UC mortality in which this was greatest in the early period,[89] and may well reflect improved acute disease management over the years allowing patients to survive to experience the longer-

term risks of the disease such as malignancy. It is equally notable that for Crohn's disease the mortality hazard does not rise with prolonged disease as was once the case[90] perhaps suggesting improved long term management.

In summary our study suggests that there is a 54% excess mortality associated with a diagnosis of IBD. In relative terms this effect is most marked in the young. Although this excess is smaller than that associated with smoking within our study (96% excess for current versus never smokers) it is an important excess being comparable to the excess associated with male sex (41%) or that reported in the UK for manual versus non-manual occupations in the UK (48% excess)[91].

Chapter 7. The risk of fracture in patients with IBD.

7.1. Introduction

This chapter will describe a study of the risk of hip fracture in IBD and the role of steroid use within this using the cohorts described in Chapter 5.

7.2. Methods

7.2.1. Identifying fractures.

For each subject we used a combination of Oxmis and Read coding to assess whether they had experienced a hip fracture Table IV-30 and when this had occurred. For each individual only the first recorded hip fracture was considered. The identification of "all fractures" was conducted in like manner using the codes listed in Table IV-31.

7.2.2. Corticosteroid use

We extracted data on the use of systemic corticosteroids from the therapy files of our subjects. All prescriptions for systemic corticosteroids (excluding topical and inhaled use) were extracted, and based upon their dates a subject's time within the study was divided into that during which the subject was considered a current user (within 90 days of a corticosteroid prescription) and that when they were not. (This can be thought of as modelling a reversible

component of the risk of corticosteroid use). For each of these time periods the incremental total corticosteroid use (as number of prescriptions to that point in time) was calculated. (This can be similarly thought of as modelling an irreversible risk due to corticosteroid use). Since only the first fracture is considered in our analysis, a fracture causes exit from the study. Hence analysis of hip fractures, and all fractures are based upon slightly different time periods. To avoid undue duplication only the results for steroid use relevant to the hip fracture study are presented.

7.2.3. Other drug use and falls.

We also extracted data on the use of the use of corticosteroids, opioid analgesics, hormone replacement therapy (HRT), bisphosphonates, calcium and vitamin D supplements and the frequency of falls. The use of these drugs was coded as prescriptions occurring never, less than once a year or more than once a year: falls were coded in like manner based on frequency of diagnostic/symptom coding for falls (Table IV-29).

7.2.4. Statistical analysis

For all analyses in this study as in the study of mortality time was calculated from the date of the first prospectively recorded IBD code (the matched case's relevant date was used for controls). Univariate analysis of fractures using the matched cohort design was

conducted by the production of crude fracture rates. Multivariate analyses were conducted using a Cox regression model, and the validity of the assumption of proportional hazards was assessed using Log Log plots and Stata's own diagnostic test. As age and sex are known to be associated with both the risk of IBD and the risk of hip fracture they were included within our models on an a priori basis. Other potential confounding factors added to this base model were retained only if they resulted in a 10% or greater change in the hazard ratio for IBD. For blood pressure and smoking the confounding variable was included in the analysis as a categorical variable with a category representing missing data. Although low BMI is known to be associated with fracture risk and is associated with IBD it was not considered as a confounder since it is likely to be on the causal pathway between IBD and fracture risk and hence to do so would be inappropriate. The multivariate analyses were repeated stratifying for disease. Tests for interaction between identified risk factors were carried out. In addition restriction analyses were carried out to examine the risks among those who were incident cases of IBD. Finally we repeated our analyses for all fractures to asses the specificity of any association to hip fractures.

All analyses were conducted using Stata version 7 (Stata Corporation, College Station, Texas 77845 USA).

7.3. Results

7.3.1. Use of corticosteroids

Table 7-1 shows the use of corticosteroids among groups of IBD patients and among their controls. Corticosteroids prescriptions occurred more often for the IBD cases (32% received 1 or more prescriptions per year compared to only 2% of controls), and they had received more such prescriptions in total (22% received more than 5 compared to only 1% of controls).

7.3.2. The use of other drugs

The use of opioid analgesics, hormone replacement therapy (HRT), bisphosphonates and calcium and vitamin D supplements in IBD patients and controls both overall and by disease type is presented as a frequency of prescriptions per year in Table 7-2. Opioid use was more common among all groups of IBD patients than among their controls. Few subjects received HRT, bisphosphonates or calcium and vitamin D supplements, and this remained true among those experiencing a hip fracture. Of these only 27 (9%) of 295 received one or more of these medications at any time.

	All IBD		UC		Crohn's		*Indeterminate*	
	% cases	% controls	% cases	% controls	% cases	% controls	% cases	% controls
Corticosteroid prescriptions (total number)								
0	51	93	53	93	46	94	60	93
1-5	27	5	28	5	28	5	21	6
6-15	13	1	13	1	15	1	11	1
16-25	4	0	3	0	5	0	4	0
>25	5	0	3	0	6	0	4	0
Corticosteroid prescriptions (Density per year)								
0	51	93	53	93	46	94	60	93
Under 1	17	5	18	5	17	5	13	5
1 or more	32	2	29	2	38	2	27	2

Table 7-1 Corticosteroid prescriptions in cases and controls.

Presented both by frequency and total count and divided by type of IBD.

	All IBD		UC		Crohn's		*Indeterminate*	
	% cases	% controls	% cases	% controls	% cases	% controls	% cases	% controls
Opioid analgesics								
0	75	94	78	94	70	94	75	93
Under 1	13	4	12	4	13	4	14	5
1 or more	12	2	10	2	17	2	12	2
Calcium and Vit D								
0	96	99	97	99	94	99	96	99
Under 1	2	0	2	0	3	0	1	1
1 or more	2	1	1	1	3	1	2	1
HRT								
0	92	94	93	94	92	94	91	94
Under 1	2	2	2	2	2	2	3	2
1 or more	6	4	5	5	6	4	6	4
Bisphosphonates								
0	98	99	98	99	98	99	98	99
Under 1	1	0	1	0	1	0	1	0
1 or more	1	0	1	0	1	0	1	0

Table 7-2 Prescription frequency of Opioids, HRT, Bisphosphonates and calcium and vitamin D supplements in cases and controls.

7.3.3. Univariate analysis of hip fractures

The IBD cohort contributed 61,130 years of follow up and 72 hip fractures and controls 306,082 years of follow up and 223 hip fractures. These corresponded to crude hip fracture rates of 11.8 per ten thousand person years for cases and 7.3 per ten thousand patient years for controls. A breakdown of hip fractures, follow up available and crude rates by disease type and sex is given in Table 7-3 and by age and sex is given in Figure 7-1. Expressing these results as hazard ratios via a univariate Cox regression model showed hazard ratios of 1.62 (95% CI 1.24-2.11) for all IBD, 1.49 (95% CI 1.04-2.15) for UC, 2.08 (95% CI 1.36-3.18) for CD, and 0.85 (95% CI 0.30-2.47) for *indeterminate* IBD compared to their respective controls. Log-log plots showed no gross violation of the proportional hazards assumptions in these models: an example is shown in Figure 7-2.

		Controls				Cases			
IBD type	sex	Hip fractures	Follow up (years/10000)	Hip fracture rate /10000 years	95 % CI	Hip fractures	Follow up (years/10000)	Hip fracture rate /10000 years	95 % CI
All	Female	172	16.38	10.50	9.05 12.20	58	3.26	17.81	13.77 23.04
	Male	51	14.23	3.58	2.72 4.72	14	2.86	4.90	2.90 8.28
Indeterminate	Female	19	2.44	7.78	4.96 12.20	4	0.49	8.10	3.04 21.57
	Male	4	1.78	2.25	0.85 6.00	0	0.36	0.00	. .
UC	Female	98	7.50	13.06	10.72 15.92	28	1.49	18.74	12.94 27.14
	Male	29	7.98	3.64	2.53 5.23	10	1.61	6.21	3.34 11.55
Crohns	Female	55	6.43	8.55	6.56 11.14	26	1.27	20.50	13.96 30.10
	Male	18	4.48	4.02	2.53 6.38	4	0.89	4.51	1.69 12.00

Table 7-3 Absolute hip-fracture rated by sex and disease group.

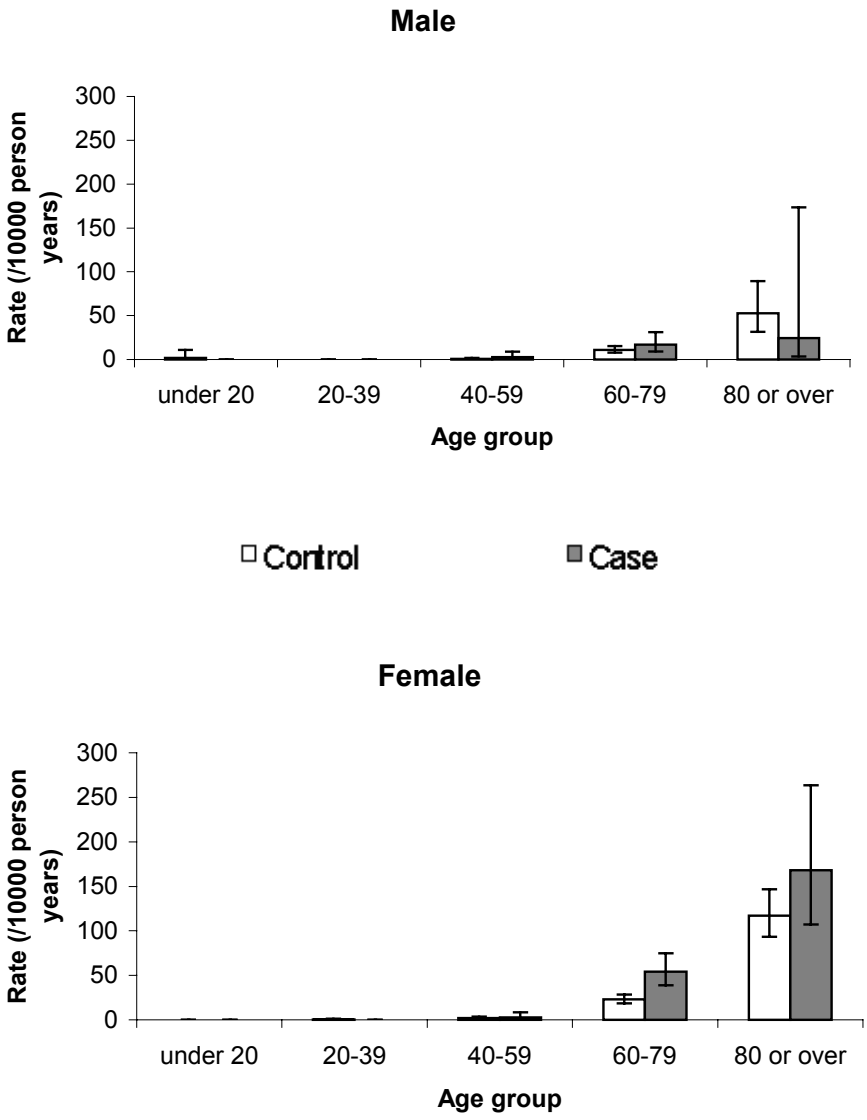

Figure 7-1 Hip fracture rates per 10000 person years by age group.

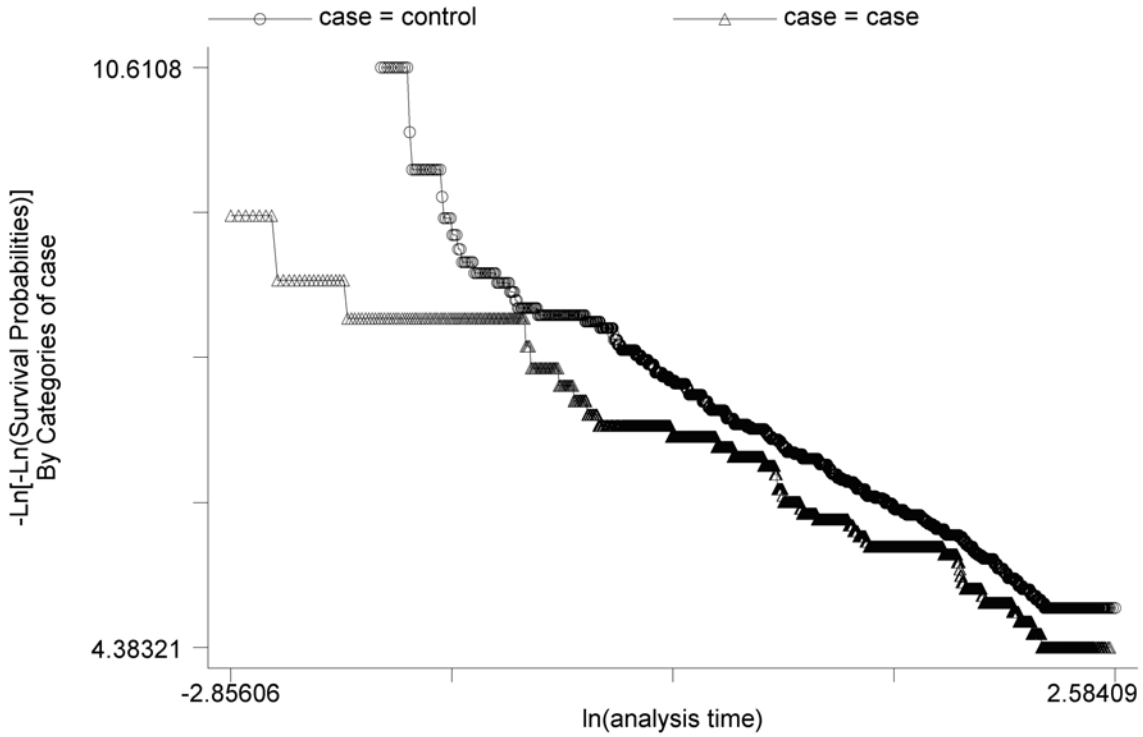

Figure 7-2 Log-log plot of the univariate model of all IBD

7.3.4. Multivariate analysis of hip fractures

In the multivariate Cox regression analysis we included age at entry to the study and sex as confounders on an a priori basis. There was evidence of appreciable confounding in multivariate analyses by both current and cumulative corticosteroid use, and by opioid use but not by smoking or by any other drug exposure we examined. Overall we found a hazard ratio for hip fracture among subjects with IBD of 1.42 (95% CI 1.05-1.91) when corrected for age, sex, corticosteroid use (both current and cumulative) and opioid use Table 7-4. Subdividing IBD cases by disease type showed that after correction for confounding the hazard ratio remained greater for Crohn's disease at 1.68 (95% CI 1.01-2.78) Table 7-6 than for ulcerative colitis (1.41 (95% CI 0.94-2.11)) Table 7-5. There was no statistically significant evidence of interaction between the effects of sex, age, corticosteroid or opioid use and IBD. Log-log plots for these models as for the univariate ones showed no gross violation of the proportional hazards assumptions.

	HR	95% CI
Not IBD Case	1.00	. .
IBD Case	**1.42**	**1.05 - 1.91**
Female	1.00	. .
Male	0.42	0.32 - 0.55
Age under 40	1.00	. .
40-59	8.13	2.42 - 27.26
60-79	98.79	31.52 - 309.62
80 or over	461.24	146.26 - 1454.53
No steroids	1.00	. .
1-5 courses	1.30	0.87 - 1.96
6-15 courses	1.06	0.53 - 2.10
16-25 courses	1.99	0.85 - 4.67
Over 25 courses	2.19	0.98 - 4.89
No current steroid use	1.00	. .
Current steroid use	1.35	0.79 - 2.32
No opioid use	1.00	. .
Occasional use	0.62	0.41 - 0.96
Regular opioid use	1.67	1.12 - 2.48

Table 7-4 Multivariate analysis of hip fracture risk for all types of IBD

	HR	95% CI
Not IBD Case	1.00	. .
UC Case	**1.41**	**0.94-2.11**
Female	1.00	. .
Male	0.39	0.27-0.56
Age under 40	1.00	. .
40-59	4.93	1.09-22.25
60-79	59.14	14.54-240.48
80 or over	331.29	80.95-1355.77
No steroids	1.00	. .
1-5 courses	1.04	0.57-1.88
6-15 courses	1.46	0.64-3.33
16-25 courses	1.66	0.45-6.18
Over 25 courses	2.77	0.95-8.09
No current steroid use	1.00	. .
Current steroid use	1.22	0.58-2.57
No opioid use	1.00	. .
Occasional use	0.60	0.34-1.07
Regular opioid use	1.37	0.76-2.48

Table 7-5 Multivariate analysis of hip fracture risk for UC.

	HR	95% CI
Not IBD Case	1.00	. .
CD Case	**1.68**	**1.01 -2.78**
Female	1.00	. .
Male	0.51	0.32 -0.82
Age under 40	1.00	. .
40-59	13.69	1.73 -108.10
60-79	150.85	20.88 -1089.82
80 or over	603.01	82.44 -4410.92
No steroids	1.00	. .
1-5 courses	1.92	1.05 -3.52
6-15 courses	0.72	0.19 -2.65
16-25 courses	2.02	0.57 -7.18
Over 25 courses	1.11	0.26 -4.78
No current steroid use	1.00	. .
Current steroid use	1.38	0.59 -3.23
No opioid use	1.00	. .
Occasional use	0.62	0.30 -1.30
Regular opioid use	1.88	1.03 -3.43

Table 7-6 Multivariate analysis of hip fracture risk for Crohn's disease

7.3.5. Restriction analyses

When limited to incident cases the hazard ratio for IBD in the multivariate model was reduced to 1.30 (95% CI 0.84-2.03). However an analysis limited to those among the incident group with no record of systemic corticosteroid use but corrected for the other elements of the model showed a hazard ratio of 1.80 (95% CI 1.06-3.08).

7.3.6. Analysis of all fractures

In the analysis using all fractures the level of risk among IBD patients was only slightly above that among controls with the univariate Cox regression giving a hazard ratio for all IBD of 1.14 (1.06-1.24). The hazard was slightly higher for UC (1.16 (1.04-1.30)) and lower for Crohn's disease (1.11 (0.97-1.28)). In the multivariate analysis these hazards were attenuated by correction of confounding and ceased to differ significantly from unity Table 7-7, Table 7-8, Table 7-9.

	HR	95% CI	
Not IBD Case	1	.	.
IBD Case	**1.03**	**0.94**	**1.14**
Female	1	.	.
Male	0.92	0.86	0.98
Age under 40	1	.	.
40-59	0.90	0.83	0.98
60-79	1.56	1.44	1.69
80 or over	3.73	3.32	4.20
No steroids	1	.	.
1-5 courses	1.27	1.12	1.45
6-15 courses	1.29	1.05	1.59
16-25 courses	1.30	0.92	1.82
Over 25 courses	1.46	1.04	2.04
No current steroid use	1	.	.
Current steroid use	1.36	1.14	1.61
No opioid use	1	.	.
Occasional use	0.52	0.45	0.61
Regular opioid use	1.12	0.97	1.31

Table 7-7 Multivariate analysis of all fractures in all cases and controls

	HR	95% CI	
Not IBD Case	1 .	.	
UC Case	**1.15**	**0.91**	**1.45**
Female	1 .	.	
Male	0.93	0.78	1.10
Age under 40	1 .	.	
40-59	0.62	0.50	0.78
60-79	1.32	1.08	1.62
80 or over	2.55	1.85	3.50
No steroids	1 .	.	
1-5 courses	0.81	0.55	1.20
6-15 courses	0.99	0.56	1.76
16-25 courses	1.31	0.57	3.01
Over 25 courses	0.68	0.23	2.04
No current steroid use	1 .	.	
Current steroid use	2.12	1.29	3.47
No opioid use	1 .	.	
Occasional use	0.58	0.40	0.82
Regular opioid use	1.15	0.77	1.71

Table 7-8 Multivariate analysis of all fractures in UC

	HR	95% CI	
Not IBD Case	1 .	.	
CD Case	**0.94**	**0.80**	**1.12**
Female	1 .	.	
Male	1.05	0.95	1.17
Age under 40	1 .	.	
40-59	0.98	0.85	1.12
60-79	1.81	1.59	2.06
80 or over	3.37	2.73	4.16
No steroids	1 .	.	
1-5 courses	1.58	1.29	1.94
6-15 courses	1.39	0.98	1.98
16-25 courses	1.32	0.76	2.29
Over 25 courses	1.50	0.87	2.59
No current steroid use	1 .	.	
Current steroid use	1.14	0.86	1.51
No opioid use	1 .	.	
Occasional use	0.45	0.35	0.59
Regular opioid use	1.14	0.90	1.46

Table 7-9 Multivariate analysis of all fractures in Crohn's disease

7.4. Discussion

We have shown that in this general population based cohort study the rate of hip fracture among patients with IBD is some 60% higher than that of their matched controls. This increase is greater in Crohn's disease in which there is a 2 fold increase in risk than in UC where it is 1.5 fold. These findings are in contrast to the only previous European cohort study, which reported only a non-significant excess of about 10% for both diseases [58], but are not dissimilar to those reported by a large North American study which found a 47% excess in CD patients and a 69% excess in UC patients [56]. In multivariate analyses these relative risks are reduced by correction for age, sex, current steroid use, cumulative steroid use and opioid use. After correction for these factors an increase in risk of 42% for IBD overall, 41% for UC and 68% for Crohn's disease remained. Within our multivariate model current use of steroids was associated with a reversible 35% increase in the risk of hip fracture, and the receipt of on average one or more prescriptions for opioid analgesics each year with a 67% increase in risk. Irrespective of all other factors hip fracture in our study remains very rare under 60 years of age both among those with and without IBD, and even over the age of 60 is far more common among females.

In this analysis we looked primarily at the risk of hip fracture for 2 reasons. Firstly this is a very suitable outcome to study when

attempting to assess the impact of osteoporosis upon the health of IBD patients, since hip fracture is clearly related to osteoporosis, and is associated with significant morbidity and mortality[92, 93]. Secondly since hip fractures will in general result in hospitalisation and correspondence, they will be less susceptible to the ascertainment bias that might occur with other fracture types if (as for both BMI and smoking behaviour) their recording were more complete for the IBD cohort than for healthy controls. It is possible that some fractures that do occur go unrecorded, and also that some diagnoses of fractures or, of IBD may be in error. Such error would be likely to be random and hence lead to an underestimate in the risk we have shown, but is unlikely to be a major problem since both hip fracture recording[94] and IBD diagnosis[77] within GPRD have been independently validated and found to be accurate in over 90% of cases. One disadvantage of the choice of hip fracture is that since this is a fracture predominantly of the elderly and IBD has its peak incidence in young adulthood, there is potential for the disease or its therapy to have had a predisposing effect prior to the period observed. These points must be born in mind when interpreting the results of our analysis of all fractures. Despite them the absence of an excess similar to that seen for hip fracture, (since ascertainment bias would be expected to increase the excess) supports the arguement that there is some degree of specificity with respect to fracture site. This in turn might suggest that the effect upon hip fracture is via weakening of bone rather than increase in trauma, but

such an interpretation should be made with caution as the data would be equally compatible with an increase in low impact injury (causing fracture in those susceptible) accompanied by a reduction in high impact injury (which might occur if for example IBD patients were less likely than average to take part in dangerous sports).

Our finding that corticosteroid use is a confounder of the increased hip fracture risk we have seen is consistent with previous studies. Corticosteroids are commonly used to treat IBD, and are known to be associated with increased risk of fracture[95]. Further they have previously been shown repeatedly to be confounders of the association with osteoporosis in IBD[51-53, 96], and in the only previous study to examine their role in it of fracture risk in IBD[57]. This latter study however was reliant upon a self-administered questionnaire for data relating to steroid use, which introduced the potential for recall bias. Our study by using prospectively gathered prescription data avoids this problem. We have also been able to look not only at the effect of cumulative use as was previously attempted, but also at the effect of current use which has recently been suggested as an important risk factor for fracture[65], and previously been shown to predict reduced bone density in Crohn's disease[96]. That there is significant risk associated with IBD after correction for available confounders including corticosteroids suggests however that they are not a complete explanation of the risk. . Our findings suggest

that they can account for less than half of the excess fracture risk in Crohn's and less than 20% of that in UC.

It is important to recognise the limitations to precise estimation of steroid exposure in our subjects. For the nearly 60% who were prevalent cases the GPRD will not have captured exposure prior to entry into the database. In addition some exposure to steroids will be prescribed by hospitals and therefore not captured. It is for this reason that our estimates of cumulative exposure are in broad categories, allocation to which should remain valid despite these limitations. The imprecision of our estimates of cumulative steroid use however means that it is possible that there is residual confounding from them, and that hence we may have underestimated the role of corticosteroids. The subgroup analyses of all incident cases, and of incident cases with no record of steroid use that we have conducted allow us to some extent to assess the importance of these limitations. Although these analyses are inevitably of very limited power, that they show increased risk in groups free from these problems suggests that their impact may not be great. These findings are consistent with the previous observation that CD patients have reduced bone mineral density at diagnosis[61].

Although we have found that hip fracture is associated with both current and cumulative corticosteroid use in IBD this does not prove

that corticosteroids cause the increased risk seen. It is equally possible that corticosteroid use is a marker of increased inflammatory activity (since they will be given when such activity occurs) and that this directly affects bone metabolism[97]. A further possibility is that the risk is at least in Crohn's disease related to bowel malfunction and the recent finding of a similar excess of hip fracture risk in persons with coeliac disease[98] might support this idea.

Our other important findings are of an increased risk of hip fracture in IBD patients using opioids regularly, which confounds the risk associated with IBD, and a low rate of use of bone protecting medications. Since an excess risk of fracture in opioid users has previously been shown[99], and there is evidence to suggest that dependence upon them is not rare in IBD[100] it is unsurprising that they should be confounders in this context. It is perhaps no more surprising since the prevention of osteoporosis has only relatively recently gained prominence in the literature that we found little use of medications aimed at doing so in this dataset collected between 1987 and 2001. This finding does however point up the opportunity for prevention that may be present.

In conclusion we have found that IBD is associated with a roughly 60% increase in risk of hip fracture. We have also found that although corticosteroids might explain some of this risk, they

certainly cannot explain it all, and probably explain rather less than half of it even in Crohn's disease where they have their greatest effect. The finding that corticosteroids have an effect not only through prolonged consumption, but also a rapid and reversible effect supports the suggestion that prophylactic therapy should be initiated acutely with corticosteroids[101, 102]. Finally our findings suggest that although the majority of the excess hip fracture risk in IBD may not be due to drug use, there is an opportunity to reduce this risk by reducing the use of opiates and increasing the use of prophylactic medication.

Chapter 8. Conclusions

8.1. Main findings

The studies presented in this thesis fall into two groups which are most easily discussed separately.

The first two studies examined hypotheses regarding the aetiology of IBD, and the possibility that this is linked to relationship between the gut and microorganisms. Within this vast area of research we have been able to add to knowledge in two small ways. Firstly we have added a further study to the literature relating to the role of season of birth as a risk factor for Crohn's disease. Our study showed no evidence of such a role. Secondly we have conducted the first study specifically designed to examine the possibility that antibiotic use might predispose to or precipitate Crohn's disease. This study found a clear association between antibiotic use and subsequent diagnosis of Crohn's disease 2 to 5 years later but since similar associations existed for other drug groups the association is likely not to be causal.

The other two studies presented look at the impact of IBD. We have looked not at the direct symptomatic effects of IBD but rather at some serious adverse consequences that may in some cases be attributable only indirectly if at all to the disease. The first of these

studies demonstrated a roughly 50% increase in risk of death among IBD patients after correcting for the confounding effects of smoking. This corresponded to a roughly 3.5 yr loss in life expectancy overall. The risk was greater in Crohn's disease than in UC, and was greater in absolute terms in the elderly but in relative terms in the young. The second of these studies examined the risk of fracture (and in particular of hip fracture) in IBD and attempted to elucidate the contribution of corticosteroid therapy to this. This study demonstrated a roughly 1.6 fold increase in hip fracture risk in IBD patients which was higher among CD patients (2.1 fold) than UC patients (1.5 fold). These effects were not found when all fractures were analysed, and were in part explained by corticosteroid use (both long and short term) and by opiate analgesic use since the inclusion of these three exposures within a multivariate model attenuated the hazard ratios seen.

8.2. Suggestions for further research

A discussion of potential future epidemiological research into IBD covering all aspects of the investigation of its aetiology and impact is clearly beyond the scope of this thesis. I shall therefore restrict myself to future research which arises fairly directly from the studies presented above.

8.2.1. Month of birth and the risk of IBD.

For the reasons outlined in the discussion of Chapter 2 it is unlikely that any very similar study to that which we undertook will yield useful results in the UK. It is perhaps unwise to suggest that seasonality will not more easily be found elsewhere however in view of the clear geographic variation in the results of similar studies into type 1 Diabetes[31], and the recent emergence of a rational which might well explain this[103].

8.2.2. Antibiotic use and the risk of Crohn's disease.

The paucity of previous examination of the possibility that antibiotics have played a role in the rise in Crohn's disease, along with the limitations of the study presented in Chapter 4 mean that there is clear potential for further research in this area. Many different studies in this area might be proposed including the repetition of our examination of the effect of antibiotics over a small number of years (since there is always the need to repeat observational studies before accepting their results). One approach with great potential advantages that could examine a subtly different hypothesis would be a case control study measuring, as it's primary exposure antibiotic use from birth onwards assessed via contemporaneous medical records, and assessing a variety of other potential confounders both from records and questionnaires. Such a study would have the same advantage of avoiding recall bias which we

were able to achieve, but would in addition be able to gain rather better data on potential confounders than we could and to examine the possibility that the exposure's effect is limited to a particular point in the life course. Such an age specific effect in early life would to some extent mirror the hygiene hypothesis which has been previously investigated[12, 13] as well as tying in with the suggestion that caesarian sections or other perinatal events might affect the risk of Crohn's disease[104]. It would also mirror the age specific effect of antibiotics that has been described in relation to the risk of asthma and allergy[105, 106].

8.2.3. Mortality in Inflammatory Bowel Disease

The need for ongoing study of the mortality associated with inflammatory bowel disease is illustrated beautifully by the recent publication of results radically different to those that we have presented from a well-conducted study in Denmark[107, 108]. This was a study of an incident cohort and calculated the relative risk of death as an SMR with the Danish general population figures being used as the comparator which found no excess in risk. Some of the potential reasons for the discrepancy between these results point to useful areas of future research. It is likely that one reason that we found a far higher level of mortality is that our case selection will be likely to have excluded those who were quiescent throughout their GPRD record. Although at one level it is easily understandable that

sick people die more than well ones, the greater elucidation of precisely which patients with IBD are at increased risk of death would be of obvious benefit. Another likely reason for the discrepancy is the differences in choice of control populations between studies. It is generally assumed that where a population based incident cohort is the case population it is reasonable to compare this to mortality figures for the general population as a comparator. The low SMR of our control population must suggest however either an incomplete recording of death in the GPRD (which could not explain the difference between our results and those from Denmark unless it were differential), or that IBD patients are drawn from a subset of the population with below average mortality. The latter explanation would be far from surprising if we consider that the ascertainment of IBD but not of death is likely to be poor among those with poor access to health care (such as the homeless). It would also fit well with existing evidence that IBD is commoner among those living in more affluent settings. Clearly the examination of this question in other cohorts is of great potential methodological consequence.

8.2.4. The risk of fracture in patients with IBD.

One of the great unanswered questions regarding IBD and bone disease is whether the observed association between corticosteroids and bone disease in this setting reflects a primary

effect of the corticosteroids or an effect of the disease activity which they are treating. This is a problem that will be extremely difficult to disentangle in adult IBD patients by observational means. A potentially useful methodology for the partial examination of this problem may be a randomised controlled clinical trial comparing steroids and elemental diet in the treatment of Crohn's disease. Although this could not reasonably provide power to examine fracture risk it would permit the evaluation of short-term changes in bone density, whether they were steroid dependant or not and over what time period if at all they were reversible. If steroids are responsible for the acute reversible increase in fracture risk which we have described then one would expect them to be associated with a marked and reversible reduction in bone density which did not occur in the diet arm of the trial.

8.3. Conclusion

The accumulating evidence that disordered relationships between the gut and it's flora may be involved in the aetiology of IBD gave rise to two hypothesese which we were able to investigate. Although we found no evidence in support of a risk related to the season of birth and a possibly non-causal relationship with the use of antibioitics this area of research remains one of great interest. Our investigation of the risks of death and of hip fracture gave rise to more clearly conclusive results than did our aetiological studies. We

demonstrated a clear increase in risk of both of these outcomes that was greater in Crohn's disease than in UC. There remain however a number of outstanding questions related to these results both in terms of methodology and of the precise causation of these risks.

Appendix I. Source data for live births

This appendix presents source data for live births registered between 1978 and 1998 that has been compiled to give live births from 1978 to 1998 for the whole of the UK.

	January	February	March	April	May	June	July	August	September	October	November	December
1978	46.6	44.3	51.5	48.8	51.1	49.4	50.6	51.3	52.7	51.6	48.4	50.2
1979	51.4	48.6	56.2	53.4	56.8	54.5	55.6	53.7	52.9	53.7	50.8	50.5
1980	54.4	51.5	56.4	55.5	57.8	54.7	57.9	54.8	55.6	55.4	50.5	51.6
1981	52.7	48.5	55.0	52.8	54.7	53.4	56.5	54.2	53.6	53.2	49.9	50.0
1982	51.5	47.7	54.3	52.2	53.8	51.0	54.5	53.4	54.2	53.0	49.4	51.0
1983	51.2	47.6	53.6	52.6	54.8	54.0	55.4	53.8	54.3	51.5	49.7	50.7
1984	51.3	48.9	53.3	50.1	54.3	53.4	55.9	55.8	55.4	55.3	52.5	50.6
1985	54.7	49.6	56.0	53.3	57.5	54.5	58.2	57.1	57.0	55.8	51.9	50.7
1986	53.6	49.6	56.7	55.2	58.2	55.7	56.7	57.4	56.7	55.9	51.1	54.2
1987	54.6	50.6	57.6	56.3	59.8	58.9	59.8	58.1	58.7	57.8	53.6	55.9
1988	57.3	55.2	60.8	58.0	60.4	58.1	60.2	59.6	59.3	55.5	53.6	55.5
1989	55.8	52.3	58.9	56.9	60.7	59.1	60.1	58.9	56.8	56.8	55.0	56.4
1990	56.5	52.9	58.9	57.2	61.4	60.7	62.5	61.2	60.3	59.9	57.6	57.1

1991	58.8	54.1	58.5	56.7	60.1	59.0	62.0	60.4	59.4	58.7	55.3	56.2
1992	58.3	55.6	58.8	57.6	59.4	58.6	61.0	58.8	58.3	56.4	53.3	53.5
1993	55.4	50.7	56.3	54.8	57.6	57.7	59.0	57.8	59.0	56.8	52.6	55.8
1994	55.4	51.0	57.9	55.4	58.1	57.1	57.3	55.5	56.1	55.5	52.2	53.1
1995	53.5	49.7	55.4	52.2	56.7	55.8	56.5	55.6	55.3	54.9	51.4	51.2
1996	53.5	50.4	53.4	50.5	53.8	53.7	57.6	56.0	56.4	56.2	53.8	54.2
1997	54.5	49.5	54.1	54.0	55.4	53.9	56.4	54.8	53.7	53.0	50.7	53.1
1998	53.4	48.8	53.6	52.4	53.0	53.1	56.4	54.4	55.3	53.6	50.1	51.6

Table I-1 Numbers of live births in England and Wales by month from 1978-98

	January	February	March	April	May	June	July	August	September	October	November	December
1978	5,262	4,902	5,611	4,852	5,555	5,429	5,283	5,681	5,378	6,027	5,277	5,038
1979	5,897	4,996	5,816	5,725	6,010	5,666	6,058	5,982	5,085	6,253	5,556	5,322
1980	5,724	5,476	5,510	5,973	5,868	5,635	6,019	5,605	5,633	6,280	5,172	5,997
1981	6,052	5,333	6,150	5,739	5,610	5,767	5,929	5,745	5,573	6,119	5,446	5,591
1982	5,472	5,106	5,997	5,658	5,239	5,366	5,549	5,693	5,462	5,908	5,437	5,309
1983	5,499	4,964	5,631	5,227	5,370	5,693	5,498	5,873	5,512	5,633	5,128	5,050
1984	5,383	4,937	5,347	5,154	5,448	5,316	5,798	5,853	5,200	6,158	5,453	5,059
1985	5,683	4,993	5,287	5,786	5,615	5,185	6,034	5,788	5,415	6,323	5,227	5,340
1986	5,578	4,859	5,086	6,000	5,592	5,566	5,723	5,339	5,563	5,947	5,003	5,556
1987	5,540	5,019	5,529	5,462	5,364	5,899	5,955	5,540	5,525	5,883	5,189	5,336
1988	5,476	5,437	6,006	5,376	5,471	5,697	5,503	5,827	5,513	5,538	5,203	5,165

1989	5,525	4,768	5,603	4,973	5,582	5,394	5,326	5,529	5,187	5,588	5,114	4,891
1990	5,725	4,926	5,496	5,287	5,624	5,430	5,957	5,816	5,160	6,275	5,439	4,838
1991	5,943	5,069	5,374	5,709	5,645	5,275	6,167	5,735	5,435	6,193	5,198	5,281
1992	5,886	4,950	5,639	5,529	5,218	5,699	5,966	5,381	5,524	5,634	5,142	5,221
1993	5,333	4,783	5,660	5,286	5,014	5,327	5,581	5,519	5,368	5,493	5,175	4,798
1994	5,338	4,692	5,534	5,027	5,188	5,359	5,138	5,336	5,095	5,270	4,984	4,695
1995	5,313	4,585	5,219	4,626	5,211	5,089	5,057	5,297	4,830	5,429	5,054	4,341
1996	5,371	4,682	4,476	4,885	4,864	4,491	5,247	5,172	4,703	5,772	4,800	4,833
1997	5,346	4,581	4,356	5,500	4,942	4,961	5,276	4,890	4,989	5,332	4,372	4,895
1998	4,924	4,308	4,919	4,807	4,485	4,956	5,085	4,800	4,911	5,081	4,479	4,564

Table I-2 Live births by month of registration, Scotland

	January	February	March	April	May	June	July	August	September	October	November	December
1978	2512	2067	1795	2189	2066	2531	2584	1917	2158	2720	1943	1757
1979	2783	2070	2267	2647	2436	2291	2674	2176	2293	2483	2275	1783
1980	2833	2052	2205	2687	2369	2492	2594	2174	2474	2536	2069	2097
1981	2406	1961	2358	2274	2265	2420	2391	2242	2357	2370	2491	1767
1982	2353	2278	2235	2152	2529	2366	2389	2442	2212	2562	2275	1900
1983	2409	2011	2380	2238	2300	2481	2239	2419	2429	2211	2189	1949
1984	2296	2076	2300	2343	2142	2418	2324	2279	2417	2313	2450	1670
1985	2603	2099	2226	2431	2446	2221	2520	2236	2447	2440	2164	1802
1986	2654	2065	2188	2643	2478	2367	2619	2046	2448	2451	2028	2165
1987	2537	2144	2319	2380	2445	2590	2404	2244	2492	2201	2155	1954
1988	2494	2248	2421	2313	2523	2356	2342	2508	2291	2277	2262	1732
1989	2349	2001	2167	2241	2277	2336	2274	2381	2112	2204	2069	1669
1990	2610	1965	2243	2172	2384	2237	2338	2192	2087	2442	2147	1682

1991	2729	1919	2028	2346	2274	2144	2319	2234	2270	2143	2034	1825
1992	2486	1931	2204	2195	2134	2327	2185	2022	2347	2113	1952	1676
1993	2191	1846	2209	2129	1938	2309	2118	2065	2178	2034	2130	1762
1994	2317	1722	2047	2090	1999	2224	1954	2113	2152	2000	1981	1690
1995	2246	1842	2072	1845	2125	2160	2054	2021	2019	2077	1937	1462
1996	2510	1875	1829	2084	2041	1854	2122	2127	2101	2268	2041	1730
1997	2369	1836	1855	2271	1995	2070	2173	1933	2162	2017	1825	1771
1998	2149	1836	2018	2043	1911	2089	2170	1873	2136	2074	1771	1598

Table I-3 Births by Month for Northern Ireland 1978-1998

Appendix II. The data format of the GPRD

(Reproduced with permission of The GP Database Research Company Limited (EPIC))

PATIENT RECORDS:

Field	Character Type	Max No. Of Characters	Description
prac	9999	4	Encrypted practice id
epatid	Any ASCII	6	Encrypted patient id
dob	YYYYMM DD	8	Date of birth
sex	9	1	Sex of patient (see *note* below)
orgreg	YYYYMM DD	8	Patients original registration date with the practice (derived by EPIC)
regstat	99	2	Registration status (see *note* below)
xferdate	YYYYMM DD	8	Transfer out date
Start_UTS	YYYYMM DD	8	Patients start of up to standard data
End _UTS	YYYYMM DD	8	Patients end of up to standard data

Note Patient Records:

SEX	0	Female
	1	Male
REGSTAT	1	Permanent
	2	Temporary
	3	Left practice
	4	Applied for Registration
	5	Contraception only
	6	Maternity only
	7	Private Patient
	8	Referral
	9	Inactive
	13	D=death
	17	Child Health Survey
	18	Minor Operations Only

MEDICAL RECORDS:

Field	Character Type	Max No. Of Characters	Description
prac	9999	4	Encrypted practice id
epatid	Any ASCII	6	Encrypted patient id
evntdate	YYYYMMDD	8	Event date
medcode	Any ASCII (case sensitive)	7	OXMIS or Read medical code (see MEDCODES)
rdoxflag	A	1	Flag indicating if the code is OXMIS or Read (see *note* below)
outcome	A	1	Outcome (see *note* below)
mclinspe	AAA	3	Clinical speciality (see *note* below)
textid	9999999	7	Identifier used to locate a 100 character text comment in the 'VMTEXT' file. These comments are confidential (see *note* below)

Note Medical Records:

RDOXFLAG	O	OXMIS code in medcode field
	R	Read code in medcode field
	U	Unmatched record – deletion on collection that could not be matched to original record
	C	Read code record which was originally in OXMIS and has been amended since practice moved to read
OUTCOME	A	Inpatient, Doctor referral to Accident & Emergency
	C	Outpatient, Self referral to Accident & Emergency
	D	Inpatient, hospital discharge summary
	E	Outpatient, Doctor referral to Accident & Emergency
	H	Inpatient, hospital admission
	L	Hospital letter
	M	Minor Surgery
	O	Other
	R	Outpatient referral
	S	Inpatient, Self referral to Accident & Emergency
MCLINSPE	DER	Dermatology
	ENT	Ear Nose & Throat
	GER	Geriatrics

GYN	Gynaecology
MED	General Medical
NEU	Neurology
OBS	Obstetrics
OPH	Ophthalmology
ORT	Orthopaedic
0TH	Other
PAE	Paediatrics
PAT	Pathology
PSY	Psychiatry
RHE	Rheumatology
SUR	General Surgery
XRA	X - Ray
URI	Genito-Urinary

'VMTEXT' *is a file containing the textid and all doctors' comments in the GPRD. Some of these comments can contain confidential information about patients so we are unable to give out this file. If you do require a comment identifiable by the 'textid' Please contact EPIC more further information.*

THERAPY RECORDS:

Field	Character Type	Max No. Of Characters	Description
prac	9999	4	Encrypted practice id
epatid	Any ASCII	6	Encrypted patient id
prscdate	YYYYMM DD	8	Prescription date
drugcode	Any ASCII	8	Encrypted Multilex drug code (see GPRDDRUG)
multflag	A	1	Flag to show whether multilex or not
dosage	Any ASCII	11	The dosage as entered by doctor
prscqty	99999	5	Prescription quantity
prscdays	999	3	Duration of the prescription in days
opno	999	3	Number of original packs
packsize	99999.99 (float)	8	Pack size
textid	9999999	7	Identifier used to locate a 100 character text entry in the medical records
dosgval	9999.99	7	The dosage value. Where possible the prescribed number of units per day has been calculated. This information together with the prescription quantity allows the duration of the prescription to be calculated.

Note **Therapy Records:**

MULTFLAG	Y	Multilex code in drugcode field
	X	Undefined PPA code
	U	Unmatched record – deletion on collection that could not be matched to original record
	C	Multilex code record which was originally a PPA and has been amended since practice moved to Multilex
PRSCTYPE	0	Repeat
	1	Acute

PREVENTION RECORDS:

Field	Character Type	Max No. Of Characters	Description
prac	9999	4	Encrypted practice id
epatid	Any ASCII	6	Encrypted patient id
evntdate	YYYYMMDD	8	Event date
prevcode	9999999999	10	Prevention code (see PREVENT)
prevval1	99999999	8	Prevention value 1 (see PREVENT)
Prevval2	99999999	8	Prevention value 2 (see PREVENT)
medcode	Any ASCII (case sensitive)	7	OXMIS or Read medical code (see MEDCODES)
rdoxflag	A	1	Flag which indicates if the code is OXMIS or Read (see *note* below)
clinspec	AAA	3	Clinical speciality (see *note* below)

Note Prevention Records:

RDOXFLAG	O	OXMIS code in medcode field
	R	Read code in medcode field
	U	Unmatched record – deletion on collection that could not be matched to original record
	C	Read code record which was originally in OXMIS and has been amended since practice moved to read

CLINSPEC	DER	Dermatology
	ENT	Ear Nose and Throat
	GER	Geriatrics
	GYN	Gynaecology
	MED	General Medical
	NEU	Neurology
	OBS	Obstetrics
	OPH	Ophthalmology
	ORT	Orthopaedic
	OTH	Other
	PAE	Paediatrics
	PAT	Pathology
	PSY	Pyschiatry
	RHE	Rheumatology
	SUR	General Surgery-
	URI	Genito-Urinary
	XRA	X - ray

LOOK UP TABLES

MEDCODES: *Medical dictionary*

Field	Character Type	Max No. Of Characters	Description
Medcode	Any ASCII (case sensitive)	7	OXMIS/Read code
rdoxflag	*A*	1	OXMIS/Read flag
Description	*Text*	60	Description of the codes

PREVENT: *Prevention code information*

Field	Character Type	Max No. Of Characters	Description
Prevcode	99999999 99	10	Prevention code
Description	text	variable	Description of code
Prevval1	text	variable	Prevention value 1
Prevval2	text	variable	Prevention value 2
Code	Any ASCII (case sensitive)	7	Medcode or date

GPRDDRUG: *Drug dictionary*

Field	**Character Type**	Max No. Of Characters	**Description**
PPAEID	9999999	7	Encrypted PPA code
MultilexEID	Any ASCII	8	Multilex Product and Formulation ID encrypted
BNFCode1	99.99.99.99	11	BNF Hierarchy code 1
BNFCode2	99.99.99.99	11	BNF Hierarchy code 2
BNFCode3	99.99.99.99	11	BNF Hierarchy code 3
GenericName Qual	Text	50	Generic Name and (abbreviated) qualifier of the product.
Formulation	Text	50	Formulation
Strength	Text	20	Abbreviated strength (includes units)

Appendix III. Papers published from this work

Card TR, Sawczenko A, Sandhu BK, Logan RF. No seasonality in month of birth of inflammatory bowel disease cases: a prospective population based study of British under 20 year olds. Gut 2002;51:814-5.

Card T, Logan RFA, Rodrigues LC, Wheeler JG. Antibiotic use and the development of Crohn's Disease. Gut (in press)

Card T, Hubbard R, Logan RFA. Mortality in Inflammatory Bowel Disease: a population based cohort study. Gastroenterology 2003 Dec;125(6):1583-90

Card T, West J, Hubbard R, Logan RFA. Hip fractures in people with Inflammatory Bowel Disease and their relationship to corticosteroid use: a population based cohort study. Gut (in press)

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