Inflammatory bowel disease in the United Kingdom: Epidemiological trends in primary care and associations with contraception

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Declaration

I, Thomas Joshua Pasvol, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed:

Abstract

Background: The epidemiology of inflammatory bowel disease (IBD) in the UK is poorly described. Primary care contraceptive prescribing data published by the NHS are not linked to individual patients. Studies have linked contraceptive pills to the development of IBD. However, there is a paucity of literature on how contraceptive formulation and duration of therapy affect IBD risk.

Aims: To describe changes in the incidence and prevalence of IBD in the UK from 2000-2018. To describe non-barrier contraceptive prescribing patterns in primary care over the same period. To investigate the associations between exposure to contraception and development of IBD.

Methods: Three epidemiological studies using IQVIA™ Medical Research Data; a cohort study examining temporal trends in IBD incidence and prevalence, a repeated cross-sectional study exploring trends in contraceptive prescribing, a nested case-control study investigating the associations between a range of contraceptives and development of IBD.

Results: Overall, the incidence of IBD is falling, but prevalence continues to rise. Some of the highest recorded incidence and prevalence rates globally were observed, with a 94% rise in incidence in adolescents since the year 2000. Over the same period, combined hormonal contraception prescribing has halved whereas progestogen-only pill prescribing has more than doubled. Methods of contraception prescribed by GPs are influenced by social deprivation. Withdrawal of a pay-for-performance incentive may have adversely affected adolescent long-acting reversible contraception uptake. Results suggest that oestrogen-containing contraception is associated with development of IBD whereas progestogen-only methods have minimal to no effect.

Conclusion: This thesis provides evidence relating to a wide range of temporal trends in the epidemiology of IBD and patterns of contraceptive prescribing in the UK. Although previous associations between oral contraceptive pills and IBD have been made, this thesis provides the first epidemiological evidence that oestrogen-containing contraceptives, but not progestogen-only methods, are associated with development of IBD.

Impact statement

The inflammatory bowel diseases are chronic illnesses which cause substantial lifelong morbidity. IBD affects people during their working lives and has considerable economic implications for the NHS and wider society. Primary goals of this project were to produce findings which can inform IBD care providers, guide service delivery and ultimately improve the lives of people living with IBD. A secondary goal was to improve the reproductive health of women seeking contraception from primary care. These goals could be met by disseminating the work inside and outside academia.

All of the studies included in this thesis have been published in international peer-reviewed journals under open access licences (1-3). Four conference presentations have arisen from the work and I have presented as an invited speaker at two large regional meetings (page 50).

My study of time trends in IBD epidemiology identified rising IBD prevalence in older people and a dramatic rise in childhood incidence. These findings will have major implications on service delivery as resources must be spread increasingly thinly over a growing patient burden. Knowledge of these trends is important as it will allow for service providers to prepare for an inevitable increase in demand. I have disseminated the results to a patient advocacy group and the publication has already been cited 20 times since its publication in August 2020. This encourages me that the findings are reaching the wider IBD community. For this study, I also developed an algorithm to assist in the validation of IBD in IQVIA^{TM}

Medical Research Data (IMRD). This algorithm could benefit researchers as it demonstrates that IMRD represents a useful resource for future epidemiological studies of IBD.

My study of contraceptive prescribing patterns identified several issues which are important to act on. Firstly, inherent contraceptive prescribing inequalities exist related to socioeconomic status. These inequalities could be further explored through future qualitative work or the use of stakeholder feedback. The results could be disseminated to contraceptive prescribers in academic literature or more widely to women of reproductive age through specialist or mainstream social media channels. These initiatives could improve education for contraceptive prescribers leading to better equality of care. Secondly, withdrawal of a pay-per-performance indicator may have adversely affected adolescent long-acting reversible contraceptive uptake. This finding requires more research focussed specifically at this age group to better understand the implications for adolescent reproductive health in the UK. Results could inform a public health campaign targeted at both teenagers and contraceptive providers (including over-the counter pharmacists) to encourage LARC uptake and reduce unplanned pregnancy in this age group.

I found that oestrogen-containing contraception is associated with development of IBD (particularly CD) and progestogen-only contraception has minimal to no effect. This study could inform a wide range of future research including basic science and epidemiological projects. This finding may also be useful for people at higher risk of IBD (i.e. those with affected relatives) and could be used to develop primary prevention strategies for this group.

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Abbreviations

Abbreviation	Definition
5-ASA	5-aminosalicylic acid
ACCESS	Asia-Pacific Crohn's and Colitis Epidemiology Study
ACU	Acceptable computer usage
AHD	Additional health data
AMR	Acceptable mortality recording
ANCA	Antineutrophil cytoplasmic antibodies
ASCA	Anti-Saccharomyces cerevisiae antibodies
BMI	Body mass index
BMJ	British Medical Journal
BNF	British National Formulary
CD	Crohn's disease
CDEIS	Crohn's Disease Endoscopic Index of Severity
CHC	Combine hormonal contraception
CI	Confidence interval
COCP	Combined oral contraceptive pill
COPD	Chronic obstructive pulmonary disorder
COVID-19	Coronavirus disease 2019
CPRD	Clinical Practice Research Datalink
CRP	C-reactive protein
CT	Computed tomography
DAG	Directed acyclic graph
DMPA	depot-medroxyprogesterone acetate
DNA	Deoxyribonucleic acid
DOB	Date of birth
ESR	Erythrocyte sedimentation rate
FSH	Follicle stimulating hormone
GI	Gastro-intestinal
GP	General practitioner
GPRD	The General Practice Research Database
GWAS	Genome-wide association study
HIV	Human immunodeficiency virus
HES	Hospital Episode Statistics
HR	Hazard ratio
HRT	Hormone Replacement Therapy
IBD	Inflammatory bowel disease
IBDU	Inflammatory bowel disease unclassified
IBS	Irritable bowel syndrome
IFN	Interferon
IL	Interleukin
IMRD	IQVIA Medical Research Data
IQR	Inter-quartile range

IRR	Incidence rate ratio
IT	Information technology
IUC	Intra-uterine contraception
IUD	Intra-uterine device
IUS	Intra-uterine system
LARC	Long-acting reversible contraception
LH	Luteinising hormone
MAR	Missing at random
MCAR	Missing completely at random
MHRA	Medicines and Healthcare products Regulatory Agency
MNAR	Missing not at random
MRI	Magnetic resonance imaging
NATSAL	The National Surveys of Sexual Attitudes and Lifestyles
NHS	National Health Service
NICE	The National Institute for Health and Care Excellence
NR	Not reported
NSAID	Non-steroidal anti-inflammatory
OCP	Oral contraceptive pill
OR	Odds ratio
OXMIS	Oxford Medical Information System
PCOS	Polycystic ovarian syndrome
PGD	Patient group direction
POP	Progestogen-only pill
PPA	Prescription Pricing Authority
PY	Person-years
QOF	Quality and Outcomes Framework
RCT	Randomised controlled trial
RR	Risk ratio
SCFA	Short-chain fatty acid
SD	Standard deviation
SES	Simple endoscopic score
SHA	Strategic Health Authority
SRC	Scientific Research Committee
SRH	Sexual and Reproductive Healthcare
STI	Sexually transmitted infection
STROBE	Strengthening the reporting of observational studies in epidemiology
THIN	The Health Improvement Network
TLR4	Toll-like receptor 4
TNF-α	tumour necrosis factor alpha
UC	Ulcerative colitis
UCCIS	Ulcerative Colitis Colonoscopic Index of Severity
UCEIS	Ulcerative Colitis Endoscopic Index of Severity
UCL	University College London
UCLH	University College London Hospitals NHS Foundation Trust

UK	United Kingdom
US	United States
USA	United States of America
VTE	Venous thromboembolic disease
WHO	World Health Organisation

Disseminated work arising from this project to date

Publications:
Pasvol TJ, Horsfall L, Bloom S, Segal AW, Sabin CA, Field N, Rait G. Incidence and prevalence of inflammatory bowel disease in UK primary care: a population based cohort study. BMJ Open 2020;10:e036584. Available at: https://pubmed.ncbi.nlm.nih.gov/32690524/

Pasvol TJ, Macgregor EA, Rait G, Horsfall L. Time trends in contraceptive prescribing in UK primary care 2000-2018: a repeated cross-sectional study. BMJ Sex Reprod Health. 2021 Nov 15:bmjsrh-2021-201260. doi: 10.1136/bmjsrh-2021-201260. Epub ahead of print
Available at: https://pubmed.ncbi.nlm.nih.gov/34782337/

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May 2019: Poster presentation – Digestive Diseases Week San Diego
'Inflammatory Bowel Disease in UK Primary Care: Socio-demographic trends in incidence 2000-2016'

February 2021: Poster presentation (abstract of distinction) – British Society of Gastroenterologists. 'Incidence and Prevalence of Inflammatory Bowel Disease in UK Primary Care: A Cohort Study'

November 2021: Oral presentation – Virtual British Association of Sexual Health and HIV
'Time Trends in Contraceptive Prescribing in UK Primary Care 2000-2018: A Repeated Cross-sectional Study'

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Chapter 1: Inflammatory bowel disease: background, epidemiology, risk factors and associations with contraception

1.1 Introduction

This background chapter summarises the current understanding of the natural history, clinical features and epidemiology of inflammatory bowel disease (IBD), with an overview of pathogenesis and environmental risk factors. A summary of hormonal contraception and patterns of contraceptive prescribing in the UK is given. What is known regarding the relationship between oral contraceptive pills and IBD pathogenesis is discussed.

1.2 Overview of inflammatory bowel disease

IBD is the term given to two idiopathic, chronic diseases that cause relapsing and remitting inflammation of the digestive tract; Crohn's disease (CD) and ulcerative colitis (UC). CD and UC share numerous overlapping epidemiological, clinical and therapeutic characteristics. However, they are distinct from one another in terms of their pathology, presentation and disease course.

Typically, IBD is diagnosed in young adults in their 20s and 30s, but can also present in childhood or later in life. Both CD and UC are currently incurable diseases which cause substantial lifelong morbidity. Patients suffer with severe debilitating symptoms, often requiring multiple medical and surgical interventions over their lifetime. People living with IBD experience reduced quality of life, fatigue, disability and increased rates of bowel cancer. Furthermore, the embarrassing and painful nature of the disease can lead to depression, anxiety and social isolation (4). Although few people die from IBD, all-cause mortality has been shown to be greater in IBD cases than healthy controls (17.1 vs 12.3 per 1,000 person-years) (5).

Previous studies have estimated that there are approximately 620,000 patients with IBD in the UK (6), with an annual cost to the health service of £6,156 and £3,084 per individual for CD and UC respectively (7).

1.2.1 Crohn's Disease

CD is a progressive disease characterised by transmural (exists across the entire gut wall), discontinuous, focal intestinal inflammation resulting in 'skip lesions' within the gut (i.e. segments of bowel which appear normal separated by areas of disease). CD is distinct from UC in that disease may affect any part of digestive tract from mouth to anus, but most commonly the distal small intestine and the proximal colon. In addition, because inflammation is transmural, ulcerated areas are often deep and CD can lead to the development of strictures (abnormal narrowings in the gut) and fistulae (abnormal connections of the gut to other segments of intestine, other organs such as the bladder or vagina or the skin surface).

1.2.1.1 Clinical features

The clinical presentation of CD depends on the location of disease within the digestive tract and by the presence of extra-intestinal manifestations such as arthropathy (joint disease), metabolic bone disease or cutaneous manifestations. Oral disease most frequently presents as aphthous ulcer formation. Oesophageal, gastric and duodenal disease, although less frequently seen, can be severe. Oesophageal disease presents as odynophagia (painful swallowing) or dysphagia (difficulty swallowing) whereas gastric disease can present as dyspepsia (indigestion), vomiting or in rarer cases gastric outlet obstruction. In small bowel disease, CD can present with symptoms of malabsorption such as diarrhoea and weight loss

or growth retardation. The ileum and caecum are the regions of bowel most commonly affected by CD and typically present as diarrhoea and abdominal pain. Individuals with deep, penetrating disease may have additional complications such as ileocaecal abscess formation and can present with peritonism or systemic symptoms such as fever. Approximately 20% of patients have isolated colonic disease which in some cases can be difficult to distinguish from UC (8). Colonic disease will usually present as diarrhoea and bloody stools. Perianal disease is often debilitating and can present in a variety of ways ranging from perianal discomfort to symptoms of perianal fistulae or perianal abscess formation. A number of patients present with anaemia which is often multifactorial from gastrointestinal bloods loss, anaemia of chronic disease and iron, vitamin B_{12} and folic acid deficiency.

1.2.1.2 Natural history of disease

CD has a remitting and relapsing nature, a key feature being a tendency to progress to stricturing or penetrating complications such as fistulae and abscess formation; in a cohort of 2,002 patients with CD, only 12% of individuals remained free of stricturing or penetrating complications after twenty years (9). However, patients with ileal lesions tend to progress faster than their counterparts with isolated colonic disease (10). Twenty years after diagnosis, perianal fistula formation has been shown to occur in 23% of individuals (11), more commonly in those with colorectal involvement. In most cases, the location of affected areas in CD tends to be relatively stable over time; ten years post-diagnosis, extension to the colon in patients with small bowel disease (or vice-versa) has been shown to occur in less than 20% of individuals (12). The cumulative probability of major surgery at five, ten and 20 years post-diagnosis has been reported as 38%, 48% and 58% respectively (13).

1.2.2 Ulcerative colitis

UC is characterised by diffuse, superficial inflammation extending from the rectum proximally but restricted to the colon and not involving the small bowel. The clinical features generally correlate with the extent of inflammation (Figure 1.1). At the time of diagnosis, an estimated 25-75% of cases have disease confined to the rectum and rectosigmoid colon, 20-30% have left-sided colitis and 25% of individuals have disease involving the entire colon (pancolitis) (14).

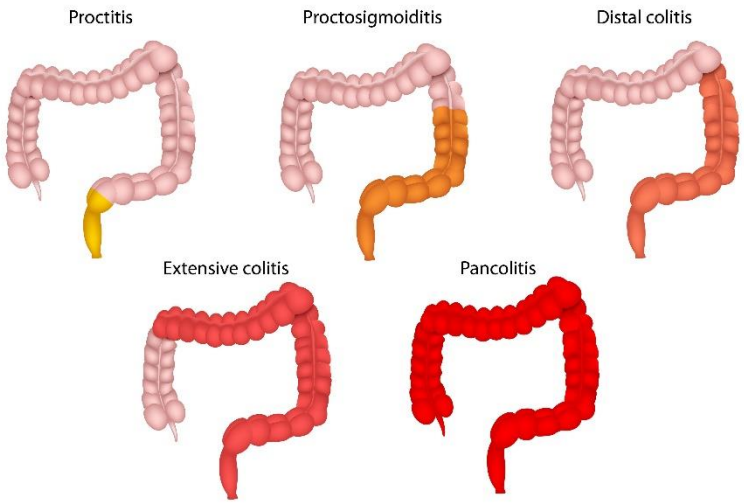


Figure 1.1. Classification of ulcerative colitis in relation to extent of inflammation. Adobe stock image. Taken from stock.adobe.com

1.2.2.1 Clinical features

Ulcerative colitis usually presents with diarrhoea and rectal bleeding and for most individuals the onset is insidious and gradual. Colicky abdominal pain, urgency, tenesmus (a feeling that stools must be passed) and a sensation of incomplete evacuation of stools are common symptoms. Patients with extensive disease may present with features such as anaemia and weight loss or rarely fulminant colitis or toxic megacolon (a severe form of

colonic distension). As with CD, individuals with UC may present with extra-intestinal manifestations.

1.2.2.2 Natural history of disease

In most individuals with UC, the disease follows a relapsing and remitting course. Triggers can be difficult to predict but can include non-adherence to therapy or inter-current infectious enterocolitis. Frequency and severity of relapses varies from individual to individual but in a ten year follow up in a Norwegian cohort of 519 patients, relapsing disease was found in 83% but 48% were relapse free during the first five years of follow up. Additionally, the cumulative colectomy rate was 9.8% after 10 years (15).

1.3 Diagnosis of IBD

The diagnosis of IBD is made using a range of investigations including laboratory studies and imaging in addition to endoscopic and histopathological findings. In a small proportion of individuals (approximately 13% of paediatric IBD and 6% of adult IBD (16)) clinicians are unable to distinguish between UC and CD. This group of patients are referred to as inflammatory bowel disease unclassified (IBDU).

1.3.1 Laboratory studies

A number of laboratory studies reflect disease activity in IBD. Importantly, haemoglobin level, platelet count, leukocyte count, serum albumin and a number of acute phase proteins such as erythrocyte sedimentation rate (ESR) and c-reactive protein (CRP). Additionally, neutrophil derived faecal markers such as calprotectin can assist in monitoring intestinal

inflammation. Stool should also be examined for white blood cells and cultures taken to rule out infectious organisms. In Crohn's disease, patients may present with anaemia relating to intestinal loss, chronic disease and malabsorption of iron, folate and vitamin B12. Complications of IBD can also be identified with laboratory studies, profound leukocytosis (elevated white blood count) in UC may indicate toxic megacolon, whereas pericholangitis and sclerosing cholangitis (a progressive disease characterised by inflammation of the bile ducts) may cause derangement in liver function tests. Additionally, serological markers can be useful the diagnostic workup for IBD. However, these are rarely used in UK clinical practice. Anti-Saccharomyces cervisiae antibodies (ASCA) are found in 60% of CD patients and 10% of UC patients, whereas perinuclear antineutrophil cytoplasmic antibodies (pANCA) are detectable in 60% of UC patients and 10% of CD patients.

1.3.2 Radiological findings

Computed tomography (CT), magnetic resonance imaging (MRI) and intestinal ultrasonography are useful in IBD to characterise disease, guide medical treatment and plan surgery (Figure 1.2). Imaging is also used to detect a wide range of complications and extra-intestinal manifestations of IBD such as abscess formation, toxic megacolon, intestinal perforation, bowel obstruction, primary sclerosing cholangitis and sacroiliitis (inflammation of the sacroiliac joints in the pelvis). Intestinal ultrasonography is becoming increasingly important in both the diagnosis and management of IBD and has the additional benefits of being inexpensive, non-invasive and well tolerated by patients (17).

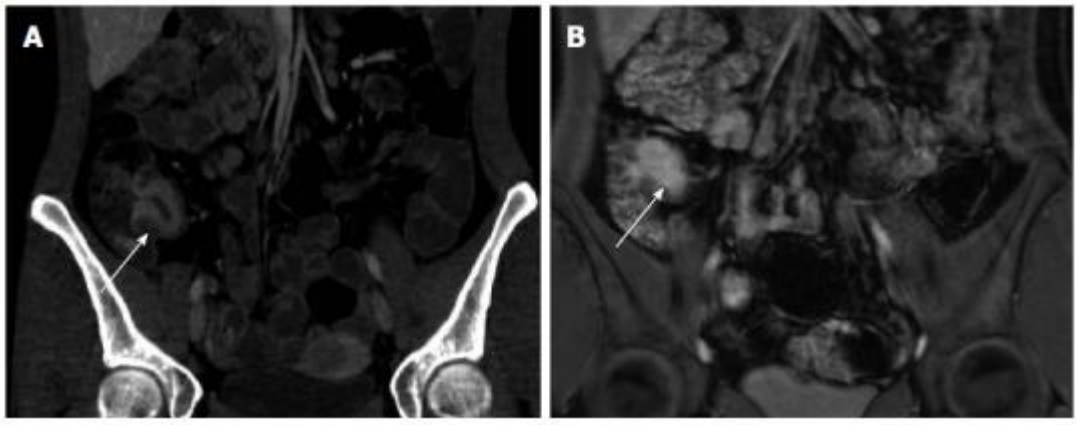


Figure 1.2. Active Crohn's terminal ileitis depicted on computed tomography enterography (A) and magnetic resonance enterography (B) in the same patient. Taken from (17). Article is open-access and distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license.

1.3.3 Endoscopic findings

Lower gastrointestinal (GI) endoscopy is required to diagnose CD, differentiate it from UC and establish extent of disease. Rectal involvement is seen in approximately 60% of patients with CD compared to nearly universally in UC (18). As opposed to in UC, endoscopic findings are characterised by discontinuous areas of inflammation with macroscopically normal colon between (skip lesions). The pattern of inflammation typically consists of ulceration, fissure formation with a 'cobblestone' appearance (gut mucosa with intersecting ulcerations). Scoring systems used to quantify endoscopic findings in CD include the Simple Endoscopic Score in Crohn's Disease (SES-CD) and the Crohn's Disease Endoscopic Index of Severity (CDEIS) (19). Capsule endoscopy may also be used in CD to monitor small bowel disease (20).

Endoscopy is essential in diagnosing and establishing the extent of UC. In UC, inflammation begins in the rectum and extends proximally through the colon up to the point where the disease ends. The characteristic endoscopic findings are erythema, loss of vascular markings, friability, granularity, ulceration and spontaneous haemorrhage. There are a

number of scoring systems used to quantify severity of disease based on macroscopic findings identified on endoscopy such as the Mayo Clinic Endoscopic Subscore, the Ulcerative Colitis Colonoscopic Index of Severity (UCCIS) and the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) (21).

1.3.4 Histopathological findings

The characteristic pattern of inflammation seen in CD is transmural (occurs through all layers of the bowel) and focal (in keeping with endoscopic findings). The bowel wall is thickened and lymphoid infiltrates are seen. The pathognomonic feature is of non-caseating granuloma formation which is seen in 21-60% of CD patients (22).

Unlike in CD, in UC inflammation is confined to the mucosa. Classically there is infiltration with neutrophils, macrophages, lymphocytes and eosinophils. There is continuous crypt architectural irregularity and goblet cell mucin depletion. Granulomas are usually not seen.

There are a number of histological scoring systems which are used to characterise IBD. For UC, there are two scoring systems which have been recommended by The European Crohn's and Colitis Organization: The Robarts Histopathology Index and the Nancy Index (23). In CD, as the lesions are discontinuous and can affect the entire gut, scoring systems are complex and at the time of writing, none have been fully validated (24).

1.4 Aetiology and pathogenesis of IBD

Although IBD has been described for over a century, the aetiology is not yet fully understood. It is generally accepted that IBD results from an abnormal immune response to

commensal gut flora in a genetically susceptible individual (Figure 1.3) (25). However, in both CD and UC, the nature of the immune abnormality, the responsible stimulus and the pattern of genetic susceptibility are yet to be fully understood.

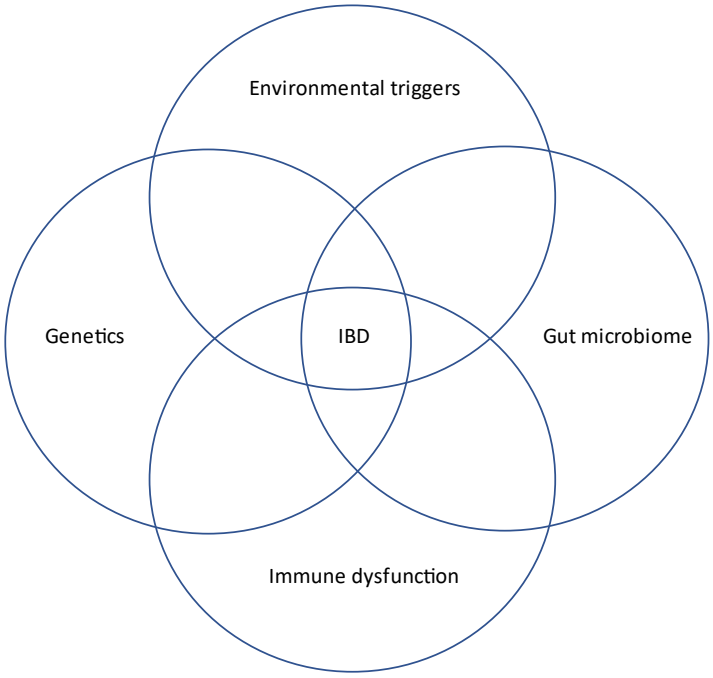


Figure 1.3. IBD develops from a complex relationship between genetics, gut microbiome, immune dysfunction and environmental factors

1.4.1 Genetics

The single strongest risk factor for developing IBD is having an affected relative. Risk is >30% in offspring of two affected parents, approximately 10% for one affected parent and 5% for siblings (26). However, the genetics of IBD is complex with genome wide association studies (GWAS) having identified over 240 loci that are thought to be associated with an increased risk of disease (27, 28). It is estimated that known IBD risk loci may account for only 8% to 13% of disease variance in CD and 4% to 7% in UC (29). However, rare genetic variants associated with severe IBD and very early onset IBD such as those associated with *IL10RA* (where IL-10 signalling is impaired in macrophages resulting in intestinal inflammation)

exhibit Mendelian inheritance patterns (30). The rates of concordance amongst monozygotic twins are higher for CD than UC, suggesting a stronger genetic influence for CD.

There are a wide range of immunological pathways which are disrupted because of genetic polymorphisms related to IBD risk loci. However, a number of common pathways are important including: maintenance of intestinal barrier wall function, innate immunity (the body's first line of defence against invading pathogens), autophagy (a key homeostatic mechanism of the body to degrade and remove unnecessary cell components), adaptive immune responses (responses carried out by white blood cells including antibody responses from B lymphocytes and cell-mediated responses from T lymphocytes), pathogen sensing and the response to oxidative stress (an imbalance between the levels of reactive oxygen species and antioxidants). Several different genes may have an impact on the same pathway (e.g. *NOD2, IRGM* and *LRRK2* influence autophagy whereas *HNF4A, MUC19* and *CDH1* affect intestinal barrier function). Additionally, changes in the pathways as a result of genetic differences may act in combination with one another (gene-gene interactions) or in combination with environmental triggers (gene-environment interactions). For example, the consequences of autophagy defects in Paneth cells (cells in the small intestine which mediate host-microbiome interactions) can be triggered by norovirus infection where abnormal autophagy can play a proviral role by facilitating replication (31, 32)). Table 1.1 lists some of the important IBD risk loci that have been identified.

Table 1.1. Key IBD risk loci identified through whole-genome sequencing and whole-exome sequencing studies. Taken from (33). License to replicate table from Springer Nature obtained 19.02.22. License number 5252450645611

Gene	Locus	IBD variant	IBD/CD/UC
NOD2	16q12.1	rs2066844	CD
		rs2066845	CD
		rs41450053	CD
ATG16L1	2q37.1	rs2241880	CD
IRGM	5q33.1	rs13361189	CD
		rs4958847	CD
LRRK2	12q12	rs33995883	CD
PTPN2	18p11.21	rs2542151	CD and UC
		rs7234029	CD and UC
IL23R	1p31.3	rs10889677A	CD
		rs2201840	CD
		rs2201841	CD and UC
		rs7517847	CD and UC
		rs1343151	CD and UC
		rs11465804	CD and UC
		rs1004819	CD and UC
		rs1495965	CD and UC
		rs11209026	CD and UC
		rs10889677	CD and UC
		rs11209032	CD and UC
Il10	1q32.1	rs1800872	CD and UC
		rs3024496	CD and UC
Il10RA	11q23.3	rs3135932	Paediatric CD and UC
Il10RB	11q23.3	rs2834167	Paediatric CD and UC
CDH1	16q22.1	rs1728785	CD and UC
		rs10431923	CD
HNF4α	20q13.12	rs6017342	UC

1.4.2 Gut microbiome

The human intestinal tract is colonised by countless microorganisms which are collectively known as the gut microbiome. Gut microbes and humans have evolved over time to exist in a mutually beneficial relationship whereby gut organisms play numerous roles in maintaining health such as synthesising important dietary components and breaking down food products. Commensal gut flora also have a role in the immune system by competing with pathogenic organisms for space and nutrients which prevents them colonising the gut and invading the mucosal barrier causing infection. If the function of the mucosal barrier is damaged or impaired, normal commensal gut flora can potentially become pathogenic by crossing the intestinal barrier, provoking an immune response and subsequently causing inflammation.

There are several lines of evidence which support a role of the gut microbiome in the development of IBD. The overall abundance of microorganisms in gut flora which may offer protection against pathogenic colonisation has been shown to be lower in patients with IBD (34, 35). The diversity of gut microorganisms is also reduced; gut biopsies showing a reduction in *Firmicutes* and *Bacteroidetes* species and an increase in *Proteobacteria* and *Actinobacteria* species (36, 37). Additionally, some CD patients have an increased number of pathogenic organisms, specifically *E. coli* (38). Germ-free mice (mice uncolonized by microorganisms) which are genetically predisposed to develop colitis (IL-10 deficient) do not develop disease or develop only mild inflammation when compared to their counterparts colonised by gut commensals (39). Additionally, in germ-free mice, transplanting faecal material from patients with IBD increases susceptibility to colitis compared to transplanting stool from healthy individuals (40). Clinically, exposure to the faecal stream is an important

step in disease recurrence following bowel resection in CD (41), suggesting that commensal gut microbes play an important role in CD pathogenesis.

1.4.3 Immune dysfunction

The mucosal immune system contains 75% of all white blood cells in the human body and produces the majority of immunoglobulin (antibodies). The mucosal immune system of the intestinal tract must strike a balance between triggering appropriate immune responses against pathogenic organisms and preventing unnecessary immune responses to harmless antigens from food and commensal gut flora. It's logical to assume that gut mucosal immunity is abnormal in IBD and there is a large and growing body of evidence relating to specific immunological changes which may provide an insight into IBD aetiology.

In IBD, inflammation occurs through activation of T cells. T-helper cells (also known as CD4+ cells) are an important type of white blood cell which 'help' the activity of other cells by releasing cytokines. Cytokines are proteins which send messages to the immune system to ensure the appropriate type of response is elicited depending on the pathogen type. Cytokines are broadly grouped as 'TH1 associated' or 'TH2 associated' depending on the type of pathogen that has been detected. Traditionally, CD has been thought of as a disease characterised by a TH1 response and UC a TH2 response. However, a more recently described class of T cells 'TH17 cells' has now been implicated in CD pathogenesis (42). Additionally, UC does not neatly fit into the classical description of a TH1 or a TH2 disease; neither IFN-y (a major TH1 cytokine) nor IL-4 (a major TH2 cytokine) are found in excess (43).

B cells produce antibodies against foreign antigens. There are a number of different classes of immunoglobulins including IgG, IgA and IgE. Inflamed IBD tissue has a predominance of IgG compared to healthy gut tissue which has an IgA predominance (44). In mice, defects in IgA production have also been shown to cause dysbiosis (an imbalance of microflora) and inflammation of the gut (45). In patients with UC, an increased abundance of IgG specific to commensal gut flora has been isolated from colonic gut biopsies, and in a mouse model, inducing anti-commensal IgG antibodies has resulted in intestinal inflammation (46). Therefore, in addition to T cells, IgG producing B cells may play an important role in IBD pathology. Other types of cells which appear to play roles in IBD pathogenesis include innate lymphoid cells whose normal function is to induce appropriate immune responses at mucosal surfaces to maintain microbiome homeostasis (47) and macrophages which function to digest foreign pathogens, secrete cytokines and activate T cells (48).

1.4.4 Environmental factors

Changes in the epidemiology of IBD across geographical location and time suggest that environmental risk factors, either alone or by gene-environment interactions, play a major role in disease pathogenesis (49). Given that IBD emerged in high-income countries in the mid-20th century and that IBD has emerged in low and middle income countries over the last 25 years, the epidemiological pattern of disease suggests that environmental factors associated with IBD may be related to industrialisation or ‘Westernisation’ of lifestyle (50).

A wide range of environmental risk factors have been implicated in the pathogenesis of IBD. These range from influences in early life such as non-breastfeeding to factors in later life

such as smoking, diet, appendicectomy, physical activity and exposure to certain drugs including antibiotics and OCPs (49, 51, 52).

1.4.4.1 Smoking

Smoking is the most consistently reported environmental risk factor in association with IBD. However, the relationship is not straightforward. Many studies have shown an increased risk of CD in smokers; a meta-analysis has shown an OR of 1.76 (95% CI 1.40-2.22) for smokers compared to non-smokers (53). Smokers also have a more aggressive disease course and a tendency to progress to treatment escalation and surgery faster; over ten years of follow up, smokers have been shown to have a 29% increased risk of needing repeat surgery compared to non-smokers (54).

In contrast, smoking appears to decrease risk of UC; a meta-analysis has shown an OR of developing UC of 0.58 (95% CI 0.45-0.75) in relation to smoking (53). Smoking cessation has been shown to increase risk of developing UC; data from The Nurses' Health Study found a hazard ratio for developing UC of 3.06 (95% CI 2.00-4.67) in the 2-5 year period after stopping smoking (55). The relationship between smoking and disease progression in established UC is unclear. A ten-year cohort study of 556 UC patients found a reduction in both steroid use (52% vs. 63% p = 0.05) and colectomy rates (32% vs. 42% p = 0.04) amongst smokers compared to non-smokers, with a reduction in progression to pancolitis (14% vs. 26% p = 0.04) (56). However, a more recent study including 6,754 patients living with UC, found that smokers had similar outcomes when compared to never-smokers: disease flare (OR 1.16 95% CI 0.92-1.25), steroid dependency (HR 0.85, 95% CI 0.60-1.11), hospitalisation (HR 0.92, 95% CI 0.72-1.18), thiopurine use (HR 0.84, 95% CI 0.60-1.11), colectomy (HR 0.78, 95% CI 0.50-1.21). Additionally, disease course did not differ between persistent smokers

and those who quit after a diagnosis of UC (57). Importantly, they concluded that the risks associated with smoking outweigh any benefits in people living with UC.

1.4.4.2 Diet

There are a number of lines of evidence which would support an argument that diet is associated with development of IBD. It is established that diet influences the composition of the gut microbiome (58). Therefore, by encouraging or discouraging growth of specific phyla this may result in dysbiosis and precipitate disease. Dietary components can have direct effects on the immune system. For instance, activation of the aryl hydrocarbon receptor by dietary ligands found in cruciferous vegetables such as broccoli and cabbage is necessary to maintain the function of innate immune cells in the gut (59). A number of dietary components such as soluble fibre and zinc play important roles in maintaining the barrier function of the intestinal wall (60). Additionally, in clinic practice, administering enteral nutrition can induce remission in IBD (61).

Although diet is likely to play a central role in IBD pathogenesis, as it is such a complicated exposure, many observational studies suffer from methodological problems and high-quality evidence is scant. That being said, it has been shown that diets containing a high amount of total fat, polyunsaturated fatty acids, omega-6 fatty acids and meat are associated with an increased risk of IBD and diets containing high fibre, and fruit and vegetable intakes are associated with decreased IBD risk (62). Additionally, more recent research has implicated consumption of ultra-processed foods as a risk factor for IBD (HR 1.82 95% CI 1.22-2.72 for >5 servings per day and 1.67 (1.18-2.37) for 1-4 servings per day when compared to no servings per day p=0.006) (63). Therefore, the so-called ‘Western

diet' consisting of large amounts of monosaccharides and disaccharides, low intake of fibre and increasing consumption of processed food could be hypothesised as a mechanism for the rise in IBD incidence in countries such as China and Japan where dietary habits have changed in line with 'Westernisation'

1.4.4.3 Antibiotics

Exposure to antibiotics has been shown to increase risk of IBD. This is a biologically plausible association, given the disruptive effect of antibiotics on the gut microbiome (64). A meta-analysis found a pooled OR for CD of 1.74 (95% CI 1.35-2.23) in those exposed to antibiotics which was increased to 2.75 (95% CI 1.72.4.38) in children. However, risk of UC was not significantly increased (OR 1.08 (95% CI 0.91-1.27)) (65). In this meta-analysis, metronidazole and fluoroquinolones were the most strongly associated with CD and penicillins were shown to have no effect. However, a more recent systematic review concluded that both penicillins and cephalosporins increase risk of CD (66).

There are a wide range of environmental factors that may increase or reduce risk of IBD. Some of the more important exposures identified from an umbrella meta-analysis examining 71 environmental factors are summarised below (Figure 1.4/Figure 1.5) (67).

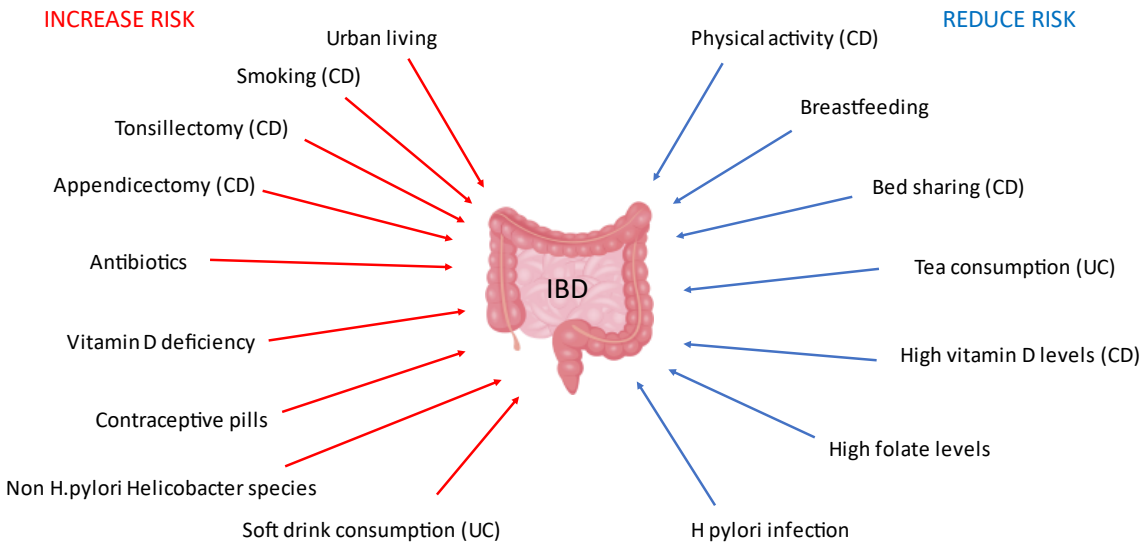


Figure 1.4. Some of the important environmental factors associated with IBD (based on (67))

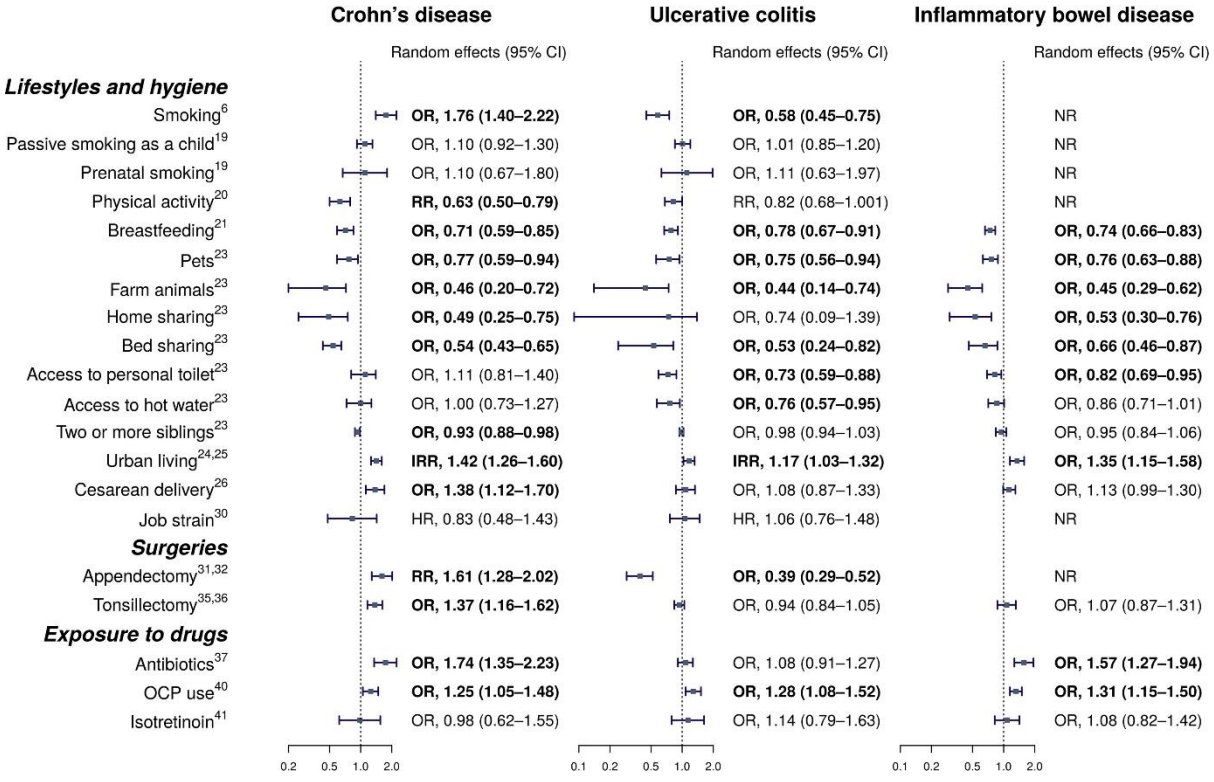


Figure 1.5. Forest plot summarising effect estimates of a meta-analyses reporting associations between IBD and environmental factors. Significant estimates are shown in bold. CI, confidence interval; HR, hazard ratio; IRR, incidence rate ratio; NR, not reported; OCP oral contraceptive pill. Taken from (67). License to replicate figure from Elsevier obtained 19.02.22. License number 5252451127459

1.5 Treatment of IBD

There is currently no cure for IBD. The goal of treatment is to reduce symptoms, achieve and maintain remission and prevent complications. IBD is treated with medications and in many cases, surgery. Classes of drugs used to treat IBD include:

- 5-Aminosalicyclic acid (5-ASA) medications such mesalazine and sulfasalazine which act within the lumen of the gut to reduce inflammation
- Corticosteroids such as prednisolone which can be used in acute flares
- Immunomodulators such as azathioprine, ciclosporin, 6-mercaptopurine and methotrexate
- Anti-tumour necrosis factor (Anti-TNF) biologic drugs including infliximab,adalimumab, certolizumab and golimumab.
- Other biologics including vedolizumab and natalizumab which are antibodies to leukocyte adhesion molecules and ustekinumab which is an anti-IL-12/23 antibody
- Small-molecule agents such as tofacitinib which inhibits Janus kinase 1-3 and ozanimod which modulates S1P receptors
- Antibiotics which can be used in managing a range of complications of IBD such as abscesses, fistulae and toxic megacolon.
- Probiotics which may have a beneficial effect on the gut microbiome
- Laxatives, antidiarrhoeal drugs and vitamin/mineral supplements which may also be used to alleviate symptoms and supplement diet in cases of nutritional deficiency.

As the IBD studies included in this thesis largely relate to incidence, prevalence and pre-diagnostic risk factors rather than disease course, the treatment of established IBD has not been discussed in detail.

1.6 The epidemiology of IBD

Historically, IBD was regarded as a disease of high-income countries such as the UK, USA, Canada and Denmark. However, epidemiological trends over time have seen disease emergence amongst newly industrialised countries such as China and more recently in lower income countries such as those in Sub-Saharan Africa.

The epidemiology of inflammatory bowel disease can be stratified into four chronological stages: disease emergence, acceleration in incidence, compounding prevalence and prevalence equilibrium (Figure 1.6) (68). Disease emergence is where sporadic IBD cases are documented (as is now seen in lower income countries). Newly industrialised countries are in the acceleration in incidence stage, this is where incidence rises rapidly but prevalence is relatively low (69), as was seen in the latter half of the 20th century in high-income countries (70). This rapid rise in incidence could be related to environmental factors associated with 'Westernisation' such as smoking and changes in diet. Alternatively, rising numbers of cases might be related to better services which can improve detection of undiagnosed IBD (e.g. improved access to gastroenterology outpatient clinics and colonoscopy). High income countries such as Canada and the UK are at the next stage, compounding prevalence (71, 72). This is where incidence is no longer rising but prevalence continues to rise. Prevalence rises because although incidence remains stable or even falling, as IBD is usually diagnosed below the age of 40 years, the IBD population is a relatively young cohort and therefore

mortality is low (i.e. more people are being diagnosed than are dying so the overall number of people with IBD increases). The fourth stage (which is largely hypothetical), refers to prevalence equilibrium. This represents a stage where a similar number of people with IBD are dying as are being diagnosed (this is likely to happen as IBD mortality will increase as the population ages); provided another dramatic increase in incidence does not occur, prevalence will flatten off.

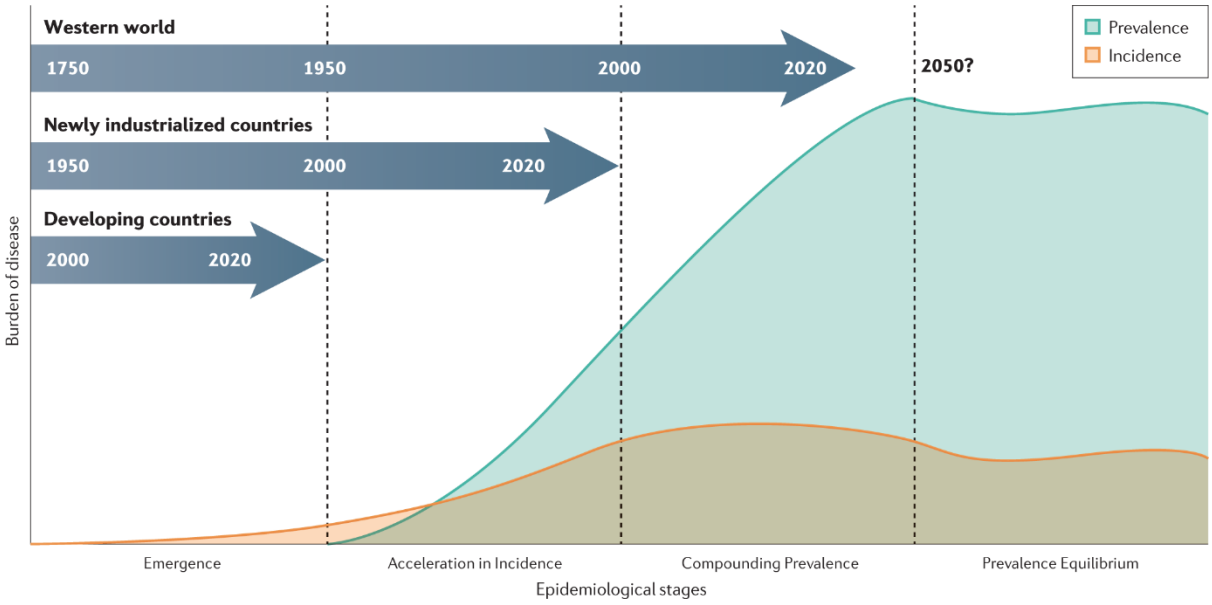


Figure 1.6. The changing pattern in the incidence (orange) and prevalence (blue) of inflammatory bowel disease across the four stages of disease evolution. Taken from (68). License to replicate figure from Springer Nature obtained 19.02.22. License number 5252450439375

Studies using local hospital records and secondary care databases have been conducted to describe the epidemiology of IBD in the UK (73-76). However, patient follow-up is challenging and loss to follow-up may introduce bias, notably where patients do not require hospitalisation and/or move geographical location. Longitudinal UK birth cohorts provide some insights (77, 78). However, case numbers are very small. The UK IBD registry has now been established providing the first ever UK-wide repository of anonymised IBD patient data

for prospective research purposes (79). Although this database holds over 82,000 patient records, it includes incomplete historic data and individuals with more quiescent disease who have minimal contact with secondary care are likely to be under-represented. More recently, estimates of incidence and prevalence of IBD were reported in a rigorously validated IBD cohort of 10,926 cases during the period 2009-2018 in Lothian, Scotland (72). They reported point prevalence estimates of 784, 284 and 432 per 100,000 on 31/08/2018 and overall incidence of 40.8, 13.6 and 19.8 per 100,000 person years for IBD, CD and UC respectively. However, it remains unknown if their findings are generalisable across the UK.

Electronic general practice (GP) health records can enable large-scale investigation of incidence in relatively rare diagnoses such as IBD (80). When this PhD was started, the largest such incidence study performed in the UK was undertaken in Northern England and included 179 incident cases of IBD diagnosed in a population of 135,723 during the period 1984 to 1995 (81).

1.7 Contraception

Contraception refers to the deliberate use of artificial methods to prevent pregnancy following vaginal sexual intercourse.

1.7.1 The menstrual cycle

To understand how contraception works, it is important to have a basic knowledge of the normal female menstrual cycle. The menstrual cycle is defined as the time from the first day of a woman's period to the day before her next period and is on average 28 days long. The menstrual cycle is made up of four phases (menstruation, the follicular phase, ovulation and

the luteal phase) and is broadly controlled by the release of two gonadotrophic hormones from the pituitary: follicle stimulating hormone (FSH) and luteinising hormone (LH), and two ovarian steroid hormones: oestrogen and progesterone.

FSH is secreted from the pituitary during the follicular phase which stimulates the development of ovarian follicles containing ova (eggs). Later in this phase, only one follicle continues to develop which produces oestrogen. The ovulatory phase then starts with a surge in LH levels mid-cycle stimulating the release of an ovum. This is the time when a woman is most fertile. The oestrogen levels decrease during the LH surge and progesterone begins to increase. The luteal phase follows during which the ruptured follicle closes forming a corpus luteum which produces progesterone. The high levels of oestrogen and progesterone cause the lining of the uterus to thicken and have a negative feedback effect on the pituitary to inhibit production of FSH and LH. If the ovum is not fertilised or doesn't implant, then oestrogen and progesterone levels fall and the lining of the womb is shed (menstruation) (Figure 1.7).

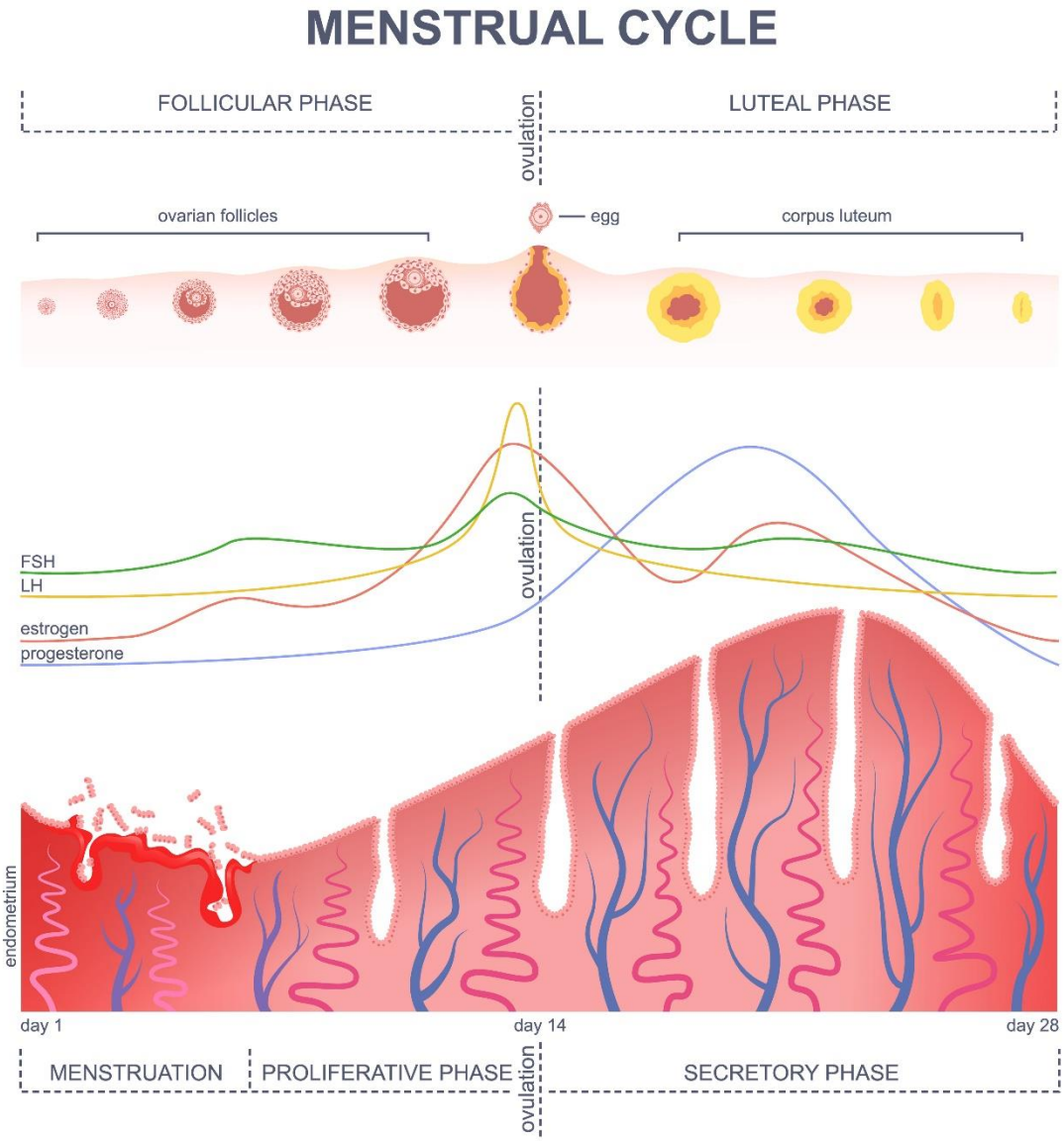


Figure 1.7. The menstrual cycle. Adobe stock image. Available at https://stock.adobe.com/

1.7.2 Methods of contraception

Since the introduction of the combined oral contraceptive pill (COCP) over 50 years ago, there have been vast improvements in the range of available contraceptive choices (Table 1.3). Hormonal contraception can be broadly split into three categories: combined hormonal contraception (CHC), progestogen-only pills (POP) and long-acting reversible contraception (LARC).

1.7.2.1 Combined hormonal contraception

CHC refers to methods which deliver both an oestrogen, usually ethinylestradiol (a synthetic oestrogen) and a progestin (a synthetic progestogen). There are three methods of CHC available in the UK including: COCPs, transdermal patches and intravaginal rings. CHC works primarily by inhibiting ovulation. The synthetic oestrogen and progestogen that are released act on the hypothalamo-pituitary-ovarian axis to supress LH and FSH and thus inhibit ovulation in addition to suppressing endogenous levels of oestrogen and progesterone. The progestogen in CHC also has effects on cervical mucus consistency, endometrial thickness and tubal mobility which may further contribute to the contraceptive effect.

Although CHC is effective at preventing pregnancy (over 99% if taken according to instructions), it is not without unwanted side effects and risks. Commonly, women may experience mood changes, breast tenderness, changes in libido and headache. However, there are serious but rare effects including an increase in risk of thromboembolic disease, cervical cancer and breast cancer. Therefore, relative and absolute contraindications to CHC exist including: increased age, smoking, obesity, hypertension and history of venous thromboembolic disease (VTE) (82).

1.7.2.1.1 Combined oral contraceptive pills

COCPs are the most used CHC in the UK. These are once-a-day pills which are designed to be taken as 28-day cycles. Pill strips typically contain 21 pills to be taken on consecutive days followed by a seven-day break before starting the next strip. The first seven pills inhibit

ovulation, then the next 14 maintain anovulation. During the seven-day break a woman will usually have a 'withdrawal bleed' following 'withdrawal' of the contraceptive hormones.

In the UK, COCPs are usually categorised by 'pill generation' – the order in which the pills were rolled out chronologically. Most pills contain ethinylestradiol and the difference between the generations is the progestogen formulation (Table 1.2).

Table 1.2. COCP generations and progestogen formulation

Generation	Progestogen
First	Norethisterone
Second	Levonorgestrel
Third	Desogestrel, gestodene, norgestimate
Fourth	Drospirenone, dienogest, nomegestrol acetate

Several newer progestogens in COCPs are used for their anti-androgenic properties which can help in the treatment of oily skin conditions such as acne. These include drospirenone, dienogest and nomegestrol acetate. Another progestogen-like drug which can be used for its anti-androgenic properties is cyproterone acetate which is combined with ethinylestradiol (co-cyprindiol). This can be used to treat acne and hirsutism and has a contraceptive effect.

1.7.2.2 Progestogen-only pills

POPs are a popular method of contraception in the UK and have fewer contraindications than COCPs. POPs have a range of contraceptive effects. POPs increase the viscosity of cervical mucus which prevents sperm entering the uterus. POPs also influence the

endometrium to prevent implantation and reduce cilial function in the fallopian tube which slows the movement of the ovum. Additionally, POPs can act to supress ovulation; 60% of women taking a levonorgestrel POP are anovulatory which is increased to 97% in those taking a desogestrel POP (83, 84). As women are not always anovulatory when taking POPs, the 'missed pill window' before additional contraceptive precautions must be taken is shorter for POPs than COCPs. For desogestrel containing POPs this is 12 hours and for levonorgestrel containing POPs this is three hours.

Unlike COCPs, POPs are taken continuously throughout the cycle without a seven-day break (i.e. 28 pills per strip). Although there are side effects associated with POPs including bleeding and mood change, POPs do not contain oestrogen. Therefore, they are not contraindicated in those at higher risk of VTE such as smokers or women with raised BMI.

1.7.2.3 Long-acting reversible contraception:

These are methods which do not depend on the user to regularly take or use them and include: contraceptive implants, intramuscular/subcutaneous injections and intra-uterine contraception (IUC). Because they require very infrequent user input to change or replace them, they dramatically reduce non-compliance related contraceptive failure (for example late or missed pills) and are the most effective reversible methods at preventing pregnancy (85). They have additional advantages of being long-lasting and more cost-effective than OCPs

1.7.2.3.1 Progestogen-only contraceptive implants

At the time of writing, the only contraceptive implant available in the UK is the etonogestrel subdermal implant (the levonorgestrel implant was withdrawn in the UK in 1999 due to the reported frequency of bleeding problems). The etonogestrel implant is a 4cm rod which is placed sub-dermally in the upper arm and releases the progestogen etonogestrel. It suppresses ovulation and has additional effects on the endometrium and cervical mucus as per other progestogen-containing contraception. The etonogestrel implant can remain in situ for three years before it must be changed. There is no increased risk for VTE with the implant but unpredictable bleeding is a common side-effect and women must be counselled on this prior to insertion.

1.7.2.3.2 Progestogen-only injectables

The main injectable contraception available in the UK is depot medroxyprogesterone acetate (DMPA). Norethisterone enantate is also available but far less frequently used (licensed for short-term use for women whose partners have had a vasectomy). Injectable contraceptives work by primarily by inhibiting ovulation but also have effects on the cervical mucus and endometrium.

DMPA is administered by deep intramuscular injection or subcutaneous injection every 13 weeks but can be administered up to seven days late with adequate contraceptive protection. The majority of women will become amenorrhoeic (their periods will stop) taking DMPA which is not acceptable for some women (86) but others may consider this a benefit (87). Suppression of ovulation with use of DMPA can lead to reductions in circulating levels of oestrogen. Although background estradiol levels have been shown to be similar to

those in the early menstrual cycle, long term use of DMPA can result in loss of bone mineral density which is recovered after DMPA is stopped (88). For this reason, DMPA is not suitable for those at increased risk of fracture such as very underweight women. Commonly reported side-effects of DMPA include altered bleeding patterns, weight gain and diffuse hair loss. After DMPA is stopped, fertility does not immediately return to normal and it has been shown that that median delay from discontinuation of DMPA to conception is approximately 5.5 months (89). However, women are usually informed that it may take up to a year for fertility to return to normal.

1.7.2.3.3 Intra-uterine contraception

IUC refers to indwelling contraceptives which are placed in the uterus. The two types of IUC available in the UK are copper intra-uterine devices (IUD) which consist of copper and plastic and can remain in situ for up to 5-10 years and intra-uterine systems (IUS) which release the progestogen levonorgestrel daily and can remain in situ for up to 3-5 years. Due to the local effect of the progestogen, the IUS can also be used to manage heavy menstrual bleeding.

When using an IUD, the copper in the device interferes with the ovum and the sperm and inhibits fertilisation. Additionally, the copper content of the cervical mucus can inhibit sperm passing through the cervix. The IUS works in a number of ways. Firstly, it is a foreign body which may contribute towards contraception. Secondly, the progestogen thickens cervical mucus to prevent sperm penetration. Importantly, high intrauterine concentrations of levonorgestrel have an effect on the endometrium to prevent implantation and within one month, extensive morphological and functional differentiation of endometrial stromal cells has occurred (decidualization) (90). Although the IUS releases progestogen, this acts

locally and has little effect on the hypothalamic-pituitary axis with serum estradiol levels remaining normal and most women continuing to ovulate (91, 92).

Although intrauterine contraception insertion is a relatively safe procedure, women must be counselled on the associated risks including vasovagal reaction and uterine perforation. STI screening must also be offered to all women at risk prior to insertion. Altered menstrual bleeding patterns are a common reason for discontinuation of intra-uterine contraception, particularly IUDs where bleeding can be heavier.

1.7.2.4 Other methods

Other non-hormonal contraceptives methods exist including barrier methods (condoms, diaphragms, cervical caps and contraceptive sponges), fertility awareness methods (timing around the menstrual cycle) and sterilisation. As this thesis focuses on hormonal contraception, these have not been discussed in detail.

Table 1.3. Summary of non-barrier contraceptive methods available in the UK. Adapted from: Your Guide to Contraception – FPA The Sexual Health Company. Available at https://www.fpa.org.uk/download/your-guide-to-contraception/.

	Effectiveness	How it works	Advantages	Disadvantages	Comments
Combined oral contraceptive pill 	Over 99% effective if always taken according to instructions (perfect use) With typical use, around 91% effective Around 9 in 100 pill users will get pregnant in a year	Contains two hormones – oestrogen and progestogen. It stops ovulation, thickens cervical mucus to prevent sperm reaching an egg and thins the lining of the uterus to prevent a fertilised egg implanting	-It usually makes periods regular, lighter and less painful -Reduces risk of cancer of the ovary, uterus and colon. -Suitable for healthy non-smokers up to the age of 50. -Fertility will return to normal after cessation.	-Not suitable for very overweight women, smokers aged over 35 or women with certain comorbidities -A low risk of some risk of serious side effects such as thromboembolic disease, breast and cervical cancer. -Can be temporary side effects such as headaches, nausea, mood changes and breast tenderness.	-Missing pills, vomiting or severe, long-lasting diarrhoea can make it less effective. -Some medicines can make it less effective. -Breakthrough bleeding and spotting is common in the first few months -women may choose not to have a monthly bleed
Progestogen-only pill	Over 99% effective if always taken according to	Contains the hormone progestogen. POPs	-Can be used if oestrogen is contraindicated.	-Periods may stop, or be irregular,	-Must be taken at the same time each day.

	instructions (perfect use) With typical use, around 91% effective Around 9 in 100 pill users will get pregnant in a year	containing desogestrel stop ovulation, thicken cervical mucus to stop sperm reaching an egg and thin the lining of the uterus to prevent implantation. Other POPs thicken cervical mucus and may stop ovulation.	-May help with premenstrual symptoms and painful periods.	light, or more frequent. -May be temporary side effects such as acne, breast tenderness, weight change and headaches.	-Not effective if taken over 3 hours late (12 hours for pills with desogestrel) or after vomiting or severe, long-lasting diarrhoea. -Some medicines may make it less effective.
Contraceptive vaginal ring 	Over 99% effective if always used according to instructions (perfect use) With typical use, around 91% effective Around 9 in 100 ring users will get pregnant in a year	A small, flexible plastic ring is put into the vagina releases oestrogen and progestogen. It stops ovulation, thickens cervical mucus to prevent sperm reaching an egg, and thins the lining of the uterus to prevent a fertilised egg implanting.	-Can be changed weekly -Is not affected by vomiting or diarrhoea. -It usually makes periods regular, lighter and less painful. -It's easy to insert and remove. -It improves acne for some women	-Not suitable for very overweight women, smokers aged over 35 or women with certain comorbidities -A low risk of serious side effects such as thromboembolic disease, breast and cervical cancer. -Can be temporary side effects such as increased vaginal discharge, headaches, nausea, mood changes and breast tenderness.	-Women must be comfortable with inserting and removing it. -Ring is used for 3 weeks out of 4. -Some medicines can make it less effective. -Breakthrough bleeding and spotting may occur in the first few months. -Women may choose not to have a monthly bleed
Contraceptive patch 	Over 99% effective if always used according to instructions (perfect use) With typical use, around 91% effective; around 9 in 100 patch users will get pregnant in a year	A small patch stuck on the skin releases Two hormones, oestrogen and progestogen. It stops ovulation, thickens cervical mucus to prevent sperm reaching an egg, and thins the lining of the uterus to prevent a fertilised egg implanting	-Can be changed weekly -Is not affected by vomiting or diarrhoea. -It usually makes periods regular, lighter and less painful. -It improves acne for some women	-Not suitable for very overweight women, smokers aged over 35 or women with certain comorbidities -A low risk of serious side effects such as thromboembolic disease, breast and cervical cancer. -Can be temporary side effects such as headaches, nausea, mood changes and breast tenderness. --Possible skin irritation.	-May be seen. -New patch is used each week for 3 weeks out of 4. -Some medicines can make it less effective. -Breakthrough bleeding and spotting is common in the first few months. -Women may choose not to have a monthly bleed
Contraceptive implant 	Over 99% effective once fitted. Fewer than 1 in 100 implant users will get pregnant in a year	Small flexible rod put under the skin of the upper arm. Releases the hormone progestogen, which stops ovulation, thickens cervical mucus to prevent sperm reaching an egg, and thins the lining of the uterus to prevent a fertilised egg implanting.	-Works for 3 years but can be taken out sooner. -Contraception for as long as the implant is in place. -When the implant is removed, periods and fertility will return to normal.	-Periods may stop, be irregular or last longer. -It requires a small procedure to fit and remove it.	-Put in using a local anaesthetic and no stitches are needed. -Tenderness, bruising and some swelling may occur. -Usually implant can be palpated, but it can't be seen. -Some medicines may stop the implant from working
Contraceptive injection	With perfect use, over 99% effective With typical use, around 94%	Releases the hormone progestogen which stops ovulation,	-Lasts for 13 weeks	-Bleeding may stop, be irregular or last longer.	-The injection can't be removed from the body so any side effects

	effective; around 6 in 100 injection users will get pregnant in a year	thickens cervical mucus to prevent sperm reaching an egg, and thins the lining of the uterus to prevent a fertilised egg implanting.	-Contraception for as long as the injection lasts -May reduce heavy, painful periods for some women.	-Periods and fertility may take time to return after stopping the injection. -Some women gain weight.	may continue for as long as it works and for some time afterwards. -Not affected by other medicines, diarrhoea or vomiting.
Intra-uterine system 	Over 99% effective once fitted. Fewer than 1 in 100 IUS users will get pregnant in a year	A small T-shaped plastic device, which slowly releases the hormone progestogen, is put into the uterus. It thins the lining of the uterus to prevent a fertilised egg implanting and thickens the cervical mucus which makes it difficult for sperm to meet an egg.	-Works for 3–5 years depending on type, but can be taken out sooner. -Contraception for as long as the device is in place -With the Mirena IUS, periods usually become lighter, shorter and sometimes less painful. -When the IUS is removed, fertility will return to normal.	-Irregular bleeding or spotting is common in the first 6 months. -Very small chance of getting an infection during the first 20 days after insertion. -Insertion can be uncomfortable.	-Women must be taught to check the IUS is in place. -Periods may stop altogether. -A check for any existing infection may be advised before an IUS is put in. -Not affected by other medicines. -If fitted after 45, the Mirena IUS can stay in place until the menopause.
Intra-uterine device 	Over 99% effective once fitted. Fewer than 1 in 100 IUD users will get pregnant in a year.	A small plastic and copper device is put into the uterus. It stops sperm reaching an egg, and may also stop a fertilised egg implanting in the uterus.	-Works as soon as it's put in. -Works for 5–10 years depending on type, but can be taken out sooner. -Contraception for as long as the device is in-situ -When the IUD is removed, fertility will return to normal.	-Periods may be heavier or longer and more painful. -Very small chance of getting an infection during the first 20 days after insertion. -Insertion can be uncomfortable	-Women must be taught to check the IUS is in place. -A check for any existing infection may be advised before an IUD is put in. -Not affected by other medicines. -If fitted after 40 it can stay in place until the menopause.
Sterilisation (female) 	The overall failure rate is about 1 in 200.	The fallopian tubes are cut, sealed or blocked either by an operation or with a procedure called hysteroscopic sterilisation. This stops the egg and sperm meeting.	-It can't easily be reversed. -Once the sterilisation has worked, lifelong contraception is provided. -Periods are unaffected.	-Other contraception is required until the sterilisation is effective. -All operations carry some risk, but risk of serious complications is low. -There's a small increased risk of ectopic pregnancy if the sterilisation fails. -A general anaesthetic may be required	-Shouldn't be chosen if in any doubt, and counselling is important. -Some women experience discomfort or some pain for a short time after sterilisation. It's important to rest and avoid strenuous activity for a while after the procedure.
Sterilisation (male) 	About 1 in 2,000 vasectomies fail.	The vas deferens that carry sperm from the testicles to the penis are cut, sealed or tied.	-It can't easily be reversed. -Once the sterilisation has worked, lifelong contraception is provided. -Usually performed under a local anaesthetic.	-Contraception must be used until a semen test shows that no sperm are left. This can take at least 8 weeks. -Some people may experience ongoing testicular pain but this isn't common. Treatment for this is often unsuccessful.	-Shouldn't be chosen if in any doubt, and counselling is important. -Some men experience discomfort or some pain for a short time after sterilisation. It's important to rest and avoid

					strenuous activity for a while after the procedure.

1.7.3 Contraceptive prescribing

1.7.3.1 Contraceptive prescribing globally

Contraceptive prescribing patterns vary widely throughout the world. In Europe and North America, OCPs are the most commonly prescribed. However, in Asian countries, IUDs are the most commonly used. Sub-Saharan Africa is the only region where injectables are the dominant method amongst women of reproductive age (Figure 1.8)

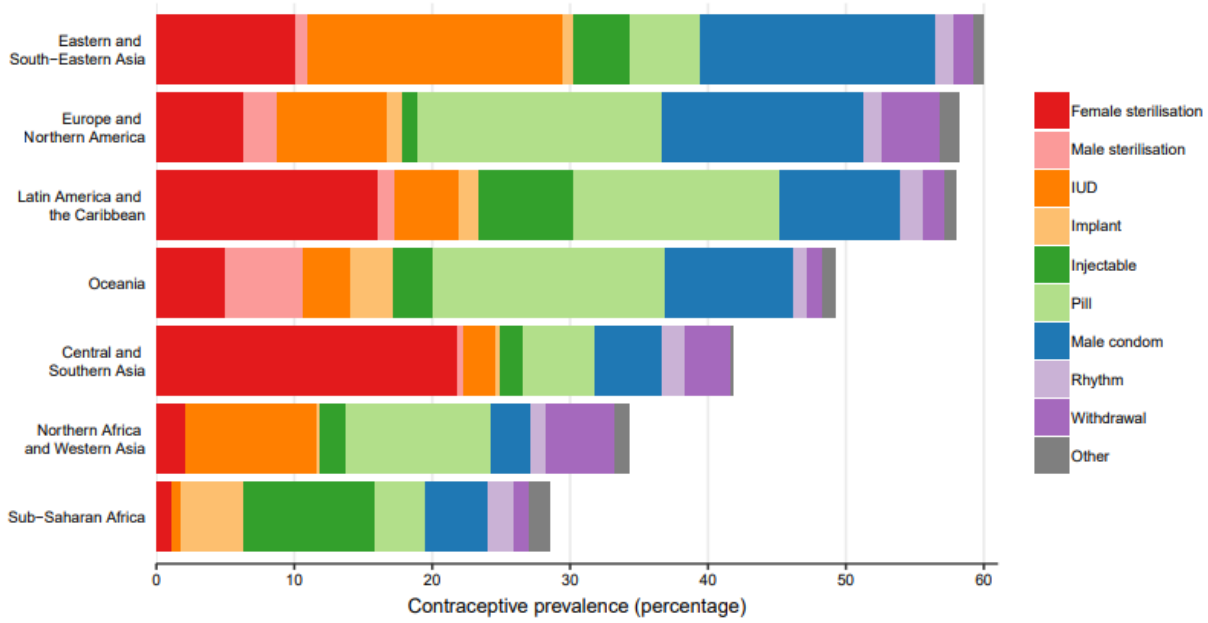


Figure 1.8. Contraceptive prevalence by method amongst women of reproductive age (15-49 years), by region, 2019. Data source: Calculations are based on the data compilation World Contraceptive Use 2019, additional tabulations derived from microdata sets and survey Taken from (93). Available at https://www.un.org/development/desa/pd/content/contraceptive-use-method-2019. Document is open-access and distributed in accordance with the Creative Commons Attribution 3.0 IGO (CC BY 3.0 IGO) license.

Globally, over the last 25 years, there has been a reduction in the prevalence of sterilisation, IUD, rhythm and withdrawal methods and an increase in the use of male condoms and hormonal methods. Temporal changes in contraceptive use also demonstrate marked heterogeneity from region to region. Since the mid 1990s, there has been an increase in

OCP use in North America, Europe, Latin America, Caribbean and Asian countries. Comparatively, as contraception has taken off in Sub-Saharan Africa, implants, injections and condoms have increased in prevalence, whereas OCP use has remained relatively low (Figure 1.9).

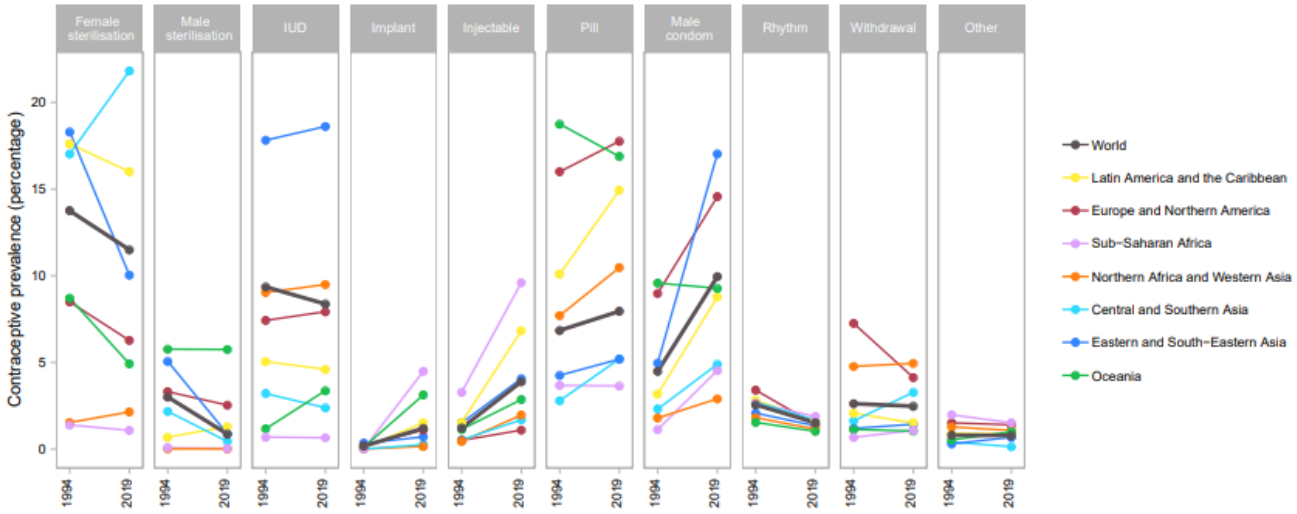


Figure 1.9. Trends in contraceptive prevalence by method among women of reproductive age (15-49 years), by region, 1994 and 2019. Data source: Calculations are based on the data compilation World Contraceptive Use 2019, additional tabulations derived from microdata sets and survey. Taken from (93). Available at https://www.un.org/development/desa/pd/content/contraceptive-use-method-2019. Document is open-access and distributed in accordance with the Creative Commons Attribution 3.0 IGO (CC BY 3.0 IGO) license.

1.7.3.2 Contraceptive prescribing in the UK

In the UK, approximately 26% of women aged 16-49 years use hormonal contraception (94). Several new hormonal methods have become available during the last 20 years, including the desogestrel POP, COCPs containing drospirenone, combined hormonal patches and vaginal rings (Table 1.3). Additionally, the UK has seen policy-related initiatives aimed at reducing unwanted pregnancy (95, 96).

In 2005, The National Institute for Health and Care Excellence (NICE) published its first LARC guideline with the aim to increase LARC uptake and reduce unintended pregnancies (97).

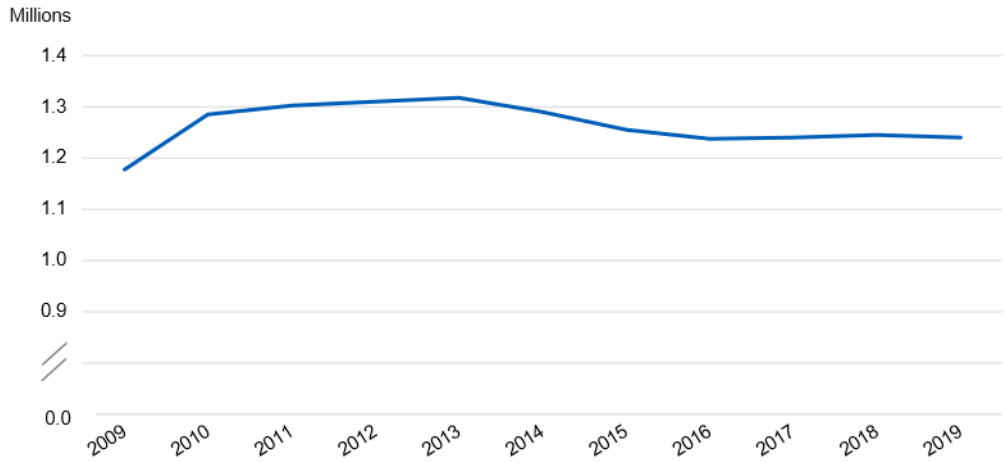
This guideline advised that all women requiring contraception should be given information about LARC.

In 2009, a pay-for-performance Quality and Outcomes (QOF) incentive for LARC counselling was introduced into general practice, with the aim of increasing LARC uptake in women attending for oral or emergency contraception (96). QOF is a way of improving the quality of patient care by financially rewarding GP practices based on certain indicators. Despite a rise in LARC uptake of 32% and a concurrent reduction in abortion rates of 38.3% (98) , this incentive was retired in 2014, and at the same time, in an effort to reduce spending, funding to sexual and reproductive health (SRH) services was reduced (99). The resulting closure of SRH services forced more women to seek contraception from other sources, such as primary care.

Detailed data on trends in contraceptive provision from SRH services is published annually by National Health Service (NHS) Digital (100). However, most women seek hormonal contraception from general practice and not SRH services. A cross sectional survey of 4,571 women age 16-44 years conducted in 2010-2012 as part of The National Surveys of Sexual Attitudes and Lifestyles (NATSAL) reported that 59.1% of women sought contraception from their GP, 28.6% from retail outlets, and 23.0% from community services (101). However, it is important to note that they included barrier methods of contraception which can be bought over-the-counter in their analysis. The proportion of women obtaining contraception from SRH services is progressively decreasing in line with reductions in funding and closure of SRH centres; only 5% of UK females aged 13 to 54 years used an SRH service for reasons of contraception between 01/04/2019 and 31/03/2020 (100). Women seeking contraception

from specialist SRH services also represent a selected group who are more likely to have complex contraceptive needs than the majority of women who obtain contraception from primary care.

Data on contraceptive prescriptions issued in primary care in England are reported in absolute numbers by NHS Digital. Over the last ten years they report relatively stable prescribing of LARC and a fall in the prescribing of user-dependant methods (i.e. OCPs, patches and vaginal rings) (Figure 1.10/Figure 1.11). However, data published by NHS digital are not linked to individual patients so demographic information such as age or social deprivation are not available. Additionally, data are not published for prescriptions dispensed in the devolved nations of the UK (100).



*Fig*ure 1.10. Number of prescriptions for long-acting reversible contraception dispensed in the community in England by calendar year. Taken from *https://digital.nhs.uk/data-and-information/publications/statistical/sexual-and-reproductive-health-services/2019-20/prescriptions-for-contraceptives-dispensed-in-the-community*

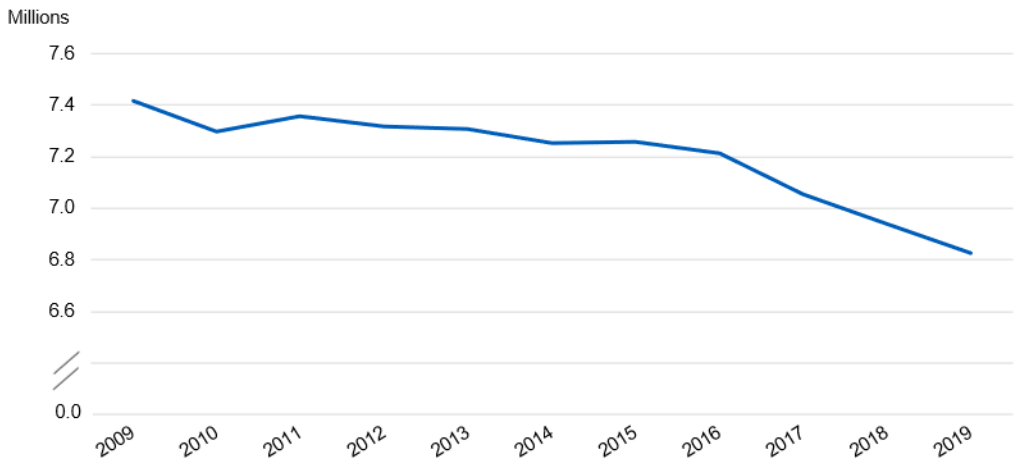


Figure 1.11. Number of prescriptions for user-dependant contraception dispensed in the community in England by calendar year. Taken from *https://digital.nhs.uk/data-and-information/publications/statistical/sexual-and-reproductive-health-services/2019-20/prescriptions-for-contraceptives-dispensed-in-the-community*

Changes in the profile of contraceptive users have been captured through comparison of NATSAL surveys (102). However, this was done by comparing two cross sectional surveys, the first taken in 2000 and the second in 2010 with no more recent data included. Two interrupted time series have used data from the Prescription Pricing Authority (PPA) and Clinical Practice Research Datalink (CPRD) to assess the impact of QOF on LARC uptake in general practice for the period 2004-2014 (98, 103). These studies focussed on LARC rather than CHC or POPs. Additionally, practices from Northern Ireland were not included in their analysis and these studies predate the withdrawal of the QOF indicator in 2014 and reductions in funding to SRH services. Cross-sectional data from The Health Improvement Network (THIN) Database has been used to describe contraceptive prescribing during the year 2008 in a cohort of 194,054 women (104). However, longitudinal trends were not described.

1.8 Contraceptive pills and inflammatory bowel disease

The association between exposure to oral contraceptive pills (OCPs) and development of IBD was first described in the 1960s and 1970s in the form of case reports (105, 106). Although OCPs have changed dramatically since their release in the UK in 1957, now containing far lower doses of sex steroids (107), case-control and cohort studies have continued to show a relationship between oral contraceptive use and IBD, with women exposed to OCPs being more likely to develop disease (108, 109). Oestrogens and progestogens in OCPs have been strongly implicated in immune system modulation (110, 111) and OCPs have been linked to a number of autoimmune and 'immune-related' conditions including hyperthyroidism, interstitial cystitis, systemic lupus erythematosus and multiple sclerosis (112). Note, for the purposes of this thesis 'OCPs' refers to both COCPs and POPs.

1.8.1 Proposed biological mechanisms

Although numerous epidemiological studies have demonstrated associations between OCPs and IBD, they shed little light on the biological mechanism mediating this relationship. However, proposed theories largely relate to the effect of increased exogenous oestrogen and reduced endogenous testosterone on the gut microbiome, gut perfusion, intestinal wall function and host immunity (Figure 1.12).

The relationship between oral contraceptives and IBD risk may be related to the modulation of endogenous androgens. CHC is associated with increased levels of exogenous ethinylestradiol and decreased levels of endogenous testosterone (113). Endogenous levels of testosterone are linked to expression of Toll-like receptor 4 (TLR4) on macrophages which

play a crucial role in the ability of the innate immune system to recognise pathogens (114). The failure of macrophages to secrete cytokines in response to foreign pathogens has been implicated in the pathogenesis of CD (115). In men, low testosterone is associated with an increase in pro-inflammatory cytokines including IL-1β, IL-6 and TNF-α (116) and is a risk factor for severe influenza A and COVID-19 infection (117, 118). Animal studies have shown that gut microbes may modulate levels of endogenous androgens and potentially drive the development of autoimmune disease (119). Therefore, it could be hypothesised that a complex relationship exists in humans between endogenous testosterone, gut microbiota and immune function. Of note, one study has demonstrated an inverse relationship between levels of circulating endogenous testosterone and risk of CD (120).

Another plausible mechanism is the effect of oestrogens on the microbiota of the alimentary canal. Oral contraceptives have been shown to increase proliferation of oral *Candida* and *Prevotella* species which can in turn increase risk of periodontitis (121); a Korean population based cohort study has linked periodontitis to UC (122). It is well established that exogenous oestrogen affects vaginal microbiota (123). However, more recent research has implicated the oestrogen-gut microbiome axis as playing a crucial role in the pathogenesis of a number of oestrogen-mediated diseases (124). If a relationship exists between oestrogen levels and the gut microbiome then one could hypothesise that changing circulating levels of oestrogen may in turn disrupt gut flora and potentially precipitate gastrointestinal disease.

Oestrogen has been shown to modulate the barrier function of the intestinal wall in rodents (125, 126). Therefore, changes in circulating oestrogen may modify the risk of translocation

of gut microbes. It has been proposed that infectious gastroenteritis can trigger IBD; individuals who have an episode of bacterial gastroenteritis are four-fold more likely to develop IBD in the following year (127). Therefore, if the barrier function of the intestinal wall is compromised by exogenous hormones then this may increase the risk of triggering IBD in a genetically susceptible individual. Additionally, a number of bacterial enteric infections such as shigellosis can be transmitted sexually and one could hypothesise that women taking contraceptives may be at greater risk of exposure (25).

Traditionally, CD is thought to be characterised by gut inflammation mediated by TH1 related cytokines (42). Whereas in UC, mucosal inflammation is thought be primarily mediated by TH2 cytokines (128). Oestrogen has been linked to inhibition of TH1 mediated cytokines and stimulation of TH2 mediated cytokines (129). Additionally, oestrogen has been implicated in the pathogenesis and disease progression in a number of TH2 mediated inflammatory conditions (130, 131). This would support a relationship between exogenous oestrogens and UC, but not CD.

Some have theorised that IBD development may be related to micro-ischaemia within the vasculature of the gut (132) and it is established that oestrogen containing contraceptives

are associated with VTE (133), risk increasing with higher doses of oestrogens (134).

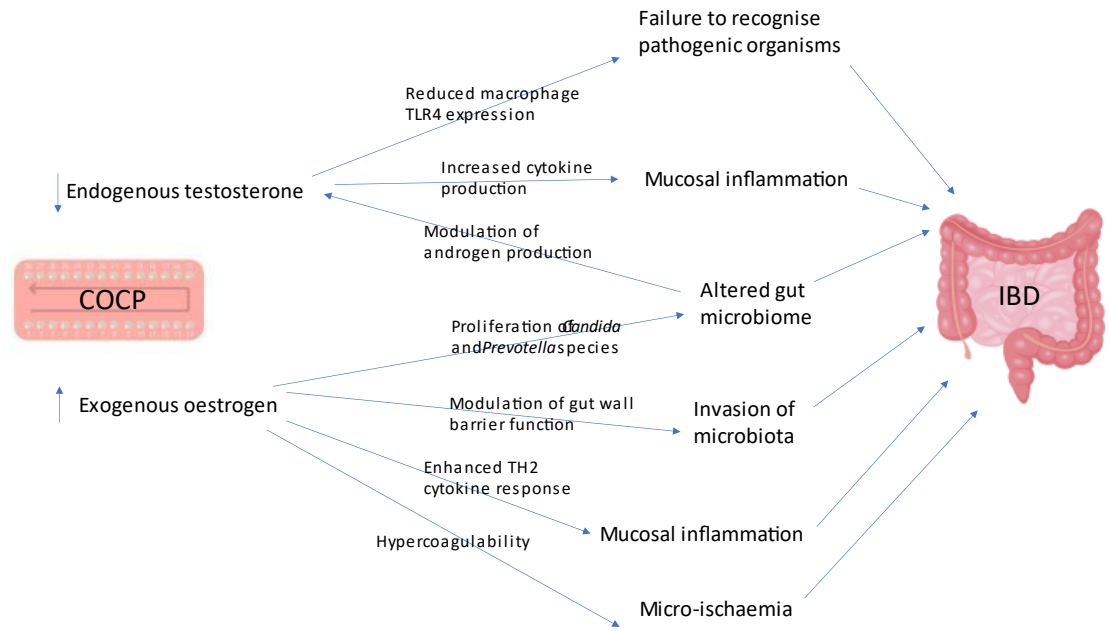


Figure 1.12. Summary of proposed biological mechanisms for the association between combined oral contraceptive pills and inflammatory bowel disease

1.8.2 Global trends

Interestingly, global patterns of OCP use appear to reflect changes in the incidence of IBD at a population level. A rapid rise in IBD incidence in high income countries was observed during the latter half of the 20th century when OCPs became available. IBD incidence is rapidly rising in Latin American and Asian countries which have seen the greatest increase in OCP use over the last 25 years (Figure 1.9). IBD cases are now beginning to emerge in Sub-Saharan Africa where hormonal contraception has become available more recently but prescribing of OCPs is comparatively lower.

1.8.3 Contraceptive pills and IBD risk

The association between IBD and contraception was described using electronic GP data in 2005 in the General Practitioner Research Database (GPRD) (now CPRD). They found that long term users of OCPs were at increased risk of developing CD (OR: 3.15; 95% CI: 1.24–7.99) and UC (OR: 2.35; 95% CI: 0.89–6.22) (135). A more modest association was found in a meta-analysis of 14 studies published in 2008 where it was demonstrated that current use of OCPs is associated with an increased risk of CD (RR 1.46, 95% CI 1.26-1.70) and UC (RR 1.53, 95% 1.21-1.94) (108). However, after adjustment for smoking, the association with UC was weaker (RR 1.28, 95% CI 1.06-1.54). Interestingly, they were able to demonstrate that CD risk increased with longer duration of OCP use (Figure 1.13). They also concluded that and following cessation of OCP, IBD risk reverted to that of the non-exposed population (former users were not at increased risk).

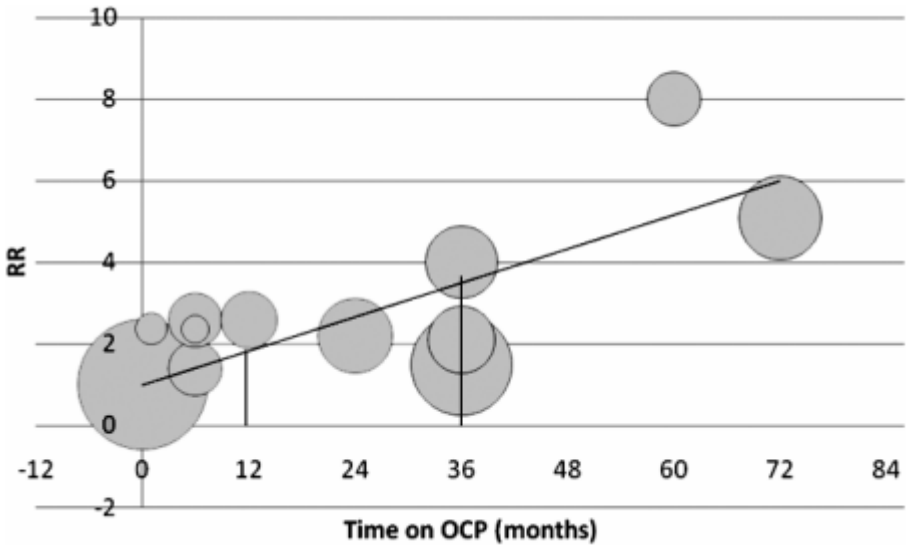


Figure 1.13. . Bubble plot of relative risk of CD with the duration of OCP use, demonstrating trend over time (unadjusted for smoking). The size of each bubble is used to show the data point's relative importance, for example, the sample size of the population. Taken from (108). License to replicate figure from Wolters Kluwer Health Inc obtained on 19.02.22. Licence number 5252460757440.

The first large prospective study to explore these associations was published in 2013. In 232,452 US nurses it was found that that current OCP use was associated with an increased risk of CD (HR = 2.82, 95% CI 1.65 to 4.82) but not UC (HR = 1.22, 95% CI 0.74–2.07) (136). Of note, this study did not find an association between other reproductive risk factors (parity, age at menarche, age at first child) and risk of IBD.

A meta-analysis from 2017 including 17 case-control and three cohort studies found there was a 24% higher risk for developing CD (OR: 1.24, 95% CI: 1.09-1.40,; I=38%) and a 30% higher risk for developing UC (OR: 1.30, 95% CI: 1.13-1.49, I=26%) in patients exposed to the OCP compared to unexposed individuals (109). However, the large US nurses cohort study was not included in their analysis. They found that all 20 included studies were of 'moderate' quality as assessed using the Effective Public Health Practice Project Model (137) (a scale assessing study quality as 'strong', 'moderate' or 'weak' based on a number of criteria such as study design, data collection methods, the inclusion of appropriate confounders and statistical analysis). They concluded that future studies are required to explore the relationship between dose and duration of OCP exposure on IBD risk.

A subsequent meta-analysis conducted in 2019 (which reported on UC but not CD) with the inclusion of prospective data from the US nurses cohort found an increased risk of UC in current OCP users compared to non-users (OR 1.49, 95% CI 1.12-1.96), but past OCP use was not associated with UC (OR 1.17, 95% CI 0.95-1.43) (138).

Although studies have reported on IBD risk with regard to duration of OCP therapy, to date only one epidemiological study has evaluated IBD risk in relation to OCP sex steroid dose

and formulation. This 1994 case-control study including 302 cases and 450 controls suggested that UC risk increases in individuals taking OCPs with higher doses of ethinylestradiol (>35mcg), but was underpowered to draw conclusions for CD (139). Additionally, this study was too small to investigate the impact of different progestogens.

1.8.4 Literature search:

To identify literature gaps relating to the relationship between contraception and IBD risk, I performed a comprehensive literature search at the start of this PhD which I repeated again in September 2021. I used a similar strategy to the meta-analysis published in 2017 (109). The search period included any study published to date. Some additional broader search terms were included: '(contracept*) AND (inflammatory bowel disease*)', '(contracept*) AND (IBD)', '(contracept*) AND (Crohn*)', '(contracept*) AND (CD)', '(contracept*) AND (ulcerative colitis)' and '(contracept* AND UC)'. References from relevant articles were also searched to identify any missed articles. I identified 23 case-control and cohort studies relating to OCPs and risk of IBD. These are summarised below (Table 1.4).

Table 1.4. A summary of all cohort and case control studies conducted between 1985 and 2021 exploring associations between contraceptive use and IBD

Author and year	Study period	Region	Study design	Study population	Sample size (women only)	Outcomes	Adjustments	Results	Conclusions
Lesko et al, 1985 (140)	1977-1983	USA & Canada	Case-control In-person interview	Age 18-69 years Cases: women admitted to hospital for treatment of CD Controls: women admitted to hospital with trauma or an acute infection	57 cases 2,189 controls	CD	Age, race, religion, education, smoking, calendar year, geographic region, number of hospital admissions	RR OCP use: CD 1.9 (1.0-3.5) RR – OCP use within a year: CD 4.3 (2.1-8.7) RR past OCP use (4 years after discontinuation): CD 1.2 (0.5-2.6) RR recent OCP use >5 years: CD 8.0 (3.1-21.)	-Increased risk of CD in OCP users
Vessey et al, 1986 (141)	1968-1974	England & Scotland	Cohort Contraceptive information 'recorded regularly throughout study'	Cohort of white married women age 25-39 years recruited at 17 family planning clinics	Cohort size 17,032 49 IBD cases	CD, UC	Age, social class, smoking	CD incidence: Never user 0.11/1,000 PY Ex-user 0.11/1,000 PY Current user: 0.23/1,000 PY UC incidence: Never user 0.08/1,000 PY Ex-user 0.06/1,000 PY Current user: 0.13/1,000 PY	-Use of OCPs potentially associated with IBD. -More so for UC than CD -Fell short of 'conventional significance values'
Cakins et al, 1986 (142)	1977-1979	USA	Case-control Not reported how information was collected	Age 10-60 years Cases: Hospital incident IBD cases Controls: Hospital and neighbourhood matched controls	101 cases 208 controls	CD, UC	None	OR OCP use UC Hospital controls: 0.62 (0.11-3.42) Neighbourhood controls: 0.57 (0.11-2.88) CD Hospital controls: 1.14 (0.44-2.96) Neighbourhood controls: 1.60 (0.59-4.37)	-Underpowered All CIs overlap with unity
Logan et al, 1989 (143)	1968-1969	UK	Cohort Classed as either current/past/never users of OCPs	Age 15-45 years 23,000 women taking the OCP and a similar number of controls were recruited and followed up prospectively	Cohort size 46,000 120 IBD cases identified	CD, UC	Age, 'social class', smoking	RR in current users compared to non/former users of OCP UC 1.3 (0.82-2.0) & 2.1 (0.96-4.5)	-Consistent with an increased risk of CD and UC in OCP users

			during each month of follow up		Across two studies			CD 1.7 (0.88-3.2) & 1.5 (0.55-4.1)	
Lashner et al, 1989 (144)	Not stated	USA	Case-control Questionnaire	Age 18-50 years Cases identified from the IBD registry of outpatients. Controls were 'friends of cases'	51 cases 51 controls	CD	Smoking	OR current OCP use: CD 0.73 (0.34-1.59) OR former OCP use: CD 1.00 (0.46-2.16) Analysing for duration of use found no association	-No association between OCP use and CD
Lashner et al, 1990 (145)	'after 1985'	USA	Case-control Questionnaire	Age 18-50 years Cases identified from the IBD registry of outpatients. Controls were 'friends of cases'	46 cases 46 controls	CD	Smoking	OR current OCP use: CD 0.70 (0.27-1.83) OR past OCP use: CD 1.14 (0.41-3.15) Analysing for duration of use found no association	-No association between OCP use and UC
Sandler et al, 1992 (146)	1950-1990	USA	Case-control Questionnaire	Age 14-75 years Cases: Identified from rosters of the Crohn's and Colitis Foundation Controls: Neighbours of the cases	273 controls 217 cases	CD, UC	Age, calendar period, education, marital status, smoking	OR ever OCP use: UC 1.10 (0.65-1.85) CD 1.49 (0.99-2.26) OR for 'years between first OCP use and index date' UC: <5 1.17 (0.57-2.38) 6-10 0.96 (0.45-2.04) 11-15 1.16 (0.30-3.84) >15 1.27 (0.37-3.91) CD: <5 1.78 (1.03-3.08) 6-10 1.36 (0.76-2.41) 11-15 1.96 (0.80-4.83) >15 0.36 (0.06-1.39)	-Use of OCPs was associated with CD -Risk increased further in smokers -Use of OCPs was not associated with UC
Persson et al, 1993 (147)	1984-1987	Sweden	Case-control Questionnaire	Age 15-79 Cases: Hospitalised patients in Stockholm Controls: A population register of Stockholm	132 cases 133 controls	CD, UC	Age	RR for OCP use: UC 1.7 (0.8-3.3) CD 1.7 (0.9-3.2)	-Use of OCPs was associated with an increased risk of both CD & UC -Crohn's disease confined to the colon and total ulcerative colitis at diagnosis

									were most strongly associated with OCPs
Katschinski et al, 1993 (148)	1986-1988	West Germany	Case-control Questionnaire	Pre-menopausal women Cases: patients recruited from clinic Controls: community controls from the same city	42 cases 57 controls	CD	Smoking, education	Unadjusted OR 1-3 years of OCP use: CD 2.2 (0.61-5.6) Unadjusted OR >3 years of OCP use: CD 21. (0.54-6.2) Adjusted OR 1-3 years of OCP use: CD 2.5 (0.75-4.6) Adjusted OR 1-3 years of OCP use: CD 3.1 (1.1-6.7)	-OCP increased risk of CD, but only in non-smokers
Boyko et al, 1994 (139)	1989-1992	USA	Case-control In-person interview	Age 15-68 years Cases: women who enrolled in a prepaid health plan in Washington State with IBD Controls: Age matched from the same health plan	302 cases 510 controls	CD, UC	Marital status, education, family income, smoking, infertility, ethnicity, number of pregnancies	RR Current OCP use: UC 2.0 (1.2-3.3) CD 2.6 (1.2-5.5) RR Past OCP use: UC 1.5 (0.9-2.4) CD 1.5 (0.7-3.3)	-Current use of OCPs associated with both CD and UC. -Past use not associated with IBD. -Risk of CD but not UC increased with increasing durations of OCP use
Corrao et al, 1998 (149)	1989-1992	Italy	Case-control In-person interview	Age 18-65 Cases: Identified using a range of sources (both inpatient and outpatient) Controls: randomly selected from cases residential areas or same hospital	346 cases 346 controls	CD, UC	Smoking, breastfeeding during infancy	OR current OCP use: UC 0.9 (0.7-1.2) CD 1.7 (1.1-2.6) OR past OCP used: UC 3.0 (2.1-4.3) CD 1.7 (0.9-3.3)	-Women who reported OCP use for at least one month before onset of symptoms had a higher risk of CD -No association was observed for UC
Sicilia et al, 2001 (150)	1992-1995	Spain	Case-control Questionnaire	10-79 years Cases: Community IBD cases Controls: From the same community as cases	42 cases 42 controls	CD	Age, cigarette smoking, appendicectomy, number of persons in house, number of bathrooms, hot	OR ever OCP use: CD 2.8 (1.01-7.77) univariate analysis CD 3.72 (0.92-14.96) multivariate analysis	-OCP use associated with CD in univariate analysis but not multivariate analysis

							water in home in infancy, family history of IBD		
Card et al, 2004 (151)	1987-1993	UK	Case-control Electronic GP database study	Age <80 years Cases and controls identified from GPRD	334 cases 818 controls	CD	Age, smoking, use of antibacterials, drugs for cardiovascular disease and drugs for nervous system diseases	OR OCP use: CD 1.48 (1.00-2.17)	-Use of OCPs associated with CD
Garcia et al, 2005 (135)	1995-1997	UK	Cohort Electronic GP database study	Age 20-84 years Cohort identified from GPRD	188 cases 5,162 controls	CD, UC	Age, calendar year, osteoarthiritis, rheumatoid arthritis, depression, anxiety, stress, asthma, COPD, diabetes, IBS, smoking, aspirin use, NSAID use, paracetamol use, HRT use	OR current OCP use: UC 1.58 (0.71-3.52) CD 1.94 (0.85-4.45) OR current OCP use: <1 month UC 0.79 (0.10-6.09) CD 2.49 (0.66-9.36) OR current OCP use: 1-12 months UC 1.31 (0.42-4.11) CD 0.61 (0.13-2.87) OR current OCP use: >1 year UC 2.35 (0.89-6.22) CD 3.15 (1.24-7.99) OR past OCP use: UC 0.67 (0.32-1.39) CD 1.04 (0.50-2.17)	-OCP use was associated with development of CD and to a lesser extent UC -Risk increased with use over extended periods of time
Bernstein et al, 2006 (152)	1984-1995	Canada	Case-control Questionnaire	Age 18-50 years Cases: drawn from IBD research registry Controls: Drawn from population-based health registry	346 cases 318 controls	CD, UC	None	Prevalence of OCP use: CD 88% UC 90% Controls 86% Mean years of use: CD 8.0 UC 6.7 Controls 6.6 Increased likelihood of OCP use in CD compared to controls OR 1.07 (1.03-1.11) p=0.0009	-No difference in prevalence of ever using OCPs between cases and controls -Women with CD started OCPs at younger ages than controls -Women with CD reported more years of use
Sicilia et al, 2008 (153)	1992-1995	Spain	Case-control Questionnaire	13-92 years Cases: Community IBD cases	77 cases 77 controls	UC	Age, cigarette smoking, appendicectomy, number of persons	OR ever contraceptive use: UC 1.43 (0.54-3.75)	-No association between OCP use and UC.

				Controls: From the same community as cases			in house, number of bathrooms, hot water in home in infancy, family history of IBD		
Han et al, 2010 (154)	Prior to 2006	New Zealand (North Island)	Case-control Questionnaire	Age 5-86 years Cases: recruited through gastro or other clinics or responded to media publicity Controls: As per cases	97 cases 324 controls	CD	None	OR Ever OCP use: CD 0.66 (0.38-1.15) OR duration of OCP use (per year of use) CD 1.02 (1.00-1.04)	-Use of OCPs overall did not increase CD risk -However, among those who had ever used the oral contraceptive pill, the duration of use was associated with developing CD
Vahedi et al, 2011 (155)	2008-2009	Iran	Case-control Questionnaire	13-74 Cases: enrolled from private clinics Controls: from the same clinics	145 cases 465 controls	CD, UC	Variables included in the multivariate analysis not stated in the manuscript	'Duration of using OCPs and UC OR 0.99 (0.98-0.99)'	-No association between 'ever OCP use' and CD or UC when compared to never use -Increased association with UC with increasing durations of OCP exposure -No difference between 'low dose' and 'high dose' oestrogens and UC or CD risk
Wang et al, 2013 (156)	2007-2010	China	Case-control Questionnaire	Age 16-70 years Cases: Identified from hospital records Controls: friends/neighbours/colleagues of cases	586 cases 586 controls	CD, UC	Unadjusted	OR OCP use: UC 2.73 (0.88 – 8.50)	-OCPs appeared to be associated with UC.

Khalili et al, 2013 (157)	1976-2008	USA	Cohort Biennial surveys	All ages Cohort of nurses enrolled in the Nurses Health Study I & II.	Cohort size 232,452 707 cases	CD, UC	Age, Age at menarche, parity, age at birth of first child, menopausal status, ethnicity, smoking, BMI, hormone use	HR for Current use of OCPs: CD 2.82 (1.65-4.82) UC 1.22 (0.74-2.07) HR for past OCP use: CD 1.39 (1.05-1.85) UC 1.18 (0.91-1.52)	-OCP use associated with CD -Modest but 'non-significant' association with UC
Vcev et al, 2015 (158)	2001-2010	Croatia	Case-control In-person or telephone interview	Approximately 13-83 years (taken from figure) Cases: identified from hospital records Controls: 'recruited on a voluntary basis'	73 cases 42 controls		Unadjusted	'longer use of contraceptives in women from the control group' (p=0.462)	-OCPs not associated with CD or UC
Sanagapalli et al, 2018 (159)	2011-2013	Asia-Pacific region	Case-control Questionnaire	Median age 43 (IQR 31-55) years Cases and controls selected from the 'Asia-Pacific Crohn's and Colitis Epidemiology Study cohort' and the 'Sydney IBD Cohort'	348 cases 590 controls	Any IBD, CD, UC	Age, smoking, Asian vs Australian cohort	Unadjusted OR for OCP use: Any IBD 1.65 (0.77-3.13) CD 1.55 (0.78-3.10) UC 1.01 (0.62-1.66) Adjusted OR for OCP use: Any IBD 1.35 (0.60-2.10) CD 1.31 (0.55-1.99) UC 1.20 (0.70-1.70)	-'Modest but not significantly increased risk of IBD amongst OCP users'
Preda et al, 2019 (160)	2017	Romania and Belgium	'Comparative study' Questionnaire	19-74 years Cases: IBD patients admitted to outpatient hospitals Controls: Employees of the hospitals	73 ~32 controls (exact number of female controls not stated in manuscript)	IBD		Belgian IBD patients reported more OCP use 53% vs 9% p<0.001 Romanian IBD patient did not report more OCP use	-Patients recruited in the Belgium study reported more OCP use

*OR/RR/HR are reported in relation to 'non-use' as the reference group unless otherwise stated. CD: Crohn's disease, UC: ulcerative colitis, CI: confidence interval, HR: hazard ratio, IBD: inflammatory bowel disease,

OCP: oral contraceptive pill, OR: odds ratio, RR: risk ratio

1.8.5 Critical appraisal of the meta-analyses:

1.8.5.1 Ortizo et al 2017 (109)

This is a well-conducted meta-analysis. The research question was clearly described. The literature search was systemic and easily reproducible. However, I felt the methodology could have been improved by the use of a broader range of search terms (for example, 'oral contraception' and 'contraceptive pill' in addition to 'oral contraceptives'). A quality assessment tool was used. However, none of the included studies scored highly (strong) using this tool. When heterogeneity was identified, results underwent a sensitivity analysis with the exclusion of specific studies. Results are presented clearly using forest plots. The discussion is well pitched, appropriate limitations such as publication bias are highlighted and gaps in the literature are identified. A limitation of this study is that the largest prospective study exploring the effect of OCPs on IBD risk was excluded by the researchers.

1.8.5.2 Wang et al 2019 (156)

The search strategy is detailed and easily reproducible. Inclusion and exclusion criteria are also clearly stated. The Newcastle-Ottawa quality scale was used (161). Results are presented well, both graphically and in the body of the text. The discussion is generally appropriate. However, the authors conclude that 'females with UC should be advised to reduce or discontinue oral contraceptive use'. They lack evidence to back up this statement and encouraging women to stop contraception is potentially harmful. Importantly, this study adds little to the body of literature. Aside from the inclusion of the US nurses cohort study published in 2013, no new studies were added since the last meta-analysis published 16 months prior (109).

1.8.6 Critical appraisal of recent literature:

Since the publication of the recent meta-analyses (109, 138), I have been able to identify only two studies published in peer-reviewed journals which describe associations between OCPs and development of IBD (159, 160).

1.8.6.1 Sanagapalli et al 2018 (159)

This case-control study of 348 IBD cases and 590 age-matched controls nested within the Asia-Pacific Crohn's and Colitis Epidemiology Study (ACCESS) cohort, aimed to examine associations between OCP exposure and development of IBD in a contemporary group of patients using newer formulations of OCP. They found 'no significant association between OCP use and the risk of IBD' (OR 1.55 (95% CI 0.78-3.10) for CD and 1.01 (95% CI 0.62-1.66) for UC when compared to non-use). This lack of association persisted after adjusting for smoking.

This is a well-designed study. The research question is novel. The groups were comparable; controls were appropriately age-matched participants recruited from the same communities. Exposure to contraception was measured in the same way for both groups using a detailed questionnaire (a commonly used approach in studies of this nature). Smoking was identified as a potential confounder and adjusted for accordingly. However, other potential confounders such as pregnancy and other reproductive factors were not explored. A sample size calculation was performed. However, despite increasing recruitment, sample size remained a limitation of the study. The statistical analyses were appropriate with results presented as OR (95% CI).

This study adds to the body of literature given that participants were primarily using newer formulations of OCP. However, it is limited by sample size; a meta-analysis has shown that the increased risk of CD may be as small as 24% in those taking OCPs (109). Given that their confidence intervals were wide, it remains unknown whether the associations (particularly for CD) would remain 'non-significant' at the 95% threshold should they have recruited more participants.

1.8.6.2 Preda et al 2019 (160)

In this European study, 53 Belgian IBD patients were matched to 21 controls and 76 Romanian IBD patients were matched to 35 controls. Participants were asked to fill in a questionnaire regarding a range of exposures and lifestyle factors. Mann-Whitney U test or Fisher's exact test was used to compare answers between the groups. They found that Belgian patients 'used significantly more OCPs before IBD onset' (53% vs 9%; $p<0.001$) whereas Romanian patients did not (11% vs 0%).

This study has numerous methodological flaws. Cases were patients diagnosed with IBD across two centres and controls were employees of the hospital. Hospital employees represent a selected group who are unlikely to be representative of the background population with regard to lifestyle factors such as smoking, diet and stress (these were exposures in the study). The sample size was extremely small with <0.5 controls per case. No adjustment for confounders was attempted. Although a wide range of exposures and lifestyle factors were compared including alcohol, coffee, NSAIDs, OCPs, smoking, antibiotics, breastfeeding, stress, education level and income, no adjustment for multiple

testing was made. Due to a range of methodological problems, I concluded that this study did not provide substantiated evidence relating to the relationship between OCPs and IBD.

1.8.6.3 Update of meta-analysis

Only one study of reasonable quality has been published on this subject since the last systematic review and meta-analysis on this topic. The results of this study do not change the overall conclusions of the available published literature. On the basis of this, I concluded that an update of the current available meta-analysis would not change our understanding of the relationship between OCP exposure and development of IBD.

1.8.7 Oral contraceptive pills and IBD disease course

Published literature on how contraceptives affect disease progression and complications in UC is scant. In the late 1970s it was reported in three small case series that patients with UC experienced disease regression after stopping the OCP (162-164). However, subsequent research has not linked OCPs to UC disease complications. In a small cohort of 74 women with UC, current or past OCP use was not associated with time to relapse (165). Additionally, a large prospective nationwide Swedish study including 6,104 women with UC found no association between OCP use and risk of surgery, steroid use or biologic use (166).

The effect of OCP on CD disease course is also unclear with conflicting available evidence. A small retrospective questionnaire study found that after a first surgical operation for CD, non-users of the OCP were more likely to undergo a second operation than users (167). Whereas a small prospective study found no association between OCP use and flare (168). However, several studies have linked the OCP to adverse health outcomes in CD. A cohort

study published in 1992 found that OCP users had a higher prevalence of relapse attacks than non-users (29/51 (57%) vs 31/87 (36%)) (169). A Canadian study drew similar conclusions; OCP use was associated with an increased risk of relapse compared to non-users (HR 3.0 (95% CI 1.5-5.9)) (170). More recently, in a large nationwide prospective study of 4,036 women with CD (median follow up 58 months), long term use of OCP was associated with an increased risk of surgery when compared to non-users (HR 1.68 (95% CI 1.06-2.67) (136). Of note, the study found that there was an increased risk of surgery in those taking COCPs but not POPs.

1.9 The NHS and primary care databases

The NHS is the publicly funded healthcare system in the UK. A number of organisations are commissioned to provide NHS services and these include acute trusts such as hospitals, mental health trusts, ambulance services, pharmacies and general practices.

In the UK, over 61.3 million people are registered with a general practice (about 90% of the population) (171). General practitioners (GPs) have an important role in looking after patients in the community and are often the first point of contact for anyone with a physical or mental health problem. GPs also act as gatekeepers to secondary care services and will refer patients accordingly when more specialist care is required. During a typical consultation (lasting approximately ten minutes), GPs will record information such as presenting symptoms, findings of clinical examination, observations such as blood pressure or weight measurements and subsequently their differential diagnosis and any treatments prescribed. Additionally, GP practices collect demographic data from their patients at

registration with the practice including but not limited to age, ethnicity, smoking status, comorbidities and prescribed medications.

Primary care databases collect anonymised information from GP health records for research purposes. A number of these databases exist including IQVIA™ Medical Research Data (IMRD), QResearch, and Clinical Practice Research Datalink CPRD (formally The General Practice Research Database (GPRD)). These databases differ depending on the computer software packages that practices use for patient management. For example, QResearch is derived from the anonymised records from practices that use the EMIS clinical computer system, whereas IMRD collects data from practices that use Vision Software. CPRD has considerable overlap with both QResearch and IMRD.

1.9.1 Data Source: The IMRD database

IMRD is a large longitudinal database containing non-identifiable patient data from UK GP clinical systems going back to 1994. Data is collected from participating GP practices that use Vision software (a Cegadim brand) to record their consultations and health records. GP practices inform their patients that they are participating in the IMRD data collection scheme. Patients retain the right to opt out of contributing data to IMRD. If a patient wishes to opt out then no data will be recorded in IMRD from that point onwards and all of their historic data is removed from the database. IMRD incorporates data supplied by THIN, a Cegadim database. Reference made to THIN is intended to be descriptive of the data asset licensed by IQVIA™ (formally IMS Health and Quintiles); an American multinational human data-science company.

The anonymised patient records are continuously updated and contain information regarding:

- Demographics (e.g. gender, age, ethnicity, registration date, date of death)
- Symptoms and diagnoses
- Referrals to secondary care
- Medications
- Investigations and test results
- Vaccinations
- Additional health data (e.g. height, blood pressure, weight, smoking status)

The anonymised data is collected and processed by IQVIA™. Before the data is made available to researchers, a range of internal validity checks are undertaken by IQVIA™. IMRD data has been approved by the NHS South-East Multi-Centre Research Ethics Committee. However, individual study protocols must also be reviewed by an independent Scientific Review Committee (SRC) to assess for feasibility and scientific merit.

IMRD contains the electronic medical records of 18.3 million patients collected from 797 general practices throughout the UK. Since the start of records in 1994, IMRD has represented approximately 6% of the UK population on average. The number of patients contributing to the database has fluctuated over the years as it is dependent on the use of Vision software by GPs. More recently, many surgeries have changed to alternative software platforms such as EMIS and over the last ten years, the number of contributing patients is decreasing (demonstrated later in Table 3.4). Three million patients are presently registered with a practice contributing to IMRD and are currently providing data. Medications,

symptoms and diagnoses are recorded in IMRD using a hierarchical system of codes called Read codes (172). Using Read codes, lists can be generated to identify individuals with a particular condition or who take one or more drugs used to treat a specific condition (2.3.3.1) (173).

IMRD has been shown to be broadly representative of the UK population in terms of age and sex (174). Mortality rates and prevalence of numerous chronic conditions such as diabetes and hypertension that have been recorded in IMRD are similar to national UK statistics (174), as is smoking prevalence (175, 176). The recording of consultations and prescriptions in IMRD has been shown to be comparable to national primary care statistics (177). Established associations between risk factors for a number of chronic conditions have been replicated using IMRD data (e.g. Smoking and myocardial infarction, blood pressure and stroke) (178).

1.9.1.1 Strategic Health Authorities

In IMRD, information regarding GP practice location is included at the level of former Strategic health authority (SHA) for England and at the level of country for Northern Ireland, Scotland and Wales. SHAs were part of the structure of the NHS for the period 2002 – 2013. Each SHA was responsible for the management of health services at a regional level. In 2006 the number of SHAs was reduced from 28 to 10. Subsequently, SHAs were abolished in 2013. For the purposes of this PhD, geographical location of GP practice in England was described using the 10 SHAs shown on the right in orange (Figure 1.14).

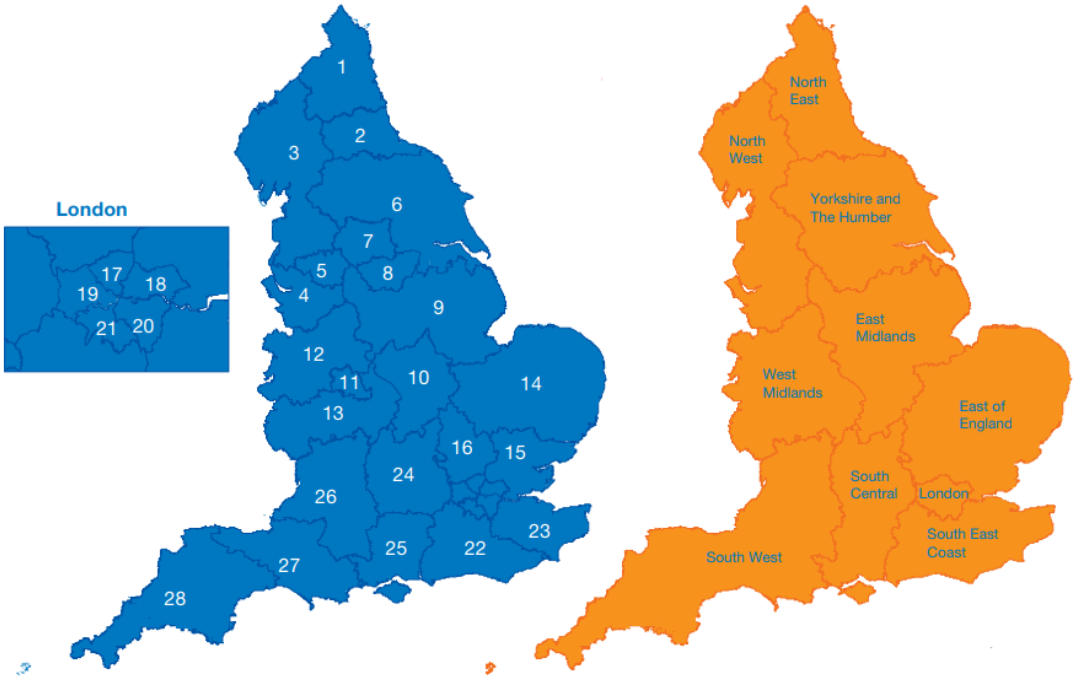


Figure 1.14. Strategic Health Authorities in England pre and post 2006. Adapted from: Strategic Health Authority Configurations Current New – NHS. Available at: https://www.nhs.uk/NHSEngland/aboutnhs/Documents/MapofSHAsFeb09.pdf

1.9.1.2 Townsend deprivation index

In IMRD, social deprivation is quantified using Townsend scores. The Townsend deprivation index is a measure of deprivation within a population that was first described by Peter Townsend in 1988 (179). It incorporates the following four variables which are commonly from census data:

- The percentage of those aged over 16 not in employment
- The percentage of households with no car-owner
- The percentage of households not occupied by an owner
- The percentage of households with overcrowding

The variables undergo a series of transformations and standardisations to give a score for a particular area or postcode; one being the least deprived and five being the most deprived. The measurement is a quintile measurement, whereby 20% of UK areas or postcodes are

represented by each quintile. However, it should be noted that some areas are more densely populated than others and therefore 20% of the population of the UK do not necessarily fall into each quintile (180).

IMRD is slightly over-representative of individuals from less deprived areas as measured by Townsend score; in 2009 23.5% of individuals contributing data to IMRD were found to be in the highest quintile, whereas 14.6% were in the lowest quintile (174). Officially, 20% of UK postcodes should make up each quintile nationwide. From 01/01/2017 onwards, Townsend scores were no longer included in IMRD. The study period for all studies in this PhD is 01/01/2000 – 31/12/2018. Therefore, for patients/practices who began contributing to IMRD in 2017 & 2018, data on social deprivation is missing.

1.9.2 Why was a primary care database used?

An electronic primary care database was used for a number of reasons. A previous validation study has been conducted in GPRD, which showed that codes for IBD inferred a 92% (95% CI 86-96%) positive predictive value for the individual having the condition (80). The Research Department of Primary Care and Population Health at UCL has a full license to use IMRD, providing access to the entire database. This was required, because a large sample size is essential to obtain precise estimates of incidence for a relatively uncommon condition such as IBD using a cohort design. Importantly, all of the general practices contributing to IMRD use exclusively electronic prescribing and the prescribing records are detailed and accurate. This was important for this PhD, where the prescription of contraception represents the primary outcome for the study described in chapter three and the primary exposure for the study described in chapter four.

1.10 Literature gaps, justification and clinical relevance

1.10.1 Updating our understanding of the epidemiology of IBD in the UK

Studies describing the epidemiology of IBD in the UK have been limited by a lack of generalisability and small sample sizes (73-78). Describing sociodemographic and temporal trends in the incidence and prevalence of IBD is an essential step in calculating disease burden, identifying 'at risk' populations and planning future service delivery.

1.10.2 Describing time trends in contraceptive prescribing

Although information on community contraceptive prescribing is published annually by NHS Digital, data are not linked to demographic information of users such as age, geographical location and social deprivation. Describing time trends in contraceptive prescribing in relation to demographic factors is crucial for the delivery of future contraceptive services to women who may be at risk of unwanted pregnancy. Stratifying by social deprivation may provide important results which could assist in developing interventions to improve health equality.

1.10.3 Investigating differential effects of contraception on IBD risk

Although associations have been made between OCPs and IBD, there is a paucity of literature on how contraceptive dose, formulation, mode of delivery and duration of therapy is associated with subsequent development of IBD (139). No studies have compared the effects of CHC and progestogen-only contraception on IBD risk. Establishing how different contraceptives affect IBD risk is likely to be of limited relevance to most clinicians

who prescribe contraception; the benefits of contraception would greatly outweigh the risks of developing a relatively rare condition such as IBD in the vast majority of individuals. However, this research may be relevant to individuals who are at higher risk of disease such as relatives of people living with IBD. Importantly, exploring the relationship between different formulations of contraception and IBD risk would be highly valuable in developing our understanding of the hormonal contribution to IBD pathogenesis. This could lead on to future basic science work to improve our understanding of the aetiological drivers.

1.11 Aims

The aims of this PhD are as follows:

- To explore socio-demographic and temporal trends in the incidence and prevalence of IBD in the UK.
- To describe socio-demographic and temporal trends in the prescribing of contraceptives in UK primary care.
- To investigate the differential effects of contraceptives on IBD risk with a focus on dose, formulation, method of delivery and duration of therapy.

1.12 Structure

The aims of this PhD have been met through a series of epidemiological studies using IMRD. An outline of the subsequent chapters included in this thesis is summarised below:

Chapter 2: This chapter describes a cohort study estimating temporal and sociodemographic trends in the incidence and prevalence of IBD between 2000 and 2018.

Chapter 3: This chapter describes a repeated cross-sectional study exploring time trends in non-barrier contraceptive prescribing in UK primary care between 2000 and 2018.

Chapter 4: This chapter relates to a nested case-control study which describes associations between a range of hormonal contraceptives and subsequent development of IBD.

Chapter 5: In this chapter, the key findings from the previous chapters are reflected on. The implications of this work on clinical practice and potential directions for future research are discussed.

1.13 Changes to the project as a result of the COVID-19 pandemic

This PhD was dramatically affected by unforeseen circumstances arising from the COVID-19 pandemic. In addition to five months of study interruption for front-line NHS redeployment and the requirement for PhD students to work from home, a planned study using another data source had to be abandoned and replaced with a new piece of work.

For the final piece of work in this project, I planned a study looking at associations between contraception and health outcomes in a cohort of patients living with IBD. This would be a valuable piece of research as literature relating to how contraceptives affect IBD disease course is scant. This study was to be undertaken in collaboration with a group from Edinburgh using The Lothian IBD Registry (a comprehensive record of all people living with IBD who receive their care in Lothian, an area of South-East Scotland). Using The Lothian IBD registry, I would have access to detailed health outcome data including endoscopy results, hospital admissions, escalations in therapy and other information such as serial calprotectin measurements and surgical procedures.

Although I had travelled to Edinburgh, met with the team, planned the project and written the research proposal, this study had to be abandoned due to the unavailability of local ethics committees for non-COVID related research and logistics of regular travel to Scotland during national lockdown.

I explored whether a similar study could be conducted using IMRD. However, although IMRD represents a useful data source to explore pre-diagnostic risk factors for IBD, aside from 'mortality' and 'diagnosis of bowel cancer', there are little robust data on IBD disease trajectory and patients are poorly phenotyped. This is because the majority of IBD management occurs in secondary as opposed to primary care. Given that mortality and cancer rates are very low in women of reproductive age with IBD, this study was not performed. As this study had to be abandoned, a new study using IMRD was designed and substituted (Chapter 3).

Chapter 2: Incidence and prevalence of recorded inflammatory bowel disease in UK primary care: a population-based cohort study

2.1 Introduction

Inflammatory bowel disease (IBD) was historically regarded as a disease of high-income western countries with a substantial rise in incidence during the latter half of the 20th century (70). However, there is evidence that the incidence rate has plateaued in western countries whilst rising rapidly in newly industrialised countries (69).

When this project was started, the largest UK IBD incidence study included 179 incident cases of IBD diagnosed in a population of 135,723 between 1984 and 1995 (81). More recently, incidence and prevalence of IBD has been estimated in a cohort of 10,926 cases during the period 2009-2018 in Lothian, Scotland (72). They reported overall incidence of 40.8, 13.6 and 19.8 per 100,000 person-years and point prevalence of 784, 284 and 432 per 100,000 on 31/08/2018 for IBD, Crohn's disease (CD) and ulcerative colitis (UC) respectively. However, it remains unknown if their findings are generalisable across the UK.

Electronic general practice (GP) health records can enable large-scale investigation of time trends in the epidemiology of relatively rare diagnoses such as IBD (80). Accurate and up to date estimates of trends in incidence and prevalence are an essential step in preparing services for the future delivery of IBD care.

2.2 Aims and Objectives

2.2.1 Aims

The purpose of this work was to investigate temporal trends in the incidence and prevalence of IBD in the UK from 2000 to the end of 2018 using electronic GP data from IQVIA™ Medical Research Data (IMRD) (1.9.1).

2.2.2 Objectives

The specific objectives using IMRD data were as follows:

1. To describe temporal trends in the recorded incidence of IBD, CD and UC in UK primary care for the period 01/01/2000 – 31/12/2018
2. To describe differences in the recorded incidence of IBD/CD/UC by sex, age, socio-economic level of deprivation and geographical location
3. To describe point prevalence estimates for IBD/CD/UC for the period 01/01/2000 – 31/12/2018

2.3 Methods

2.3.1 Study design

A longitudinal cohort study using electronic UK general practice (GP) records from the IMRD database.

2.3.2 Study population

2.3.2.1 Inclusion and Exclusion Criteria

All individuals who contributed data for the period from 1st January 2000 to 31st December 2018 were included. Individuals with data missing for year of birth, sex or date of registration were excluded. Patients who were not permanently registered with the practice contributing IMRD data were excluded (i.e. patients attending the surgery but registered elsewhere or patients not registered with a GP at all). Patients with out of sequence records (e.g. registration date before year of birth) were excluded. To assess representativeness of the cohort following exclusions I compared descriptive characteristics of the cohort before and after exclusions (Table 2.2).

2.3.2.2 Dynamic cohort design

This was a dynamic cohort study; individuals entered and exited the cohort at different times chronologically and contributed different amounts of follow-up to the study. Person-time was captured for each individual contributing to the cohort. The denominator for all incidence calculations was person-years of follow up.

2.3.2.2.1 Cohort entry

Cohort entry was the latest date of:

- Date of registration with the GP practice plus nine months to account for pre-existing disease at registration (2.3.2.2.1.1)
- The start of the study period (01/01/2000)
- The date the practice achieved published measures of acceptable mortality recording (2.3.2.2.1.2)

- The date the practice achieved published measures of acceptable computer usage (2.3.2.2.1.2)

2.3.2.2.1.1 Lewis plots

It has been shown that in electronic GP databases, incidence rates for numerous medical conditions are higher than expected during the period immediately following GP registration (181). This due to historical medical information being transferred to patients' records on registration to a GP contributing data to a primary care database. Thus, in some cases, an established prevalent diagnosis is associated with a date shortly after registration to the practice rather than when the individual was actually diagnosed with the condition. Therefore, failure to exclude individuals contributing data during this time-period may lead to misinterpretation of prevalent cases as incident cases and in turn overestimate incidence rates.

A method used to mitigate the above problem is use 'Lewis plots' which plot incidence rates against time of registration with GP (182). This allows the researcher to explore at which point following GP registration the incidence rate reaches baseline. I constructed Lewis plots which demonstrated that incidence of IBD reached baseline nine months after GP registration (Figure 2.1). Therefore, in this study, individuals only contributed person-time follow up nine months after they had registered with a practice contributing to IMRD (Figure 2.2).

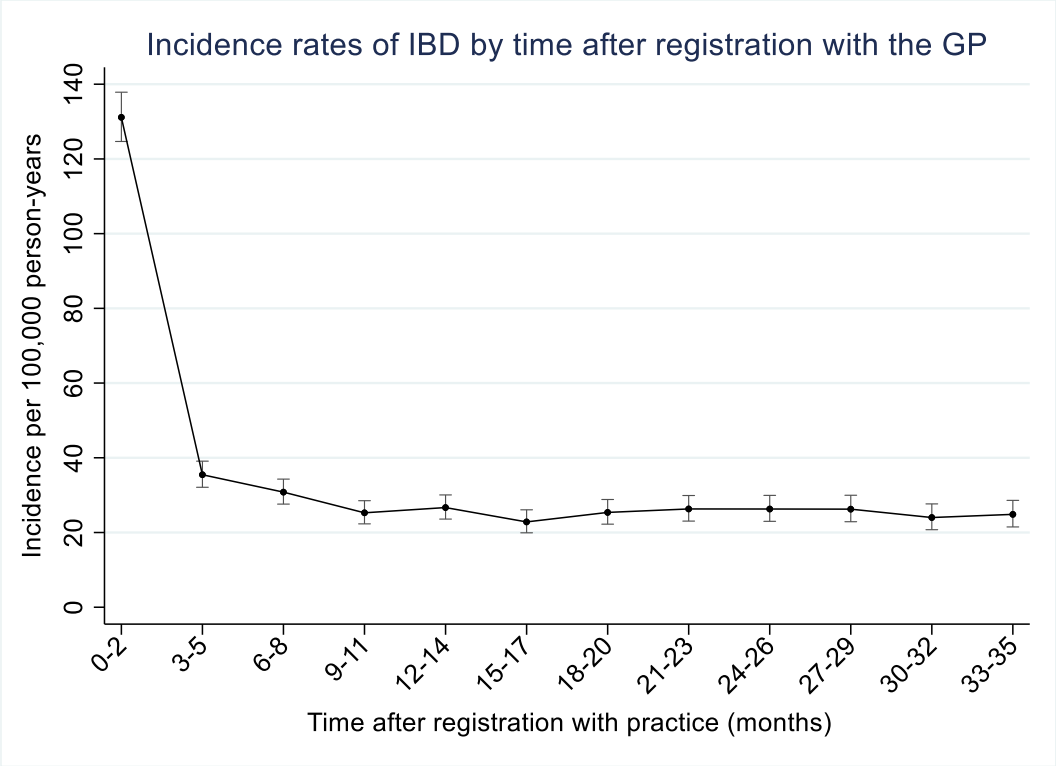


Figure 2.1. Lewis plot showing incidence of IBD by time after GP registration

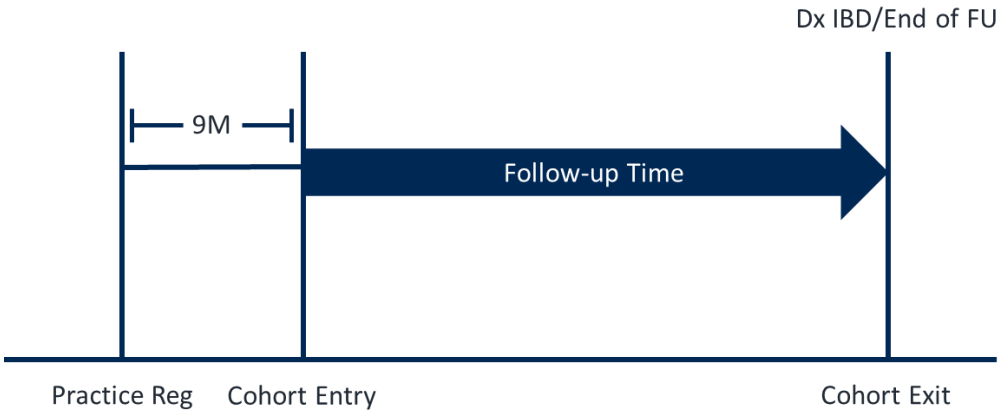


Figure 2.2. Schematic of follow-up for a single individual included in the cohort

2.3.2.2.1.2 Acceptable computer usage and acceptable mortality recording

The AMR and ACU dates were developed to identify periods of incomplete computer usage by GP practices, for example during the period of transition from paper to electronic medical records. AMR and ACU have been used as data quality indicators for numerous studies using IMRD data (183).

The acceptable mortality recording (AMR) date is defined as the time from when the observed recorded mortality rate for a practice is similar to national mortality rates, taking into account the demographics of the practice which the population serves in terms of age and gender (184).

The acceptable computer usage (ACU) date is defined as the time from which average recording rates for consultations, prescriptions and health measurements within a GP practice meet pre-defined criteria (two therapy records, one medical record and one additional health data record per patient per year on average). Using the ACU date in combination with the AMR date has been shown to produce time trends in incidence which are more consistent with external data sources (183).

2.3.2.2.2 Cohort exit

Cohort exit was defined as the earliest date of the following:

- The first diagnosis of any IBD
- De-registration with the GP practice contributing data
- The practice stopped contributing data to IMRD
- The end of the study period (31/12/2018)
- Death

2.3.3 Outcomes

The main outcomes of interest were newly diagnosed CD, UC or 'any IBD'. Three separate Read code lists (one for 'any IBD', one for CD and one for UC), adapted from those used in previous literature (80, 81, 185) were generated for all three main outcomes using published methodology (173) (2.3.3.1). The 'any IBD' Read code list included specific and general terms for IBD (comprising CD, UC, IBDU and unspecified IBD). Therefore, the 'any IBD' group comprised all of those diagnosed with CD or UC and additionally those with either IBDU or who had only non-specific Read codes for IBD in their notes such as 'inflammatory bowel disease' (Figure 2.3).

As a quality filter, individuals were only included in the study as cases if they had at least two IBD Read codes recorded on separate dates or at least one IBD Read code plus at least one prescription for a drug commonly used to treat IBD (Appendix 6.4.2). These included:

- Any aminosalicylate (rectal or oral) listed in chapter 1.5 of the British National Formulary (BNF) (186)
- Any rectal steroid preparation listed in chapter 1.5 of the BNF (186)
- Immunomodulators: azathioprine, mercaptopurine, methotrexate, ciclosporin
- Biologics: infliximab, adalimumab, ustekinumab, vedolizumab

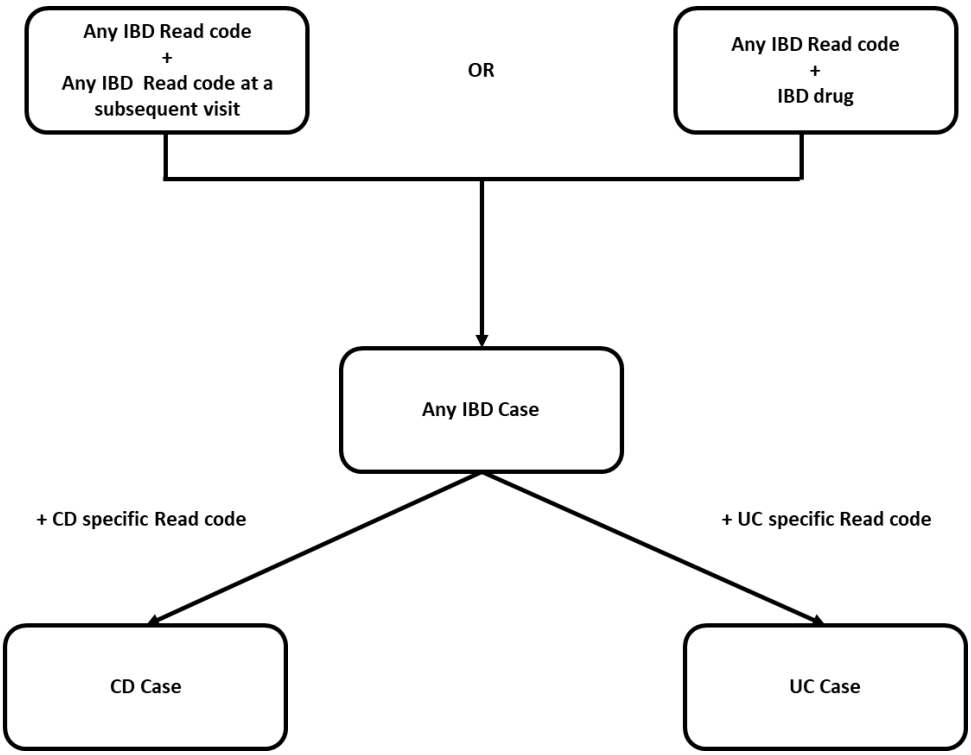


Figure 2.3. An algorithm summarising how 'any IBD', CD and UC cases were identified in IMRD

As 'incident IBD cases' (who have not been prescribed 'IBD drugs') were required to have their diagnosis verified on a subsequent GP visit, we anticipated that this would result in under-ascertainment of those diagnosed in the final months of the study period. Thus, temporal trends in incidence are graphically presented for the period 2000-2017 as opposed to 2000-2018. The date at which the first recording of any IBD code or IBD drug prescription was made was classified as the incident date. The CD and the UC group were mutually exclusive (an individual could not be diagnosed with both for the purposes of this study). For individuals who had been given a code for both UC and CD in their lifetime, the most recent code recorded was used as their final diagnosis.

2.3.3.1 Read code lists

Published guidelines were used to develop separate Read code lists for a wide range of variables included in this thesis (173). For this study, this was done for 'any IBD', 'CD', 'UC', 'endoscopies' and 'symptoms associated with IBD'. Similar methodology was used to develop a wide range of prescription code lists for this thesis. In this study, a prescription code list was developed for 'drugs used to treat IBD'. The following methodology was used to develop Read code and prescription code lists (Taken from (173)) :

1. Identifying a list of key words and synonyms for the illness/disease.
2. Converting the Read code dictionary into a Stata file containing the Read code and description fields, and dropping duplicate Read codes.
3. Sorting the Read code dictionary and browsing to identify relevant Read code stems.
4. Converting the Read code dictionary 'description' field to lower case and searching for key words (identified in step one) using the Stata *foreach* command.
5. Sorting the Read code dictionary and browsing to identify further code stems.
6. Searching the Read code dictionary 'readcode' field for relevant Read codes using the Stata *foreach* command.
7. Excluding irrelevant codes.
8. Comparing to code lists published in previous literature using primary care databases to research IBD and modifying accordingly (80, 81, 185)
9. Presenting to a panel for scrutiny and validation. For this study, this included a gastroenterologist (Dr Stuart Bloom), a gastrointestinal scientist (Prof Anthony Segal), and a GP (Prof Greta Rait).

Full Read code and prescription lists are shown in appendix 6.3 and appendix 6.4

2.3.4 Covariates

The following covariates were included in the analyses:

- Birth gender
- Age by five-year bands and by Montreal/Paris classification (187, 188) (2.3.4.1)
- Geographical region at the level of former Strategic Health Authority (SHA) for England and at the level of country for the devolved nations of the UK (1.9.1.1)
- Measure of social deprivation by Townsend score (1.9.1.2)
- Calendar year (modelled as both a categorical and continuous variable).

2.3.4.1 Montreal/Paris classification

The Montreal classification system was developed in 2005 with a view to establish an integrated classification system for phenotyping IBD. It includes a number of variables including age at onset of disease, disease location and severity (187). In 2011, a number of changes were made to this system to account for differences in paediatric disease – The Paris Classification (**Error! Reference source not found.**) (188). To categorise incident cases by age, I used the 'A' variable from the Paris classification which relates to 'age of onset of disease'. The levels of this variable are: A1a (0-9 years); A1b (10-17 years); A2 (17-40 years) and A3 (40+ years).

Table 2.1. Montreal and Paris classifications for Crohn's disease. Taken from (189). Licence to replicate table from Oxford University Press obtained on 20.02.22. License number 5252990110173

	Montreal	Paris
Age at Diagnosis	A1: below 17 y A2: 17-40 y A3: Above 40 y	A1a: 0–<10y A1b: 10–<17 y A2: 17–40 y A3: >40 y
Location	L1:terminal ileal± limited cecal disease L2: colonic L3: ileocolonic L4: Isolated upper disease*	L1: distal 1/3 ileum ± limited cecal disease L2: colonic L3: ileocolonic L4a: upper disease proximal to Ligament of Treitz* L4b: upper disease distal to ligament of Treitz and proximal to distal 1/3 ileum*
Behavior	B1: non-stricturing non-penetrating B2: stricturing B3: penetrating p: perianal disease modifier	B1: nonstricturing nonpenetrating B2: stricturing B3: penetrating B2B3: both penetrating and and stricturing disease, either at the same or different times p: perianal disease modifier
Growth	n/a	G_0: No evidence of growth delay G_1: Growth delay

2.3.5 Validation

2.3.5.1 Validation of IBD in primary care databases

One study from 2002 assessed the validity and completeness of a primary care database for studies of IBD (80). In the validation study, mailed surveys were sent to the GPs caring for a random sample of 170 individuals who had received an Oxford Medical Indexing System (OXMIS) code (a coding system which can be cross-referenced to Read codes (189, 190)) for IBD in The General Practice Research Database (GPRD) (now Clinical Practice Research Datalink (CPRD)) (1.9). One hundred and fifty-two (92%) surveys were returned and the diagnosis of IBD was considered highly probable or probable in 144 (92%, 95% CI 86-96%) cases. Cases were considered 'highly probable' if the GP had evidence of a gastroenterology

consultation, surgery or intestinal biopsy that confirmed the diagnosis. Cases were considered 'probable' if the GP had evidence of endoscopic or radiographic findings suggestive of IBD. Of 12 surgeries and 25 hospitalisations reported in the survey, 11 (92%) and 19 (76%) were identified in the database respectively.

Smaller studies of IBD using primary care databases have validated their cases using scrutiny of individual paper records or writing to GPs for confirmation of diagnosis (81, 135). However, the two forementioned studies included 568 and 444 patients with IBD respectively. I anticipated identifying over 20,000 incident cases of IBD using my methodology. Hence, writing to GPs individually or requesting free text notes was not feasible given time and budget constraints.

2.3.5.2 Validation in this study

In this study, an algorithm adapted from Abrahami et al (185) was developed to assist in the validation of the diagnosis of IBD in IMRD. This involved checking whether study subjects receiving a new code for IBD during the study period had a record of: 1) at least one presentation with symptoms suggestive of IBD (abdominal pain, diarrhoea, bloody stools, weight loss); 2) a prescription for a drug commonly used to treat IBD; 3) an endoscopy; 4) a referral to a gastroenterologist (Appendix 6.3.12/Appendix 6.4.2/Appendix 6.3.13).

This was an exploratory piece of work and these criteria did not have to be met for an individual to qualify as an 'IBD case' in the primary analysis. This is for two reasons. Firstly, if IBD drugs were required to meet diagnostic criteria, then new diagnoses towards the end of the study period (who haven't started drugs yet) and patients who do not require drugs

would be missed. Secondly, a number of these criteria are not met in primary care. For instance, endoscopies are not performed in the GP surgery and biologics are not usually prescribed by GPs. Therefore, I anticipated that these events would be under-recorded in the primary care notes. This could result in under-ascertainment of cases and a resulting underestimate in incidence/prevalence. Therefore, although these criteria may help to confirm a diagnosis, for the purposes of this study, they were not required in the primary analysis.

2.3.6 Analysis

StataCorp. 2017. *Stata Statistical Software*: Release 15. College Station, TX: StataCorp LLC was used for all analyses.

2.3.6.1 Descriptive analysis

Descriptive characteristics were summarized using numbers and percentages for categorical variables and medians and interquartile ranges (IQR) for non-normally distributed continuous variables.

2.3.6.2 Analysis of temporal trends

Crude incidence estimates for the diagnosis of IBD, CD and UC were calculated per 100,000 person-years at risk with 95% confidence intervals assuming a Poisson distribution. This was done using the *stset* and *stsplit* functions in Stata. Lexis expansions were used to expand the observations as per specific age bands (191).

2.3.6.3 Multivariable analysis

Multivariable mixed Poisson regression was used to model incidence of IBD, CD and UC adjusting for sex, age, calendar year, Townsend Deprivation Score and geographical location using the *poisson* command in Stata.

A Poisson model is used to model the probability that a certain number of events occur during a fixed time interval. A Poisson model is appropriate for these data because they meet all Poisson assumptions:

a) The dependant variable consists of count data (i.e. the dependant variable consists of non-negative integers with no natural upper bound). IBD diagnoses can be counted in absolute numbers
b) The events are independent of one another. At a population level, the occurrence of one person developing IBD does not affect the probability of another person developing IBD.
c) The average rate at which events occur is independent of any occurrences. IBD diagnoses are not anticipated to be clustered events are occurring at random.
d) The event is relatively rare and two events cannot occur at exactly the same instant. Two patients cannot technically be diagnosed with IBD at exactly the same time.

Individuals with missing data on Townsend score were included in the primary analysis using 'missing' as a level to the Townsend variable. A complete-case analysis (exclusion of those patients with missing Townsend score) was also performed.

The Wald test was used to derive p-values for categorical variables in the regression model and to test for multiplicative interactions. Because this study focussed on temporal trends in IBD incidence, I explored interactions between calendar year and all other covariates. Recent studies have reported rising incidence of paediatric IBD in the UK (192, 193) and I was particularly interested in an age-time interaction. As another study conducted as part of this thesis relates to risk of IBD in association with contraceptives, I also ran a regression model including an age-gender interaction term to establish if the risk of IBD is different between men and women of reproductive age.

2.3.6.4 Multi-level models

The multivariable analysis was performed using a range of regression models. The initial model used was a single-level Poisson regression model which did not account for data clustering. However, the data collected in IMRD is from general practices all over the country which may be considerably heterogenous in their computer annotation and coding practices. As events (outcomes) need to be occurring independently to meet Poisson model assumptions, I used a two-level Poisson regression model that included 'GP practice' as a random effect to account for clustering by practice. This was done using the *xtpossion* command in Stata. A three-level model was developed using the *meqrpoisson* command which had individual subjects (patients) nested within GP practices which were nested within Strategic Health Authorities (1.9.1.1).

2.3.6.5 Prevalence

Point prevalence was calculated by dividing all cases of IBD (both incident and prevalent) by the total number of individuals contributing data to the cohort on the 1st of July (midpoint of

the year) for each calendar year. Annual point prevalence was also stratified by age group. To provide the most up to date estimates of IBD epidemiology that were available to me, prevalence was also calculated on the last day of the study period (31/12/18).

2.3.6.6 Sensitivity analysis

In the sensitivity analysis I broadened my case definition to include any individual who had a single IBD medical Read code (as opposed to two medical Read codes or one medical Read code plus one relevant prescription). This analysis was performed as I had concerns about the sensitivity of the diagnostic algorithm used for the primary analysis; potentially cases could be missed if the case definition was 'too strict'. A less strict algorithm could be more sensitive at picking up IBD cases. However, perhaps less specific; for instance if a patient with another disease (e.g. diverticulitis or ischaemic colitis) was accidentally mislabelled as IBD on one occasion then they would be counted as an IBD case in the study. Results of both algorithms are compared in section 2.4.10, and the rationale for my chosen algorithm is explained.

2.3.7 Ethical approval

The contribution of patient level data to IMRD was approved by the NHS South-East Multicentre Research Ethics Committee in 2003. Under this approval, anonymised patient data can be provided to researchers following independent scientific review without the need for additional Research Ethics Committee approval. For this study, independent ethical approval was sought from the Scientific Research committee. Approval was obtained on 29/09/2018 (SRC reference 18THIN082 –Appendix 6.2.1).

2.3.8 Patient and public involvement

The University College London Hospitals NHS Foundation Trust (UCLH) IBD Patient Panel is a group of eight women and eight men, most of whom have IBD (a mix of CD and UC) but also includes parents of children with IBD. They meet regularly to advocate for patients who receive their care at UCLH. In the early stages of this project, I circulated my research proposal amongst this group and it was added to the agenda of one of their meetings. I received encouraging written feedback:

"The UCLH IBD Patient Panel agrees that there is a knowledge gap around hormonal contraceptives and IBD and that the outcomes from this study could be very beneficial for patients of child-bearing years in the management of their IBD and symptoms. We also approve of using the electronic databases available to study the changing epidemiology of Inflammatory Bowel Disease. We therefore welcome this study and believe it's long overdue".

2.4 Results

2.4.1 Descriptive characteristics

11,325,025 individuals (78,985,977 person-years of follow up) were included in the cohort. 5,541,508 (48.9%) were male. 7,944,975 (70.0%) were registered with a GP practice in England, 1,690,503 (14.9%) Scotland, 1,285,722 (11.4%) Wales and 403,825 (3.6%) Northern Ireland. Median (IQR) age at cohort entry was 32.2 (17.5-49.6) years and median (IQR) follow up was 5.4 (2.0-11.6) years (Table 2.2). Townsend data were missing for 2,309,202 (20.4%) individuals. There were no other missing data for all included covariates.

When comparing descriptive characteristics of the cohort before and after exclusions, I found similar proportions of individuals for all included covariates (Table 2.2)

Table 2.2. Descriptive characteristics of the study cohort with and without exclusions

	With exclusions (primary analysis) N (%)	**Without exclusions N (%)**
Overall	11,325,025	14,025,196
Sex		
Male	5,541,508 (48.9%)	6,773,212 (48.3%)
Female	5,783,517 (51.1%)	7,250,780 (51.7%)
Region		
East Midlands	250,241 (2.2%)	285,404 (2.0%)
East of England	681,280 (6.0%)	811,957 (5.8%)
London	1,567,229 (13.8%)	1,899,242 (13.5%)
North East	188,105 (1.7%)	236,782 (1.7%)
North West	913,503 (8.1%)	1,048,480 (7.5%)
Northern Ireland	403,825 (3.6%)	492,117 (3.5%)
Scotland	1,690,503 (14.9%)	2,154,171 (15.3%)
South Central	1,205,719 (10.6%)	1,519,024 (10.8%)
South East Coast	1,136,732 (10.0%)	1,474,958 (10.5%)
South West	821,442 (7.3%)	1,100,326 (7.8%)
Wales	1,285,722 (11.4%)	1,561,503 (11.1%)
West Midlands	921,961 (8.1%)	1,125,743 (8.0%)
Yorkshire & Humber	258,763 (2.3%)	315,489 (2.2%)
Townsend, quintile		
Missing	2,309,202 (20.4%)	3,047,820 (21.7%)
1	2,048,238 (18.1%)	2,451,519 (17.5%)
2	1,861,962 (16.4%)	2,304,476 (16.4%)
3	1,957,933 (17.3%)	2,396,952 (17.1%)
4	1,822,026 (16.1%)	2,221,716 (15.8%)
5	1,325,664 (11.7%)	1,602,713 (11.4%)
Age at cohort entry (years)	**Median (IQR)**	
	32.2 (17.5-49.6)	31.9 (17.9-50.3)

2.4.2 Overall trends in incidence

I identified 65,700 cases of any IBD, including 24,991 cases of CD and 36,705 cases of UC. Among these, 22,560 cases of any IBD (8,077 for CD and 12,369 for UC) were incident diagnoses made during study follow up. Overall crude incidence estimates were 28.6 (95% CI 28.2-28.9), 10.2 (95% CI 10.0-10.5) and 15.7 (95% CI 15.4-15.9)/100,000 person-years for 'any IBD', CD and UC respectively.

Table 2.3. Crohn's disease: Events, years of follow up, incidence rates and adjusted IRRs by sex, age, calendar year, geographical location and social deprivation

	Incident diagnoses (N)	Person-years of follow up	Rate per 100,000 person-years (95% CI)	Adjusted IRR (95% CI)*
Overall	8,077	78,985,977	10.2 (10.0 to 10.5)	
Sex				
Male	3,669	39,344,776	9.3 (9.0 to 9.6)	1 (reference)
Female	4,408	39,641,200	11.1 (10.8 to 11.5)	1.20 (1.15 to 1.25)
Age, years				
0-9	130	8,333,057	1.6 (1.3 to 1.9)	0.11 (0.09 to 0.13)
10-16	711	6,173,205	11.5 (10.7 to 12.4)	0.77 (0.71 to 0.84)
17-40	3,422	22,989,836	14.9 (14.4 to 15.4)	1 (reference)
40+	3,814	41,489,880	9.2 (8.9 to 9.5)	0.62 (0.59 to 0.64)
Year				
2000	267	2,487,569	10.7 (9.5 to 12.1)	1 (reference)
2001	305	2,950,069	10.3 (9.2 to 11.6)	0.97 (0.82 to 1.14)
2002	373	3,470,051	10.8 (9.7 to 11.9)	1.00 (0.85 to 1.17)
2003	401	3,888,506	10.3 (9.3 to 11.4)	0.95 (0.82 to 1.11)
2004	438	4,294,535	10.2 (9.3 to 11.2)	0.94 (0.80 to 1.09)
2005	524	4,517,797	11.6 (10.6 to 12.6)	1.07 (0.92 to 1.24)
2006	544	4,661,555	11.7 (10.7 to 12.7)	1.07 (0.93 to 1.24)
2007	505	4,821,244	10.5 (9.6 to 11.4)	0.96 (0.83 to 1.12)
2008	518	4,911,773	10.6 (9.7 to 11.5)	0.97 (0.84 to 1.13)
2009	534	4,968,127	10.8 (9.9 to 11.7)	0.99 (0.86 to 1.15)
2010	503	4,890,379	10.3 (9.4 to 11.2)	0.95 (0.82 to 1.10)
2011	524	4,961,164	10.6 (9.7 to 11.5)	0.97 (0.84 to 1.13)
2012	557	5,015,375	11.1 (10.2 to 12.1)	1.02 (0.88 to 1.18)
2013	447	4,896,536	9.1 (8.3 to 10.0)	0.84 (0.72 to 0.97)
2014	487	4,641,166	10.5 (9.6 to 11.5)	0.96 (0.82 to 1.11)
2015	379	4,068,609	9.3 (8.4 to 10.3)	0.84 (0.72 to 0.98)
2016	317	3,504,868	9.0 (8.1 to 10.1)	0.80 (0.68 to 0.95)
2017	282	3,141,578	9.0 (8.0 to 10.1)	0.79 (0.67 to 0.94)
2018	172	2,895,075	5.9 (5.1 to 6.9)	0.52 (0.43 to 0.63)
Region				
East Midlands	164	1,708,234	9.6 (8.2 to 11.2)	1 (reference)
East of England	483	4,430,646	10.9 (10.0 to 11.9)	1.18 (0.96 to 1.44)
London	780	8,729,721	8.9 (8.3 to 9.6)	0.94 (0.77 to 1.14)
North East	135	1,373,155	9.8 (8.2 to 11.6)	1.03 (0.80 to 1.34)
North West	857	7,223,549	11.9 (11.1 to 12.7)	1.27 (1.05 to 1.54)
Northern Ireland	475	3,622,539	13.1 (12.0 to 14.4)	1.43 (1.16 to 1.75)
Scotland	1,537	12,487,571	12.3 (11.7 to 12.9)	1.36 (1.13 to 1.64)
South Central	761	7,992,664	9.5 (8.9 to 10.2)	1.01 (0.83 to 1.23)
South East Coast	738	7,849,262	9.4 (8.7 to 10.1)	1.04 (0.85 to 1.26)
South West	569	5,623,041	10.1 (9.3 to 11.0)	1.08 (0.89 to 1.32)
Wales	854	9,553,344	8.9 (8.4 to 9.6)	0.98 (0.81 to 1.19)
West Midlands	562	6,701,459	8.4 (7.7 to 9.1)	0.89 (0.73 to 1.09)

Yorkshire & Humber	162	1,690,792	9.6 (8.2 to 11.2)	1.00 (0.78 to 1.28)
Townsend, quintile				
Missing	1,381	13,648,636	10.1 (9.6 to 10.7)	1.08 (0.99 to 1.17)
1	1,588	16,603,422	9.6 (9.1 to 10.1)	1 (reference)
2	1,439	14,388,767	10.0 (9.5 to 10.5)	1.02 (0.95 to 1.10)
3	1,481	13,909,220	10.7 (10.1 to 11.2)	1.07 (1.00 to 1.15)
4	1,251	12,043,308	10.4 (9.8 to 11.0)	1.03 (0.96 to 1.12)
5	937	8,392,624	11.2 (10.5 to 11.9)	1.08 (0.99 to 1.17)

*Adjusted for other variables considered; Sex, ageband, year, region, Townsend quintile, respectively

*IRRs compared to the reference group for each categorical variable

Table 2.4. Ulcerative colitis: Events, years of follow up, incidence rates and adjusted IRRs of CD and UC by sex, age, calendar year, geographical location and social deprivation

	Incident diagnoses (N)	**Person-years of follow up**	**Rate per 100,000 person-years (95% CI)**	**Adjusted IRR (95% CI)***
Overall	12,369	78,985,977	15.7 (15.4 to 15.9)	
Sex				
Male	6,561	39,344,776	16.7 (16.3 to 17.1)	1 (reference)
Female	5,808	39,641,200	14.7 (14.3 to 15.0)	0.87 (0.84 to 0.90)
Age , years				
0-9	87	8,333,057	1.0 (0.8 to 1.3)	0.05 (0.04 to 0.07)
10-16	458	6,173,205	7.4 (6.8 to 8.1)	0.38 (0.35 to 0.42)
17-40	4,416	22,989,836	19.2 (18.7 to 19.8)	1 (reference)
40+	7,408	41,489,880	17.9 (17.5 to 18.3)	0.92 (0.89 to 0.96)
Year				
2000	463	2,487,569	18.6 (17.0 to 20.4)	1 (reference)
2001	527	2,950,069	17.9 (16.4 to 19.5)	0.96 (0.85 to 1.09)
2002	580	3,470,051	16.7 (15.4 to 18.1)	0.89 (0.79 to 1.01)
2003	662	3,888,506	17.0 (15.8 to 18.4)	0.91 (0.81 to 1.03)
2004	742	4,294,535	17.3 (16.1 to 18.6)	0.93 (0.82 to 1.04)
2005	726	4,517,797	16.1 (14.9 to 17.3)	0.86 (0.77 to 0.97)
2006	758	4,661,555	16.3 (15.1 to 17.5)	0.87 (0.78 to 0.98)
2007	803	4,821,244	16.7 (15.5 to 17.9)	0.89 (0.80 to 1.00)
2008	872	4,911,773	17.8 (16.6 to 19.0)	0.95 (0.85 to 1.07)
2009	815	4,968,127	16.4 (15.3 to 17.6)	0.88 (0.79 to 0.99)
2010	763	4,890,379	15.6 (14.5 to 16.8)	0.84 (0.75 to 0.94)
2011	737	4,961,164	14.9 (13.8 to 16.0)	0.80 (0.71 to 0.90)
2012	763	5,015,375	15.2 (14.2 to 16.3)	0.82 (0.73 to 0.92)
2013	740	4,896,536	15.1 (14.0 to 16.2)	0.82 (0.73 to 0.92)
2014	675	4,641,166	14.5 (13.5 to 15.7)	0.79 (0.70 to 0.89)
2015	576	4,068,609	14.2 (13.0 to 15.4)	0.77 (0.68 to 0.87)
2016	480	3,504,868	13.7 (12.5 to 15.0)	0.74 (0.65 to 0.84)
2017	397	3,141,578	12.6 (11.4 to 13.9)	0.68 (0.60 to 0.78)
2018	290	2,895,075	10.0 (8.9 to 11.2)	0.54 (0.47 to 0.63)
Region				
East Midlands	299	1,708,234	17.5 (15.6 to 19.6)	1 (reference)

East of England	769	4,430,646	17.4 (16.2 to 18.6)	1.01 (0.86 to 1.19)
London	1,336	8,729,721	15.3 (14.5 to 16.2)	0.94 (0.81 to 1.09)
North East	249	1,373,155	18.1 (16.0 to 20.5)	1.08 (0.88 to 1.32)
North West	1,139	7,223,549	15.8 (14.9 to 16.7)	0.93 (0.80 to 1.08)
Northern Ireland	585	3,622,539	16.2 (14.9 to 17.5)	1.02 (0.87 to 1.21)
Scotland	1,915	12,487,571	15.3 (14.7 to 16.0)	0.97 (0.84 to 1.13)
South Central	1,285	7,992,664	16.1 (15.2 to 17.0)	0.92 (0.79 to 1.07)
South East Coast	1,234	7,849,262	15.7 (14.9 to 16.6)	0.95 (0.81 to 1.10)
South West	854	5,623,041	15.2 (14.2 to 16.2)	0.88 (0.75 to 1.03)
Wales	1,350	9,553,344	14.1 (13.4 to 14.9)	0.87 (0.75 to 1.01)
West Midlands	1,087	6,701,459	16.2 (15.3 to 17.2)	0.96 (0.82 to 1.12)
Yorkshire & Humber	267	1,690,792	15.8 (14.0 to 17.8)	0.91 (0.74 to 1.10)
Townsend, quintile				
Missing	2,054	13,648,636	15.1 (14.4 to 15.7)	0.95 (0.89 to 1.02)
1	2,792	16,603,422	16.8 (16.2 to 17.5)	1 (reference)
2	2,376	14,388,767	16.5 (15.9 to 17.2)	0.97 (0.92 to 1.03)
3	2,246	13,909,220	16.2 (15.5 to 16.8)	0.96 (0.91 to 1.01)
4	1,782	12,043,308	14.8 (14.1 to 15.5)	0.88 (0.83 to 0.94)
5	1,119	8,392,624	13.3 (12.6 to 14.1)	0.80 (0.74 to 0.86)

*Adjusted for other variables considered; Sex, ageband, year, region, Townsend quintile, respectively

*IRRs compared to the reference group for each categorical variable

2.4.3 Any IBD incidence

For the period 2000-2017, incidence of 'any IBD' fell from 31.7 (95% CI 29.5-34.0) to 25.0 (95% CI 23.3-26.8) per 100,000 person-years at an average rate of 1.0% (95% CI 0.7-1.3; p<0.0001) per calendar year (Figure 2.4). Incidence of 'any IBD' remained relatively stable for those aged 17-40 years (A2 disease) and those aged 0-9 years (A1a disease). However, for those aged over 40 years (A3 disease), crude incidence fell from 37.8 (95% CI 34.5-41.4) to 23.6 (21.3-26.0) per 100,000 person-years at an average rate of 2.3% (95% CI 1.9-2.7; p<0.0001) per calendar year and for those aged 10-16 years (A1b disease), incidence rose from 13.1 (95% CI 8.3-19.5) to 25.4 (95% CI 19.5-32.4) per 100,000 person-years at an average rate of 3.0% (95% CI 1.7-4.3; p<0.0001) per calendar year (Figure 2.5).

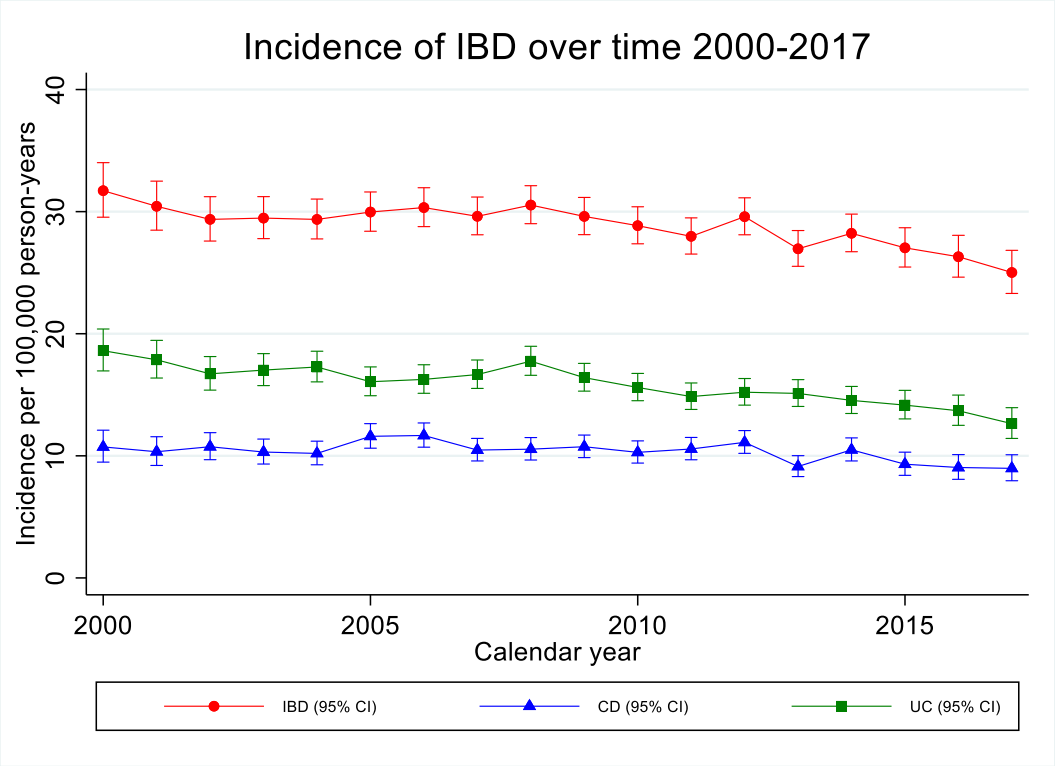


Figure 2.4. Crude incidence estimates of IBD, stratified by calendar year, over the period 2000-2017

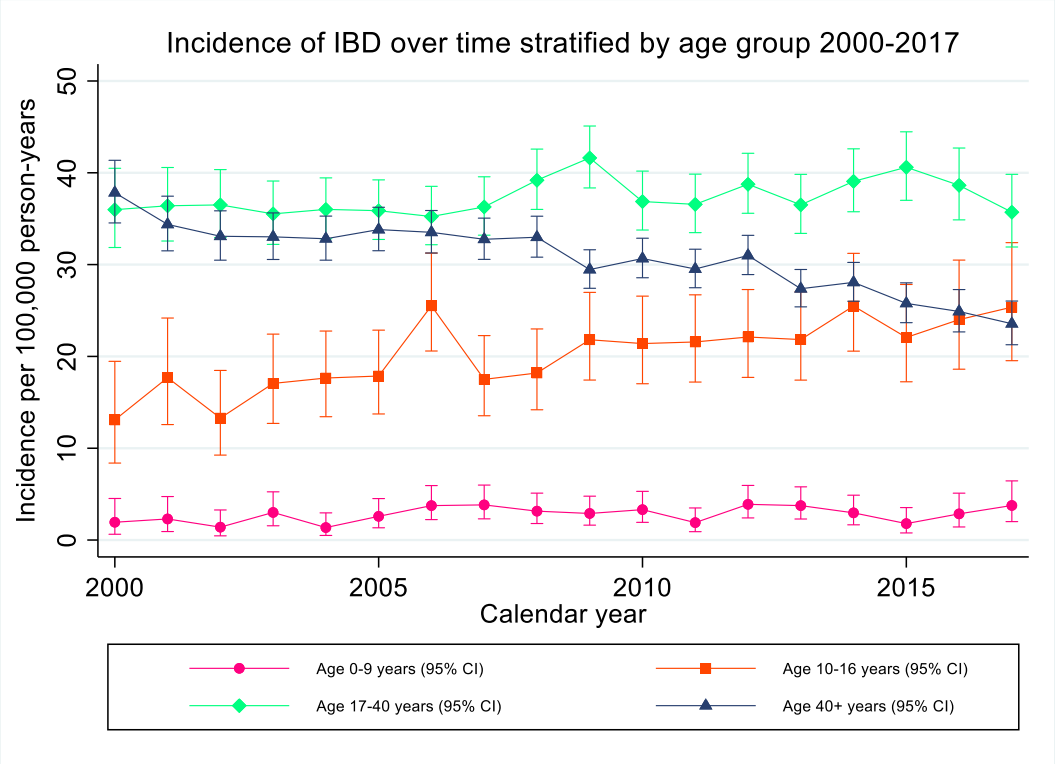


Figure 2.5. Crude incidence estimates for any IBD, stratified by Montreal/Paris age classification and calendar year, over the period 2000-2017

2.4.4 CD incidence

During the study period, CD incidence fell from 10.7 (95% CI 9.5-12.1) to 9.0 (95% CI 8.0-10.1) per 100,000 person-years at an average rate of 1.1% (95% CI 0.6-1.5; p<0.0001) per calendar year (Figure 2.4). However, in children <17 years, incidence rose from 3.9 (95% CI 2.2-6.2) to 6.9 (95% CI 4.9-9.3) per 100,000 person-years at an average rate of 2.9% per calendar year (95% CI 1.3-4.4; p<0.0001) (Figure 2.6). Although overall unadjusted incidence was higher for boys than for girls (7.4 (95% CI 6.8-8.0) vs 4.1 (95% CI 3.6-4.6) per 100,000 person-years), a significant rise in incidence was observed for both sexes (average 2.7% (95% CI 0.8-4.6) and 3.3% (95% CI -0.6-6.0) rise per calendar year for boys and girls respectively). No change in incidence was observed for children aged 0-9 years. However, for adolescents aged 10-16 years, incidence rose from 7.6 (95% CI 4.2-12.8) to 13.1 (95% CI 9.0-18.4) per 100,000 person-years at an average rate of 2.8% (1.2-4.5; p=0.001) per calendar year.

Incidence of CD was highest in Northern Ireland, Scotland and the North West (13.1 (95% CI 12.0-14.4), 12.3 (95% CI 11.7-12.9) and 11.9 (95% CI 11.1-12.7) per 100,000 person-years respectively) and lowest in Wales, London and the West Midlands (8.9 (95% CI 8.4-9.6), 8.9 (95% CI 8.3-9.6) and 8.4 (95% CI 7.7-9.1) per 100,000 person-years respectively) (Figure 2.7). I observed no association between social deprivation and incidence of CD after adjusting for sex, calendar year, age and geographical location (Table 2.3).

2.4.5 UC incidence

Incidence of UC dropped by a greater extent than CD over the study period; from 18.6 (95% CI 17.0-20.4) to 12.6 (95% CI 11.4-13.9) per 100,000 person-years at an average rate of 1.6% (95% CI 1.2-1.9; p<0.0001) per calendar year (Figure 2.4). The fall in incidence was most pronounced for those aged over 40 years, in whom a 45% drop in incidence was observed, falling from 24.1 (95% CI 21.5-26.9) to 13.3 (95% CI 11.6-15.2) per 100,000 person-years (average 3.1% (95% CI 2.6-3.6; p<0.0001) decrease per calendar year).

In children aged <17 years, incidence rose from 2.0 (95% CI 0.9-3.9) to 5.0 (95% CI 3.4-7.2) per 100,000 person-years (average 2.5% (95% CI 0.5-4.4; p=0.01) rise per calendar year) (Figure 2.6). The rise in incidence was largely driven by adolescent boys aged 10-16 years in whom incidence rose by 3.4% (95% CI 0.8-6.2; p=0.01) per calendar year. No significant change in incidence was observed in girls aged 10-16 years or children of either sex aged 0-9 years.

Incidence of UC was highest in the North East, the East of England and the East Midlands (18.1 (95% CI 16.0-20.5), 17.4 (95% CI 16.2-18.6) and 17.5 (95% CI 15.6-19.6) per 100,000 person-years respectively) and lowest in Wales, the South West and London (14.1 (95% CI 13.4-14.9), 15.2 (95% CI 14.2-16.2) and 15.3 (95% CI 14.5-16.2) per 100,000 person-years respectively) (Figure 2.7).

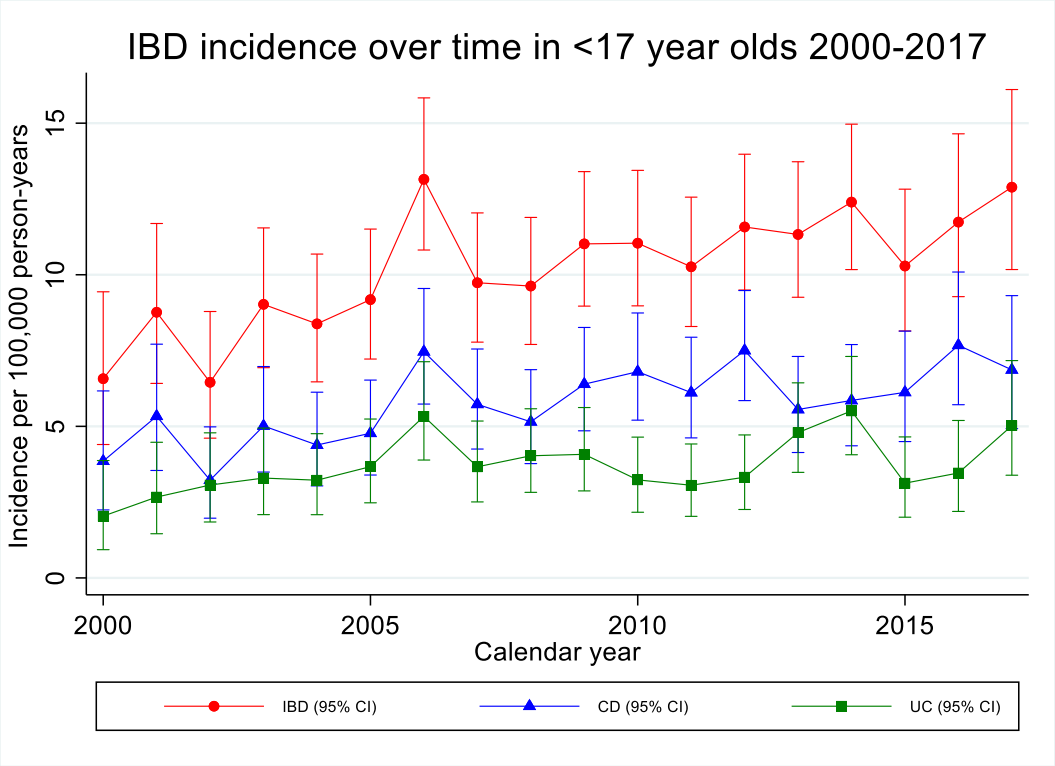


Figure 2.6.Crude incidence estimates of IBD in children <17 years, stratified by calendar year, over the period 2000-2017

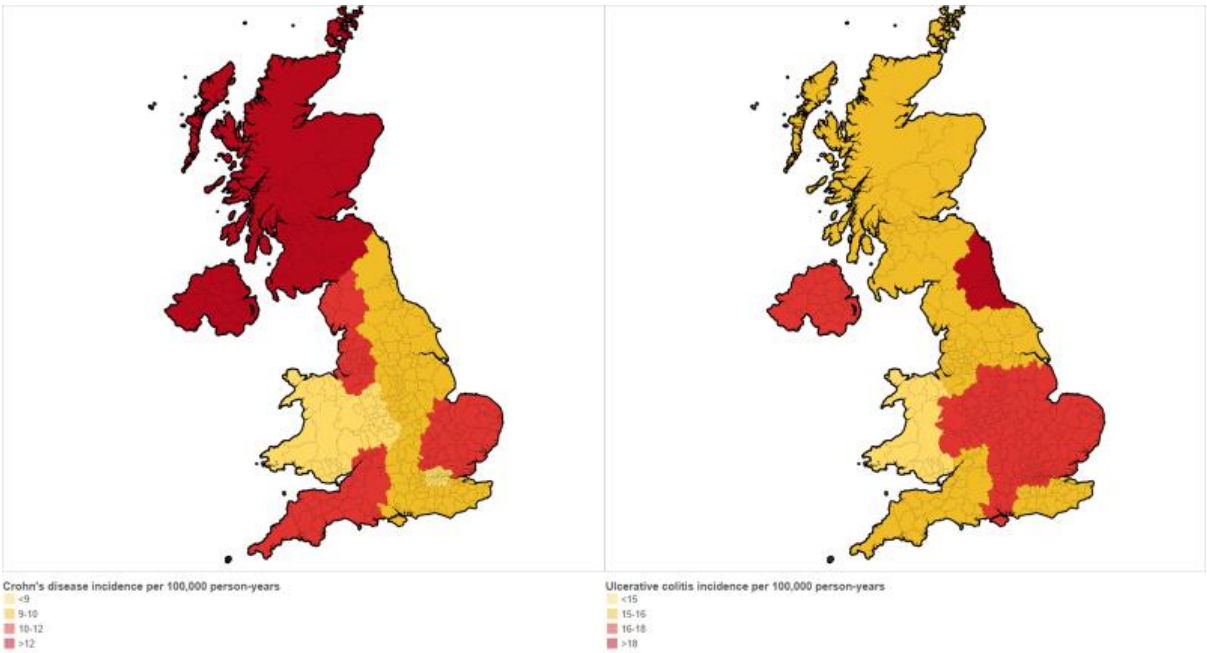


Figure 2.7. Map showing overall crude incidence of CD and UC stratified by geographical region

2.4.6 Social deprivation

I observed no association between social deprivation and incidence of CD after adjusting for sex, calendar year, age and geographical location. I observed higher incidence of UC in individuals from the least deprived quintile compared to most deprived (16.8 (95% CI 16.2-17.5) vs 13.3 (95% CI 12.6-14.1) per 100,000 person-years, adjusted IRR 0.80 (95% CI 0.74-0.86; p<0.0001) (Figure 2.8).

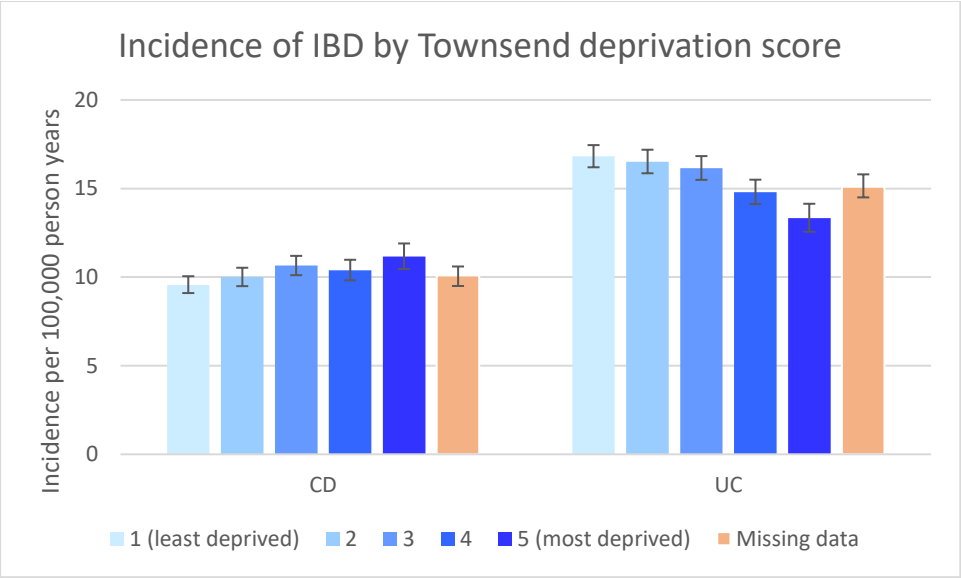


Figure 2.8 Unadjusted Incidence (95% CI) of CD and UC by Townsend deprivation score

2.4.7 Gender specific differences in age at diagnosis

In terms of age at onset, I observed a bimodal distribution for 'any IBD' and UC and a unimodal distribution for CD (Figure 2.9). For CD, overall incidence was higher in women. However, I observed this difference to be most pronounced in those aged 20-40 years. The peak in incidence of CD was earlier in men (15-20 vs 20-25 years) (Figure 2.11). For UC, incidence was similar between men and women for the peak in early life. However, the peak in later life was greater in men than women (Figure 2.12).

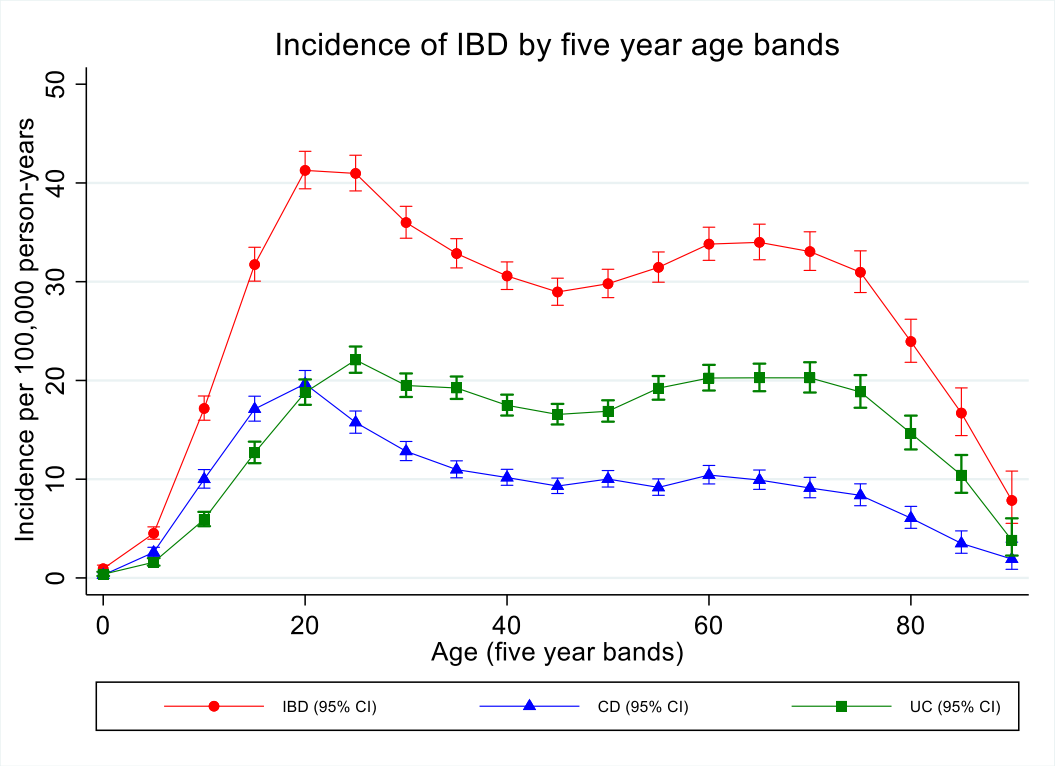


Figure 2.9. Incidence of Inflammatory bowel disease by five-year age bands

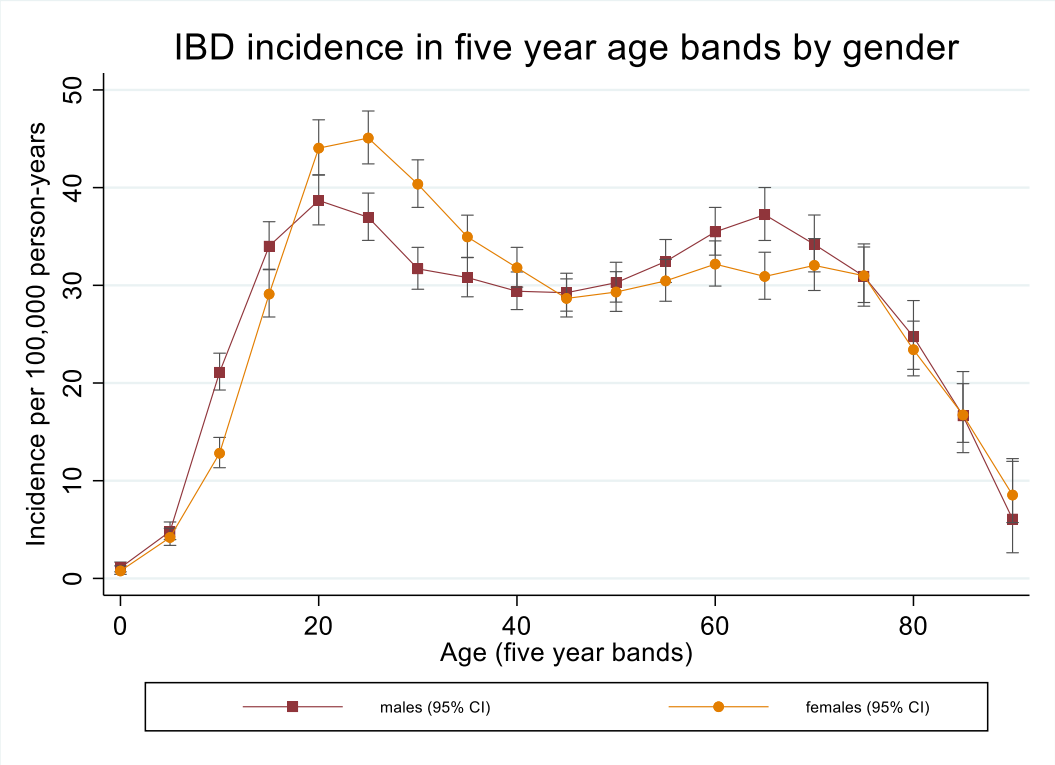


Figure 2.10. Incidence of IBD overall in five-year age bands by gender

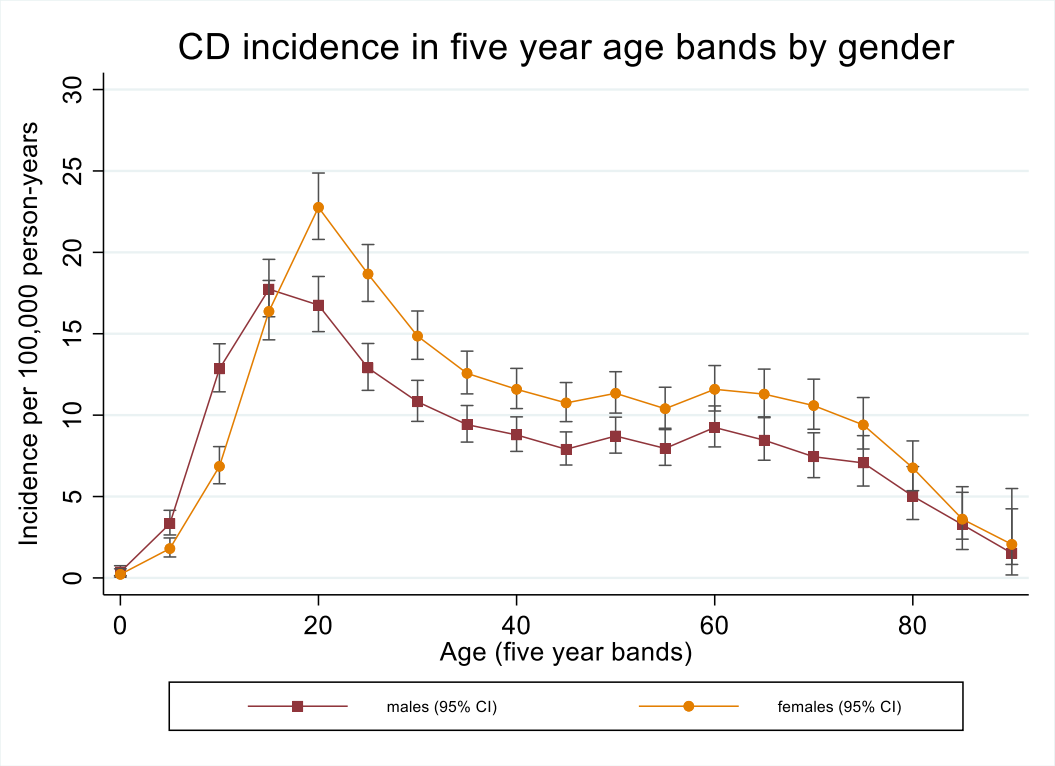


Figure 2.11. Incidence of CD in five-year age bands by gender

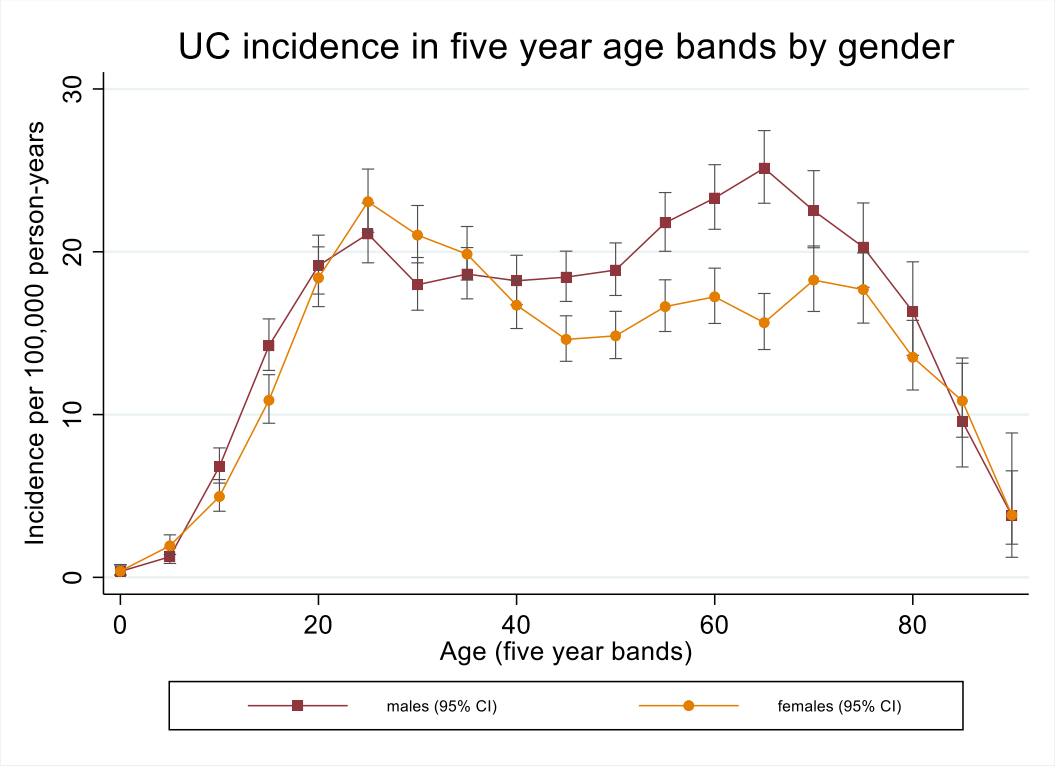


Figure 2.12. Incidence of UC in five-year age bands by gender

2.4.8 Interactions between covariates

I found evidence of an age-time interaction for all three main outcomes (p<0.00001, p=0.0046, p<0.00001 for 'any IBD', CD and UC respectively). Age band specific age-time interaction coefficients confirmed increasing incidence in adolescents ages 10-16 years, decreasing incidence in those aged 40+ years and stable incidence in age groups 0-9 and 17-40 years (Table 2.5). For example, between 2000 and 2017, incidence of IBD increased by 2.7% per year on average for 10-16 year-olds but decreased by 2.2% per year for people aged over 40 years.

Table 2.5. Interaction coefficients (adjusted IRR) for age-time interactions (time treated as a continuous linear variable)*

Ageband (years)	Any IBD (95% CI)	CD (95% CI)	UC (95% CI)
0-9	1.019 (0.993-1.048)	1.032 (0.996-1.070)	1.017 (0.973-1.063)
10-16	1.027 (1.015-1.039)	1.025 (1.009-1.041)	1.024 (1.004-1.044)
17-40	1.003 (0.999-1.008)	0.992 (0.984-0.999)	1.005 (0.998-1.012)
40+	0.978 (0.974-0.982)	0.980 (0.972-0.987)	0.970 (0.965-0.976)

*Adjusted for other variables considered; Sex, ageband, year, region, Townsend quintile, respectively

I observed a gender-age interaction for all three main outcomes (p<0.00001). In adolescents, incidence of IBD was 47.9% lower in girls than boys. In adults of all ages, incidence of CD was higher in women than men; however, more so for those aged 17-40 years than those aged 40+ years (34.1% vs 28.0%). In those over 40 years, incidence of UC was 21.8% lower in women than men (Table 2.6).

Table 2.6. Interaction coefficients (adjusted IRR) for sex-age interactions (IRRs presented are for women with men as baseline)*

Ageband (years)	Any IBD (95% CI)	CD (95% CI)	UC (95% CI)
0-9	0.861 (0.66-1.120)	0.570 (0.396-0.819)	1.469 (0.935-2.307)
10-16	0.621 (0.553-0.697)	0.568 (0.482-0.669)	0.691 (0.569-0.840)
17-40	1.171 (1.121-1.224)	1.341 (1.249-1.439)	1.056 (0.989-1.127)
40+	0.942 (0.908-0.979)	1.280 (1.200-1.365)	0.782 (0.745-0.820)

*Adjusted for other variables considered; Sex, ageband, year, region, Townsend quintile, respectively

I observed a modest gender-time interaction, the fall in IBD incidence over time was 0.6% per calendar year for men and 1.3% per calendar year for women (Table 2.7/Figure 2.13)

Table 2.7. Interaction coefficients (adjusted IRR) for sex-time interactions (time treated as a continuous linear variable)*

Gender	Any IBD (95% CI)	CD (95% CI)	UC (95% CI)
Men	0.994 (0.990-0.998)	0.997 (0.990-1.00)	0.986 (0.981-0.992)
Women	0.987 (0.983-0.991)	0.983 (0.977-0.990	0.983 (0.977-0.988)

*Adjusted for other variables considered; Sex, ageband, year, region, Townsend quintile, respectively

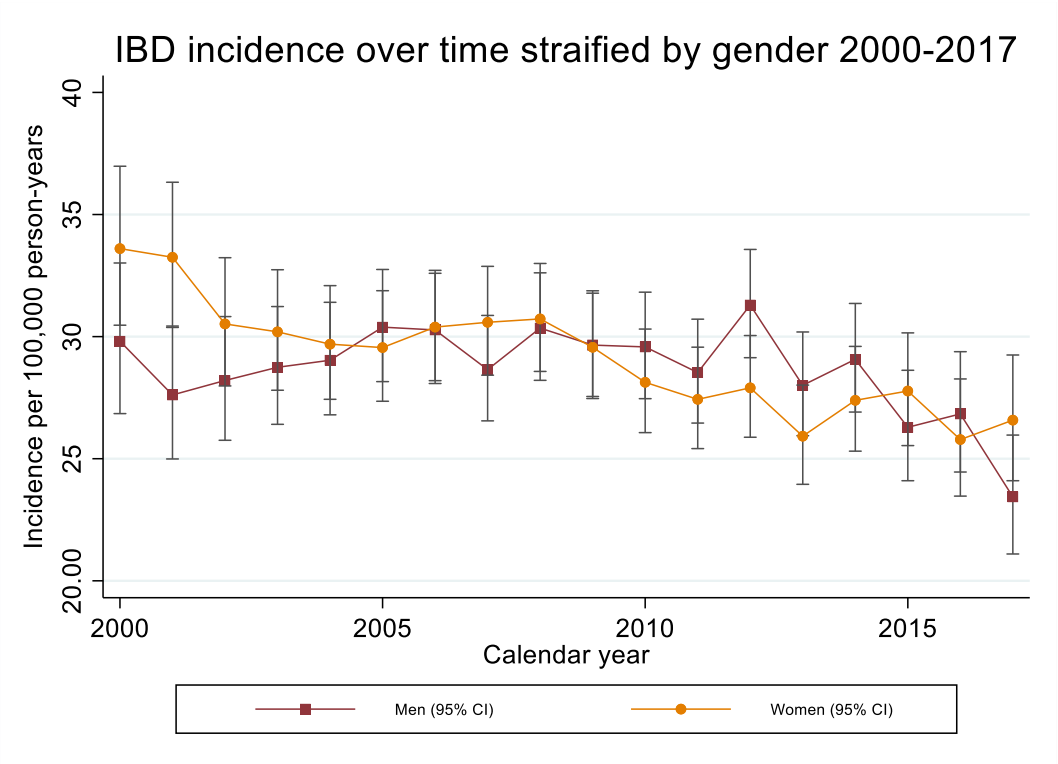


Figure 2.13. IBD incidence over time stratified by gender

The inclusion of a 'region-time' interaction term showed stable IBD incidence in The East Midlands, The North East, The North West, Scotland and Wales. IBD incidence was falling in all other regions (Table 2.8). For example, in the North West, the age-time interaction coefficient was 1.004 (95% CI 0.993-1.016), therefore neither falling or rising on average per calendar year. However, in the South West, the interaction coefficient was 0.980 (0.968-0.992); an estimated fall in incidence of 0.8-3.2% per calendar year on average. No overall

increase in IBD incidence was observed in any geographical region over the study period (Table 2.8).

Table 2.8. Interaction coefficients (adjusted IRR) for region-time interactions (time treated as a continuous linear variable)*

Strategic Health Authority	Any IBD (95% CI)	CD (95% CI)	UC (95% CI)
East Midlands	0.994 (0.973-1.015)	1.001 (0.972-1.031)	0.980 (0.943- 1.017)
East of England	0.992 (0.979-1.006)	0.985 (0.965-1.006)	0.994 (0.975-1.014)
London	0.989 (0.980-0.998)	0.994 (0.978-1.010)	0.980 (0.970-0.990)
North East	0.979 (0.952-1.007)	0.945 (0.907-0.984)	0.989 (0.955-1.026)
North West	1.004 (0.993-1.016)	1.003 (0.987-1.020)	0.996 (0.983-1.008)
Northern Ireland	0.980 (0.967-0.993)	0.974 (0.954-0.995)	0.977 (0.957-0.997)
Scotland	0.998 (0.991-1.006)	0.989 (0.979-1.000)	0.996 (0.985-1.007)
South Central	0.987 (0.975-0.998)	0.989 (0.973-1.005)	0.984 (0.972-0.997)
South East Coast	0.983 (0.972-0.993)	0.997 (0.980-1.014)	0.972 (0.959-0.987)
South West	0.980 (0.968-0.992)	0.974 (0.954-0.994)	0.975 (0.961-0.989)
Wales	0.994 (0.984-1.004)	0.993 (0.976-1.010)	0.986 (0.973-0.999)
West Midlands	0.987 (0.977-0.997)	0.988 (0.972-1.005)	0.984 (0.971-0.997)
Yorkshire & Humber	0.981 (0.967-0.996)	0.986 (0.955-1.019)	0.973 (0.951-0.995)

*Adjusted for other variables considered; Sex, ageband, year, region, Townsend quintile, respectively

I did not observe an important interaction between social deprivation and time period (IBD p=0.65, CD p=0.27, UC p=0.95) (Table 2.9).

Table 2.9. Interaction coefficients (adjusted IRR) for townsend-time interactions (time treated as a continuous linear variable)*

Townsend	Any IBD (95% CI)	CD (95% CI)	UC (95% CI)
One	0.990 (0.984-0.997)	0.998 (0.987-1.001)	0.984 (0.975-0.993)
Two	0.991 (0.985-0.998)	0.988 (0.976-0.999)	0.988 (0.979-0.996)
Three	0.989 (0.093-0.996)	0.987 (0.976-0.998)	0.984 (0.976-0.993)
Four	0.996 (0.988-1.003)	0.995 (0.985-1.006)	0.987 (0.977-0.998)
Five	0.987 (0.978-0.996)	0.982 (0.969-0.996)	0.981 (0.969-0.994)
Missing	0.989 (0.981-0.996)	0.985 (0.974-0.996)	0.983 (0.974-0.993)

*Adjusted for other variables considered; Sex, ageband, year, region, Townsend quintile, respectively

2.4.9 IBD Prevalence

Despite falling incidence, IBD prevalence rose consistently over the study period. Rising by 59.1% (from 455 to 724 per 100,000 people) for any IBD, 70.4% (from 162 to 276 per 100,000 people) for CD and 46.0% (from 272 to 397 per 100,000 people) for UC (Figure

2.14). Point prevalence estimates on at the end of the study (31/12/2018) were 725, 276 and 397 per 100,000 people for 'any IBD', CD and UC respectively.

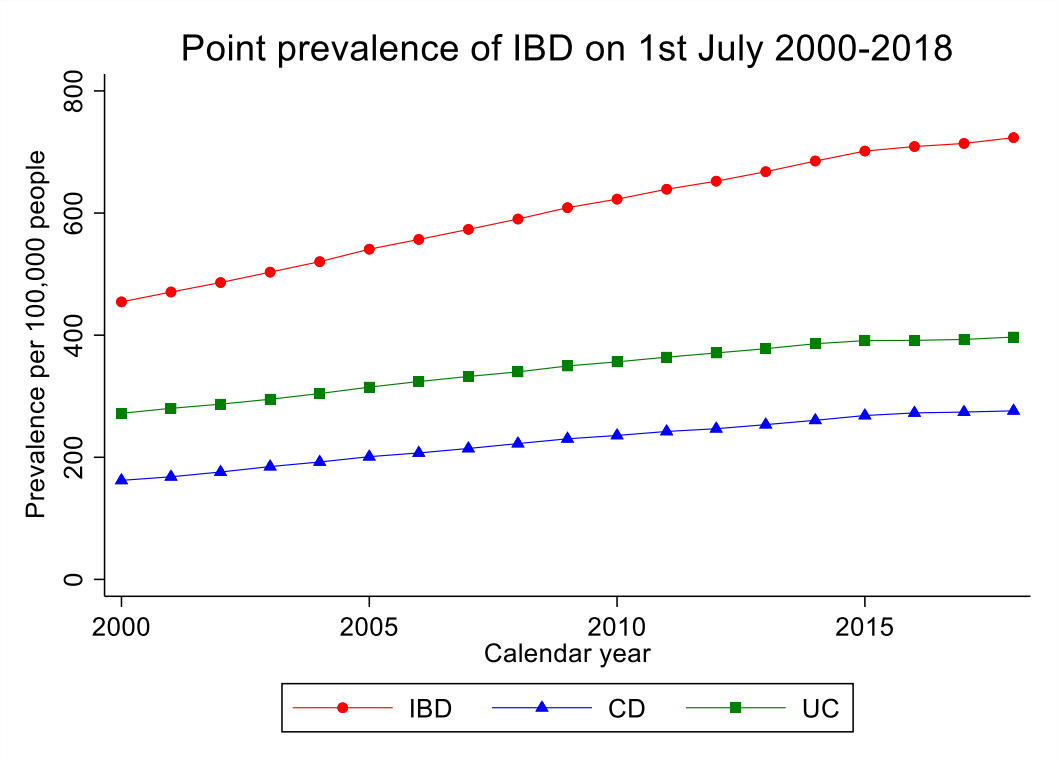


Figure 2.14. Point prevalence estimates for IBD on the first of July for each calendar year 2000-2018

Prevalence rose amongst all age groups, the largest percentage increase in adolescents, but the greatest in absolute numbers in older adults. Rising by 30.2% (from 5 to 7 per 100,000 people) in those aged 0-9 years, 260% (from 30 to 109 per 100,000 people) in those aged 10-16 years, 57.7% (from 384 to 606 per 100,000 people) in those aged 17-40 years and 60.3% (from 648 to 1,039 per 100,000 people) in those aged over 40 years (Figure 2.15).

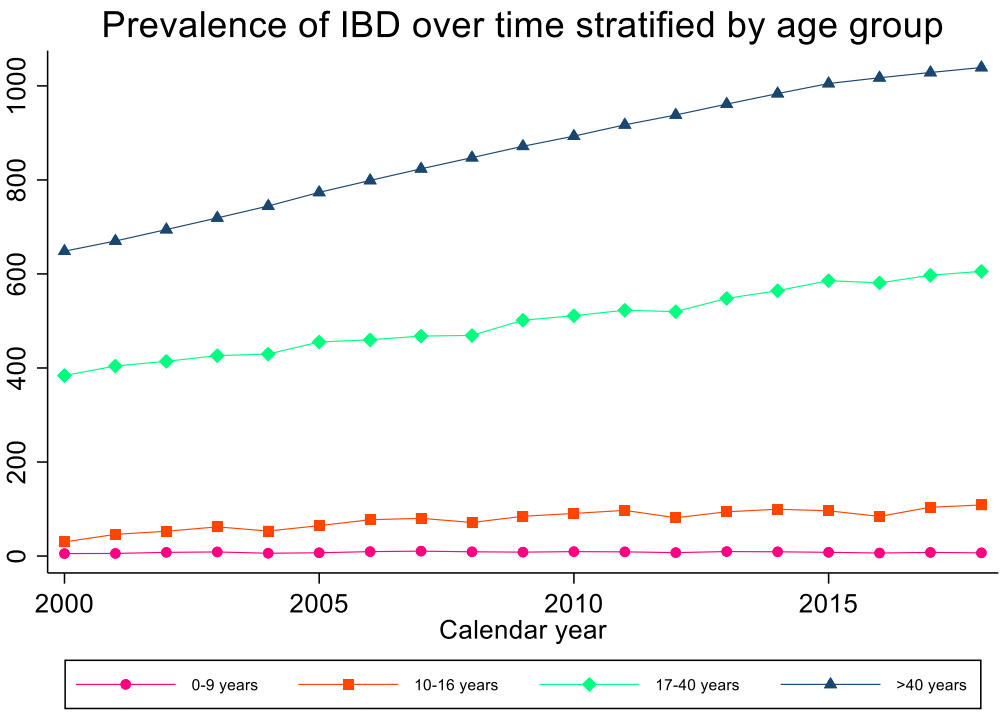


Figure 2.15. Point prevalence estimates for IBD on the first of July for each calendar year 2000-2018 stratified by age group

2.4.10 Sensitivity analysis

When broadening the case definition to include any individual who had a single IBD medical Read code, I observed an increase in overall incidence rates from 28.6 (95% CI 28.2-28.9) to 36.6 (95% CI 36.2-37.0) per 100,000 person-years for 'any IBD', 10.2 (95% CI 10.0-10.5) to 12.9 (95% CI 12.7-13.2) per 100,000 person-years for CD and 15.7 (95% CI 15.4-15.9) to 19.3 (95% CI 19.0-19.6) per 100,000 person-years for UC. Over time, I observed a similar fall in incidence of UC, decreasing from 21.8 (95% CI 20.0-23.8) to 17.9 (95% 16.4-19.4) per 100,000 person-years (average decrease 1.3% (95% CI 0.9-1.6) per calendar year). However, no temporal decrease in CD incidence was observed (Figure 2.16). When stratifying IBD incidence by five-year age bands, the peak in incidence later in life was higher and occurred later than in the primary analysis (Figure 2.17).

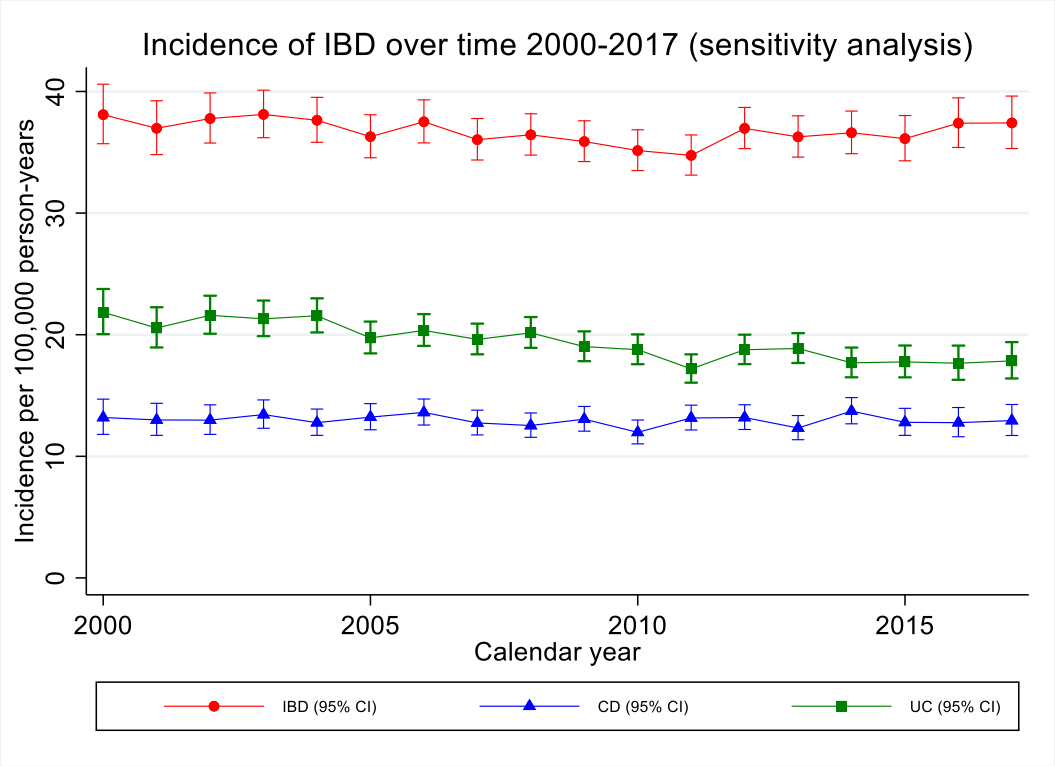


Figure 2.16. Crude incidence estimates of IBD for the period 2000-2017 (sensitivity analysis)

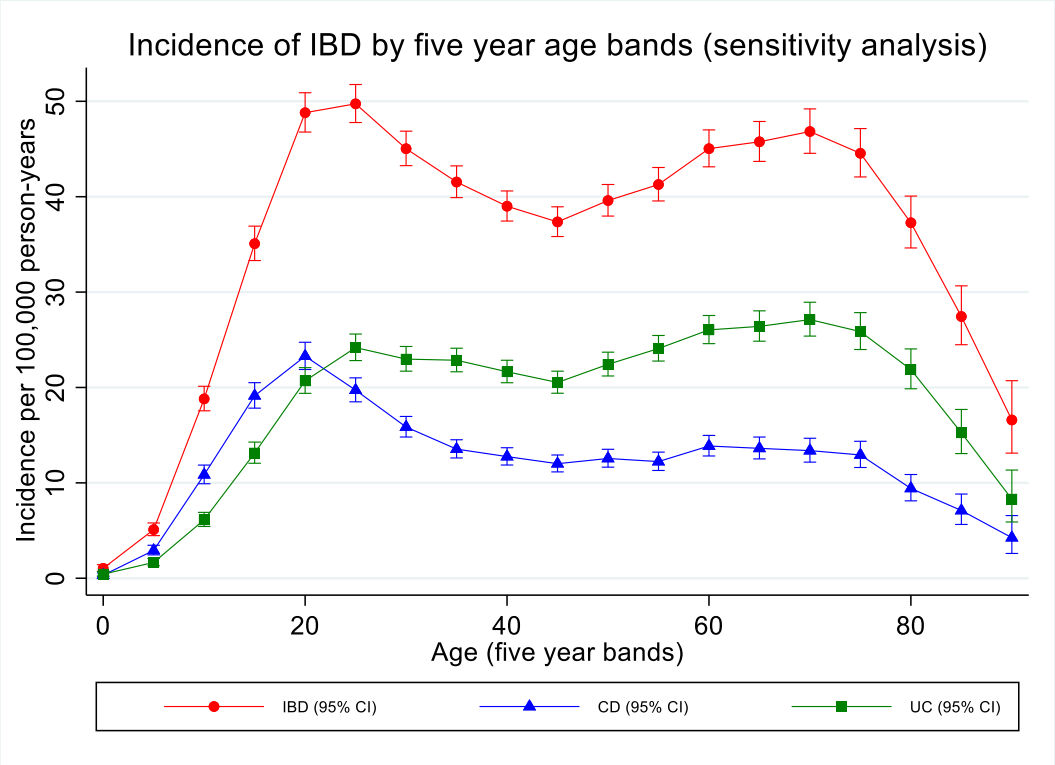


Figure 2.17. Incidence of Inflammatory bowel disease by five year age bands (sensitivity analysis)

2.4.11 Dealing with missing data

There were no missing data in this study for all covariates except Townsend deprivation score (20.4% missing). Two methods of dealing with missing data were used; categorisation (including a 'missing' level to the Townsend variable - used for the primary analysis) and complete case analysis. Crude incidence rates and IRRs were similar using both methods of dealing with missing data (Table 2.10). Categorisation was used for the primary analysis as this provided a larger sample size, thus allowing us to describe temporal trends in incidence for small sub-groups (e.g. children aged 0-9 years).

Table 2.10. Incidence rates and adjusted IRRs of CD and UC by sex, age, calendar year, geographical location and social deprivation

	Incidence of IBD (categorisation) n= 11,325,025		**Incidence of IBD (complete case analysis) n= 8,992,832**	
	Rate per 100,000 person-years (95% CI)	**Adjusted IRR (95% CI)***	**Rate per 100,000 person-years (95% CI)**	**Adjusted IRR (95% CI)***
Overall	28.6 (28.2 to 28.9)		28.7 (28.3 to 29.1)	
Sex				
Male	28.5 (28.0 to 29.1)	1 (reference)	28.7 (28.2 to 29.3)	1 (reference)
Female	28.6 (28.1 to 29.1)	1.00 (0.97 to 1.02)	28.6 (28.0 to 29.2)	0.99 (0.96 to 1.02)
Age , years				
0-9	2.9 (2.6 to 3.3)	0.08 (0.07 to 0.09)	3.0 (2.6 to 3.4)	0.08 (0.07 to 0.09)
10-16	20.4 (19.3 to 21.6)	0.55 (0.52 to 0.58)	21.0 (19.7 to 22.2)	0.56 (0.53 to 0.60)
17-40	37.1 (36.3 to 37.9)	1 (reference)	37.2 (36.3 to 38.1)	1 (reference)
40+	30.2 (29.7 to 30.7)	0.81 (0.79 to 0.83)	30.2 (29.7 to 30.8)	0.81 (0.78 to 0.83)
Year				
2000	31.7 (29.5 to 34.0)	1 (reference)	32.0 (29.6 to 34.5)	1 (reference)
2001	30.1 (28.2 to 32.2)	0.95 (0.86 to 1.05)	29.4 (27.3 to 31.6)	0.92 (0.83 to 1.02)
2002	29.4 (27.6 to 31.3)	0.92 (0.84 to 1.01)	29.5 (27.5 to 31.5)	0.91 (0.82 to 1.01)
2003	29.5 (27.8 to 31.3)	0.92 (0.84 to 1.01)	29.2 (27.4 to 31.1)	0.90 (0.82 to 0.99)
2004	29.2 (27.6 to 30.9)	0.91 (0.83 to 1.00)	29.2 (27.5 to 31.0)	0.90 (0.82 to 0.99)
2005	30.1 (28.5 to 31.7)	0.94 (0.86 to 1.02)	29.8 (28.1 to 31.6)	0.92 (0.83 to 1.01)
2006	30.3 (28.7 to 31.9)	0.94 (0.86 to 1.03)	30.2 (28.5 to 32.0)	0.93 (0.85 to 1.02)
2007	29.7 (28.2 to 31.3)	0.93 (0.85 to 1.01)	29.6 (28.0 to 31.3)	0.91 (0.83 to 1.00)
2008	30.5 (29.0 to 32.1)	0.95 (0.87 to 1.04)	30.7 (29.0 to 32.4)	0.94 (0.86 to 1.04)
2009	29.6 (28.1 to 31.2)	0.92 (0.85 to 1.01)	29.9 (28.3 to 31.6)	0.92 (0.84 to 1.01)
2010	28.9 (27.4 to 30.5)	0.90 (0.83 to 0.99)	29.4 (27.8 to 31.1)	0.91 (0.82 to 1.00)
2011	28.0 (26.6 to 29.5)	0.87 (0.80 to 0.95)	28.2 (26.6 to 29.9)	0.87 (0.79 to 0.95)
2012	29.6 (28.1 to 31.1)	0.92 (0.84 to 1.01)	29.2 (27.5 to 30.8)	0.89 (0.81 to 0.98)

2013	27.0 (25.5 to 28.5)	0.84 (0.77 to 0.92)	27.1 (25.5 to 28.8)	0.83 (0.76 to 0.92)
2014	28.2 (26.7 to 29.8)	0.88 (0.80 to 0.96)	28.7 (27.0 to 30.5)	0.88 (0.80 to 0.97)
2015	27.0 (25.5 to 28.7)	0.84 (0.76 to 0.92)	27.3 (25.5 to 29.1)	0.83 (0.75 to 0.92)
2016	26.3 (24.6 to 28.1)	0.81 (0.73 to 0.89)	26.2 (24.3 to 28.2)	0.79 (0.71 to 0.88)
2017	25.0 (23.3 to 26.8)	0.76 (0.69 to 0.85)	24.8 (22.8 to 26.9)	0.74 (0.66 to 0.83)
2018	19.3 (17.7 to 21.0)	0.59 (0.52 to 0.65)	18.8 (16.9 to 20.8)	0.55 (0.48 to 0.63)
Region				
East Midlands	30.0 (27.4 to 32.8)	1 (reference)	30.1 (27.5 to 33.0)	1 (reference)
East of England	30.8 (29.1 to 32.4)	1.04 (0.92 to 1.19)	30.6 (28.8 to 32.4)	1.03 (0.90 to 1.17)
London	26.3 (25.2 to 27.4)	0.90 (0.80 to 1.01)	27.2 (26.0 to 28.6)	0.94 (0.83 to 1.06)
North East	29.9 (27.1 to 33.0)	1.01 (0.86 to 1.19)	30.1 (27.2 to 33.1)	1.02 (0.86 to 1.20)
North West	31.0 (29.7 to 32.3)	1.05 (0.93 to 1.18)	30.6 (29.3 to 32.0)	1.03 (0.91 to 1.17)
Northern Ireland	32.4 (30.6 to 34.3)	1.14 (1.00 to 1.30)	32.7 (30.7 to 34.9)	1.15 (1.01 to 1.32)
Scotland	32.8 (31.8 to 33.8)	1.16 (1.03 to 1.30)	33.2 (32.1 to 34.4)	1.18 (1.05 to 1.33)
South Central	27.6 (26.4 to 28.7)	0.91 (0.81 to 1.03)	27.4 (26.2 to 28.6)	0.90 (0.80 to 1.02)
South East Coast	27.1 (26.0 to 28.3)	0.94 (0.83 to 1.06)	27.4 (26.1 to 28.7)	0.94 (0.83 to 1.07)
South West	26.9 (25.6 to 28.3)	0.91 (0.80 to 1.03)	26.7 (25.3 to 28.1)	0.90 (0.79 to 1.02)
Wales	24.6 (23.6 to 25.7)	0.86 (0.76 to 0.97)	23.8 (22.6 to 25.1)	0.83 (0.73 to 0.94)
West Midlands	26.9 (25.7 to 28.2)	0.91 (0.80 to 1.03)	26.7 (25.4 to 28.1)	0.90 (0.79 to 1.02)
Yorkshire & Humber	27.5 (25.1 to 30.2)	0.91 (0.78 to 1.07)	27.7 (25.1 to 30.5)	0.92 (0.79 to 1.08)
Townsend, quintile				
Missing	27.9 (27.1 to 28.9)	1.01 (0.96 to 1.06)	N/A	N/A
1	28.7 (27.9 to 29.6)	1 (reference)	28.7 (27.9 to 29.6)	1 (reference)
2	29.3 (28.4 to 30.2)	1.00 (0.95 to 1.04)	29.3 (28.4 to 30.2)	0.99 (0.95 to 1.04)
3	29.4 (28.5 to 30.3)	1.00 (0.96 to 1.04)	29.4 (28.5 to 30.3)	1.00 (0.95 to 1.04)
4	28.0 (27.0 to 28.9)	0.95 (0.91 to 0.99)	28.0 (27.0 to 28.9)	0.94 (0.90 to 0.99)
5	27.3 (26.2 to 28.5)	0.91 (0.86 to 0.96)	27.4 (26.2 to 28.5)	0.90 (0.86 to 0.95)

*Adjusted for other variables considered; Sex, ageband, year, region, Townsend quintile, respectively

2.4.12 Multi-level regression models

For the primary analysis, IRRs for IBD incidence were calculated using a two-level Poisson regression model including 'GP practice' as a random effect to account for data clustering by GP practice. In a separate analysis, I used a single-level Poisson regression model that does not account for data clustering by practice. Associations between all covariates and the primary outcome were similar in magnitude for both models (Table 2.11). A three-level model which accounts for the nesting of GP practices within strategic health authorities was also developed. However, the model would not converge. This is likely to be explained by

the complexity of the model in such a large dataset; 11,325,025 subjects nested within 'GP practices' (a categorical variable with 744 levels) nested within 'strategic health authorities' (a categorical variable with 13 levels).

Table 2.11. Adjusted associations between study covariates and diagnosis of IBD using single-level and two-level models

Covariate	Two-level model (primary analysis)	Single-level model
	Adjusted IRR (95% CI)	**Adjusted IRR (95% CI)**
Sex		
Male	1 (reference)	1 (reference)
Female	1.00 (0.97 to 1.03)	1.00 (0.97 to 1.03)
Age, years		
0-9	0.08 (0.07 to 0.09)	0.08 (0.07 to 0.09)
10-16	0.55 (0.51 to 0.58)	0.55 (0.51 to 0.58)
17-40	1 (reference)	1 (reference)
40+	0.82 (0.79 to 0.84)	0.82 (0.79 to 0.84)
Year		
2000	1 (reference)	1 (reference)
2001	0.96 (0.87 to 1.06)	0.96 (0.87 to 1.06)
2002	0.92 (0.84 to 1.01)	0.92 (0.84 to 1.01)
2003	0.92 (0.84 to 1.01)	0.92 (0.84 to 1.01)
2004	0.91 (0.84 to 1.00)	0.92 (0.84 to 1.00)
2005	0.93 (0.85 to 1.02)	0.94 (0.86 to 1.02)
2006	0.95 (0.87 to 1.03)	0.95 (0.87 to 1.03)
2007	0.92 (0.85 to 1.01)	0.93 (0.85 to 1.01)
2008	0.95 (0.87 to 1.04)	0.96 (0.88 to 1.04)
2009	0.92 (0.85 to 1.01)	0.93 (0.85 to 1.01)
2010	0.90 (0.83 to 0.98)	0.90 (0.83 to 0.99)
2011	0.87 (0.80 to 0.95)	0.88 (0.80 to 0.96)
2012	0.92 (0.84 to 1.01)	0.93 (0.85 to 1.01)
2013	0.84 (0.77 to 0.92)	0.84 (0.77 to 0.92)
2014	0.88 (0.80 to 0.96)	0.88 (0.81 to 0.96)
2015	0.84 (0.76 to 0.92)	0.84 (0.77 to 0.92)
2016	0.81 (0.73 to 0.89)	0.81 (0.74 to 0.90)
2017	0.77 (0.69 to 0.85)	0.77 (0.70 to 0.85)
Region		
East Midlands	1 (reference)	1 (reference)
East of England	1.04 (0.91 to 1.18)	1.04 (0.94 to 1.15)
London	0.90 (0.80 to 1.01)	0.91 (0.83 to 1.00)
North East	1.01 (0.86 to 1.18)	1.02 (0.89 to 1.16)
North West	1.04 (0.92 to 1.17)	1.06 (0.96 to 1.16)
Northern Ireland	1.13 (0.99 to 1.28)	1.15 (1.04 to 1.28)
Scotland	1.14 (1.02 to 1.28)	1.16 (1.05 to 1.27)

South Central	0.91 (0.80 to 1.02)	0.92 (0.84 to 1.01)
South East Coast	0.94 (0.83 to 1.06)	0.94 (0.86 to 1.04)
South West	0.90 (0.79 to 1.02)	0.91 (0.82 to 1.00)
Wales	0.85 (0.76 to 0.96)	0.86 (0.78 to 0.95)
West Midlands	0.90 (0.80 to 1.02)	0.92 (0.83 to 1.01)
Yorkshire & Humber	0.91 (0.78 to 1.06)	0.92 (0.81 to 1.04)
Townsend (quintile)		
Missing	1.01 (0.96 to 1.06)	0.99 (0.95 to 1.04)
1	1 (reference)	1 (reference)
2	1.00 (0.96 to 1.04)	1.00 (0.96 to 1.05)
3	1.01 (0.96 to 1.05)	1.01 (0.97 to 1.05)
4	0.95 (0.91 to 1.00)	0.95 (0.91 to 1.00)
5	0.91 (0.86 to 0.96)	0.91 (0.86 to 0.96)

*Adjusted for other variables considered; Sex, ageband, year, region, Townsend quintile, respectively

*IRRs compared to the reference group for each categorical variable

2.4.13 Validation of the diagnosis of IBD in IMRD

28,354 (98.2%) individuals who received a diagnostic Read code for IBD during the study period had least one clinical event supportive of the diagnosis of IBD with 25,332 (87.7%) having at least two supportive events (Table 2.12). This compared to 22,515 (99.8%) and 21,006 (93.1%) for the incident cases in our primary analysis; the diagnostic criteria were stricter in the primary analysis – 'two medical Read codes' OR 'one medical Read code plus one IBD drug prescription'.

Table 2.12. Algorithm for IBD cases accompanied by clinically relevant supporting events

Supporting event, n (%)	**Incident IBD Cases in primary analysis (n=22,560)**	**Incident IBD cases in sensitivity analysis (one Read code only) n= 28,879**
Symptoms	18,736 (83.0%)	23,351 (80.9%)
Referral to gastroenterology	8,699 (38.6%)	10,669 (36.9%)
Endoscopy	15,050 (66.7%)	18,784 (65.0%)
Treatment with IBD drugs	21,637 (95.9%)	24,173 (83.7%)
Number of supporting events		
None	45 (0.2%)	525 (1.8%)
One	1,509 (6.7%)	3,022 (10.5%)
Symptoms	203 (13.5%)	1,060 (35.1%)
Referral to gastroenterology	16 (1.1%)	102 (3.4%)
Endoscopy	54 (3.6%)	362 (12.0%)
Treatment with IBD drugs	1,236 (81.9%)	1,498 (49.6%)

Two	5,786 (30.9%)	7,940 (27.5%)
Symptoms + referral to gastroenterology	97 (1.7%)	416 (5.2%)
Symptoms + endoscopy	244 (4.2%)	1,250 (15.7%)
Symptoms + treatment with IBD drugs	3,570 (61.7%)	3,947 (49.7%)
Referral to gastroenterology + treatment with IBD drugs	368 (6.4%)	432 (5.4%)
Referral to gastroenterology + endoscopy	20 (0.3%)	105 (1.3%)
Endoscopy + treatment with IBD drugs	1,487 (25.7%)	1,790 (22.5%)
Three	9,839 (52.5%)	11,493 (39.8%)
Symptoms + referral to gastroenterology + endoscopy	244 (2.5%)	886 (7.7%)
Symptoms + referral to gastroenterology + treatment with IBD drugs	1,975 (20.1%)	2,115 (18.4%)
Symptoms + endoscopy + treatment with IBD drugs	7,022 (71.4%)	7,778 (67.7%)
Referral to gastroenterology + endoscopy + treatment with IBD drugs	598 (6.1%)	714 (6.2%)
Four - Symptoms + referral to gastroenterology + endoscopy + use of IBD drugs	5,381 (28.7%)	5,899 (20.4%)

2.5 Discussion

2.5.1 Overall summary

This is one of the largest observational studies undertaken to investigate trends in IBD epidemiology. Although incidence of IBD remained relatively stable for those aged 17-40 years and those aged 0-9 years, we observed a 38% fall in incidence for those aged over 40 years and a 94% rise in incidence in the adolescent population. Prevalence continues to rise with a 59.1% increase in disease burden since the turn of the century. The most recent incidence and prevalence estimates are in line with some of the highest rates of adult and paediatric IBD reported internationally (69, 194-196).

2.5.2 Strengths

Study strengths include the large sample size and the prospective collection of health care records representative of 'real-life' clinical practice. Unlike previous incidence/prevalence studies that have relied on external data sources to estimate denominator population characteristics, I was able to extract demographics and person-time follow up for all individuals in the cohort, including those who did not develop IBD. Additionally, IMRD has

been shown to be broadly representative of the UK in terms of age, sex, mortality rates and prevalence of numerous comorbidities (174) allowing me to draw inferences from the data and relate this to the UK population. Not only has the diagnosis of IBD been validated in a similar GP database (80), but I have demonstrated that most individuals coded for IBD in IMRD have multiple recorded clinical events that would be in keeping with IBD. This would support the argument that IMRD represents an important and useful resource for further epidemiological studies of IBD.

2.5.3 Limitations

Limitations arise when conducting GP database research, particularly as the primary use of the software that contributes to IMRD is for patient management purposes rather than medical research. Thus, data can be incomplete and will often only reflect those recorded events that are deemed to be relevant to the patient's care. Given that I was also reasonably strict with the case definition, this may have resulted in under-ascertainment of cases. Although I find reason to be confident in the validity of the data, I was unable to confirm the cases by evidence of radiological, endoscopic or histological findings. Therefore, it is possible that some individuals were misclassified. There was a small risk of duplication of medical records. This could occur if a patient de-registered with one practice contributing to IMRD then subsequently registered with another IMRD practice during the observation period. This is likely to be the case for a very small number of individuals as IMRD only covered 5-6% of UK GP practices during the study period. Although the total number of individuals contributing may be a slight overestimate, this would have no effect on incidence or prevalence rates. This is for two reasons; 1) Duplicated records would cover different time periods during the study without overlap 2) I took steps to ensure that

prevalent cases of IBD newly transferring to practices were not counted as incident cases (182). Therefore, incident cases were not counted twice.

2.5.4 Comparisons of incidence with existing literature

Data from a multi-centre European study (including two UK sites in North West London and East Yorkshire) reported site incidence rates of 2.6 and 8.4 /100,000 person-years for CD and 15.9 and 8.2 /100,000 years for UC (197). However, only a small number of UK cases were included (n=167). Incidence rates of 8.3 (3.4-13.2) and 13.9 (95% CI 7.5-20.3)/100,000 person-years for CD and UC respectively have been reported in North-East England for the period 1990-1994 (81). I report overall incidence rates of 10.2 (95% CI 10.0-10.5) and 15.6 (95% CI 15.3-15.9)/100,000 person-years for CD and UC respectively in a far larger recent cohort and at a national level. I report considerable geographical variation in IBD incidence across the UK with notably high CD incidence in Scotland and Northern Ireland and high UC incidence in the East of England (Figure 2.7). This may reflect variation in lifestyle factors such as dietary habits and importantly smoking (it is estimated that 14.4% adults in England smoke compared to 15.9% in Scotland and 16.3% in Northern Ireland (198)).

A Danish study based on nationwide registry data (1995-2012) observed comparable incidence rates: 8.9 (95% CI 8.3-9.5) and 10.3 (95% CI 9.7-11.0) per 100,000 person-years for CD and 23.4 (95% CI 22.4-24.5) and 23.2 (95% CI 22.2-24.3) per 100,000 person-years for UC in males and females, respectively (199). In contrast to my results, they observed overall rising incidence rates of IBD, but their study was conducted in a different country over an earlier time-period including the 1990s when a rise in IBD incidence was described in many

high-income countries. Although they adjusted for age in their analysis, temporal trends in incidence stratified by age group were not reported.

2.5.5 Comparison with other studies using IMRD/THIN

Since the start of this project and subsequent publication of the work, two newer studies have also used IMRD/THIN to describe temporal trends in IBD epidemiology (200, 201). Both studies report higher incidence rates than in my study (Table 2.13). However, similar overall temporal trends were observed. The differences in results can be explained by case definition; both studies used a single IBD Read code as their case definition whereas our definition required additional criteria to be met (2.3.3).

Table 2.13. Comparison of my results with other recently published literature using THIN/IMRD

	Pasvol et al (primary analysis) (1)	**Pasvol et al (sensitivity analysis) (1)**	**King et al (200)**	**Freeman et al (201)**
Any IBD incidence per 100,000 PY (95% CI)	28.6 (28.2-28.9)	36.6 (36.2-37.0)	Not reported	69.5 (68.6–70.4)
CD incidence per 100,000 PY (95% CI)	10.2 (10.0-10.5)	12.9 (12.7-13.2)	14.3 (14.0-14.7)	Not reported
UC incidence per 100,000 PY (95% CI)	15.7 (15.4-15.9)	19.3 (19.0-19.6)	23.2 (22.8-23.6)	Not reported

I conducted a sensitivity analysis using a single IBD Read code as the case definition. In this sensitivity analysis, the observed peak in incidence of UC for older individuals was higher than the peak in incidence for younger individuals (Figure 2.16); this would be unusual in clinical practice. An explanation for this could be that a number of these patients, who perhaps had colitis of a different aetiology, had been misclassified as IBD. On the basis of this, one Read code alone was deemed not specific enough for the diagnosis of IBD in my primary analysis.

The group of researchers from Warwick University reported IBD prevalence of 142.1 (95% CI 140.7-143.5) per 10,000 in 2016 and a peak in incidence of 76.4 per 100,000 person-years in 2010 (201). These are by far the highest incidence and prevalence rates reported globally (higher than The Faroe Islands which is thought to have the highest disease burden in the world (69)). There are several explanations for this in addition to the use of a single IBD Read code. Firstly, they did not include children in their study who have a lower incidence of IBD than people in their 20s and 30s. Secondly, they used a very broad case definition which included 'microscopic colitis' (a chronic inflammatory disease of GI tract which although by definition is an 'inflammatory bowel disease' is not usually grouped under the umbrella term IBD with CD and UC) and 'left-sided colitis' - a Read code which is not specific to IBD. Finally, they included patients who had been prescribed IBD drugs but had never actually been coded for IBD. Thus, if a patient was accidentally prescribed an IBD drug such as mesalazine but didn't have IBD then this would have been included as a case. For the forementioned reasons, I feel it is likely that their results represent an overestimate of disease burden in the UK.

2.5.6 Case validation

Reassuringly, 24,173 (83.7%) of individuals with a single Read code for IBD had a record of a drug prescription for IBD. However, only 18,784 (65.0%) had a record of an endoscopy and 10,669 (36.9%) a gastroenterology outpatient appointment. An explanation would be the lack of linkage to secondary care records; it is likely that events occurring in secondary care are more frequently uncaptured in the primary care health record compared to those occurring in the GP surgery.

The validation work could have been strengthened with linkage to Hospital Episode Statistics (HES) data. HES is a database containing the details of all outpatient appointments, hospital admissions and accidence and emergency attendances in England (202). Linkage to HES data would assist in confirming cases through interactions with secondary care such as gastroenterology outpatient appointments, endoscopies and admissions to hospital for disease flare or surgery. Additionally, linkage to HES data may identify additional cases which were missed using the primary care records. Although linkage to HES data would have strengthened the project, unfortunately this was outside of the budget for this PhD.

2.5.7 Trends in paediatric IBD incidence

In keeping with published literature, I observed a rising incidence of paediatric IBD during the early 21st century (203) and I provide further evidence of male preponderance in paediatric IBD when compared to adult onset disease (192, 193). Uniquely, in this study I have demonstrated rising incidence of adolescent IBD in the context of stable incidence in those aged 17-40 years and falling incidence in the over 40s. This may represent a general shift towards earlier diagnosis of IBD for all age groups except the very young (age 0-9 years). Given that IBD most commonly presents in the second to fourth decade of life (204, 205), rising incidence in adolescents might be explained by a number of factors, including improvements in referral pathways and the introduction of new diagnostic tools (e.g. faecal calprotectin testing or capsule endoscopy) resulting in cases being picked up earlier. However, one would expect stepwise increases in incidence when new diagnostic tools are rolled out, which I did not observe. Moreover, if rising incidence of adolescent IBD is due to improved referral pathways, a corresponding rise in incidence might be expected in very young children as well as adolescents. It could be argued that changes in GP coding practice

may be contributing. But again, one would expect comparable changes in younger age groups if this were the case. On the other hand, if the epidemiological patterns I observed reflect real increases in the incidence of pathology this is of great concern and could represent earlier manifestation of disease related to increased exposure to environmental triggers in childhood and adolescence. Alternatively, exposure to novel environmental triggers, causing IBD in children who would have historically not developed the disease.

2.5.8 Trends in adults over 40 years old

I observed a fall in IBD incidence in adults aged over 40 years during the study period. This could be explained by a general trend towards IBD being picked up earlier as diagnostic tools and referral pathways become more sophisticated (unmasking of prevalent disease). However, there may be changes in environmental factors which are contributing. For instance, hormone replacement therapy (HRT) has been shown to increase risk of UC (206) and HRT uptake in the UK changed dramatically over the study period. HRT peaked in popularity in the late 1990s (207). However, In 2002, The Women's Health Initiative Study was stopped early due to safety concerns of HRT including breast cancer and heart disease (208). This attracted substantial negative media attention and the 'HRT scare' resulted in many post-menopausal women coming off HRT. Additionally, the UK regulatory authorities issued a safety restriction regarding HRT, and current guidelines recommend that doctors should prescribe the lowest effective dose of oestrogen for symptomatic relief (207). This has resulted in hormone content of HRT being lower for many women. If falling IBD incidence in peri/post-menopausal women is associated with reductions in exposure to exogenous oestrogens, then this would support a hypothesis that combined hormonal contraception (CHC) may drive IBD pathogenesis in women of reproductive age.

2.5.9 Social deprivation

I observed lower incidence of UC in areas of higher social deprivation. This may be related to smoking which is thought to be protective against UC (209) . The association between social deprivation and IBD requires further hypothesis-driven work to explore the underlying causal factors which may include smoking, physical activity, and dietary habits.

2.5.10 Gender disparities

I observed a disparity in IBD incidence between men and women with A2 disease (diagnosed aged 17-40). This was largely driven by increased incidence of CD in women of this age. There are a number of potential explanations for this. Overall, women of this age group tend to attend their GP more than men (210). This may have resulted in fewer males having their IBD diagnosis recorded by the GP and thus underestimation of incidence in men for this study. However, if there is a true increased incidence in women of childbearing age then this would support the hypothesis of a hormonal contribution to disease pathogenesis, and the investigation of exogenous oestrogens as an environmental risk factor for IBD could be justified.

2.5.11 IBD prevalence

My prevalence estimates were very similar to those reported in a well-validated IBD cohort in Lothian, Scotland (72); my estimate of IBD prevalence for Scotland on 31/08/2018 was 810 per 100,000 compared to 832 per 100,000 reported by their group. Although my study lacked linkage to secondary care records, the similar prevalence estimates would support the argument that few cases were missed. In 2018, 67,150,000 people were estimated to be

living in the UK from which one might extrapolate from the data in my study that there were approximately 487,000 people living with IBD in the UK at that time.

This study demonstrates compounding prevalence of IBD (1.6). This has also been demonstrated in Canada (211) and in Scotland where prevalence is estimated to reach 1.0% by 2028 (72). IBD prevalence is expected to continue to rise until the IBD population ages and mortality increases, at which point the rising prevalence should level off and reach equilibrium, provided incidence rates remain stable or falling (68).

2.5.12 Impact on service delivery

The lifetime incremental cost of CD and UC has recently been estimated at $416,352 and $369,955 respectively, with those diagnosed at an early age incurring the highest cost burden (212). I report rising incidence rates of IBD in younger populations and an overall increase in IBD prevalence of 59.1% over a 19-year period. Thus, not only will services need to be attuned to an increased patient burden and an ageing demographic, but also to rising new diagnoses in young people who will require lifelong care. This is in the context of significant financial challenges to the NHS.

2.5.13 Conclusion

Although I observed a stable or falling incidence of IBD in adults over an 18-year period, my results are consistent with some of the highest reported global incidence and prevalence rates for IBD, with a 94% rise in incidence in adolescents. These findings are concerning and suggest detailed prospective studies are required to understand the aetiological drivers.

Chapter 3: Time trends in contraceptive prescribing in UK primary care 2000-2018: A repeated cross-sectional study

3.1 Introduction

Over the last 20 years, a number of new contraceptive methods have become available including the desogestrel progestogen only pill (POP), combined oral contraceptive pills (COCPs) containing drospirenone, combined hormonal patches and vaginal rings. Over the same time-period, the UK has seen several policy-related initiatives aimed at reducing unwanted pregnancy (95-97).

Long-acting reversible contraception (LARC) methods are the most effective reversible methods of contraception at preventing pregnancy and are also less costly than oral contraceptive pills (OCPs) (213). In 2009, provision of information relating to LARC was linked to the GP income by way of Quality and Outcome Framework (QOF) standards (96). QOF is a way of improving the quality of patient care by financially rewarding GP practices based on certain indicators. QOF has shown success in numerous other areas such as asthma recognition, stop smoking support and stroke risk assessment. Despite an increase in LARC uptake and a reduction in abortions (98), the LARC QOF indicator was withdrawn in 2014. At the same time, in an effort to reduce spending, reductions in funding to SRH services were introduced resulting in closure of many centres (99). The model of UK contraceptive care is currently in a period of flux with falling numbers of SRH special centres and a move towards the provision of over-the-counter POPs (214).

Data on contraceptive prescribing in SRH services are published annually, but the majority of women obtain their contraception from primary care and not community SRH centres (101). Although pooled primary care contraceptive prescribing data are published by NHS digital

(100), data are not linked to individual patients, so demographic information of users such as age, geographical location and social deprivation are not available.

Describing trends in contraceptive prescribing and how they relate to demographic factors is an essential step in planning future service delivery as the model of contraceptive care undergoes change.

3.2 Aims and Objectives

3.2.1 Aims

The purpose of this work was to investigate sociodemographic and temporal trends in the prescribing of contraceptives from 2000 to the end of 2018 using electronic GP data from the IQVIA™ Medical Research Data (IMRD) database. Describing trends in contraceptive prescribing will inform later work included in this PhD, where contraception is the main exposure of interest.

3.2.2 Objectives

The specific objectives were as follows:

1. To describe temporal trends in contraceptive prescribing in UK primary care for the period 01/01/2000 – 31/12/2018
2. To describe differences in contraceptive prescribing by, age, social deprivation and geographical location

3.3 Methods

3.3.1 Study design

A repeated cross-sectional study using electronic UK general practice (GP) records from the IMRD database (1.9.1)

3.3.2 Study population

3.3.2.1 Inclusion and Exclusion Criteria

All women aged 15-49 years who contributed data to IMRD for the period 1st January 2000 to 31st December 2018 were eligible for inclusion. 15-49 years was selected as this is the World Health Organisation (WHO) definition of 'women of reproductive age' (215).

Individuals with data missing for year of birth, sex or date of registration were excluded. Patients who were not permanently registered with the practice contributing IMRD data were excluded (i.e. patients attending the surgery but registered elsewhere or patients not registered with a GP at all). Patients with out of sequence records (e.g. registration date before year of birth) were excluded.

3.3.2.2 Repeated cross-sectional design

To collect repeated cross-sectional data, I firstly developed a dynamic source cohort of women (2.3.2.2).

3.3.2.2.1 Cohort entry

Cohort entry was the latest date of:

- Date of registration with the GP practice
- The start of the study period (01/01/2000)
- The date the patient turned 15 years old
- The date the practice achieved published measures of acceptable mortality recording (2.3.2.2.1.2)
- The date the practice achieved published measures of acceptable computer usage (2.3.2.2.1.2)

3.3.2.2.2 Cohort exit

Cohort exit was defined as the earliest date of the following:

- De-registration with the GP practice contributing data
- The practice stopped contributing data to IMRD
- The end of the study period (31/12/2018)
- The patient turned 50 years old
- The first recording of any medical event which would usually preclude future use of contraception under normal circumstances (hysterectomy, bilateral salpingo-oophorectomy or sterilisation) (Appendix 6.3.9)
- The first prescription for post-menopausal hormone replacement therapy (HRT) (Appendix 6.4.1)
- Death

3.3.2.2.3 Repeated-cross sectional data

Separate cross-sections were then identified for each calendar year (2000-2018). To be included, each woman was required to contribute data to the source cohort for the entire calendar year from 1st January to 31st December. A woman could contribute data to multiple cross-sections. In each cross-section, a woman's age was defined as the age she would be on 1st July for that year (i.e. the midpoint of the year).

3.3.3 Outcomes

The main outcome of interest was the prescription of non-barrier contraceptives. Barrier methods were not included as these are most frequently obtained over-the-counter rather than being prescribed in primary care. Prescription code lists for all the following 11 types of contraceptives were developed and reviewed by a GP (Prof Greta Rait) and an expert in reproductive health (Prof E Anne MacGregor) (Table 3.1/Appendix 6.4):

Table 3.1. Categories of included non-barrier contraceptives

Combined Hormonal contraception	Progesterone only pills	Long-acting reversible contraception
Second generation COCPs	Desogestrel containing POP	Contraceptive injections
Third generation COCPs	Older POPs*	Subdermal contraceptive implants
Fourth generation COCPs		Intrauterine systems and devices
Co-cyprindiol		
Transdermal contraceptive patches		
Intravaginal rings		

*Pills containing norethisterone, levonorgestrel, norgestrel, etynodiol diacetate

Contraceptives were categorised into three broad groups: CHCs, POPs and LARC.

COCPs were subdivided by pill generation (Table 1.2). First generation pills containing higher levels of hormones were not included in the study as they are no longer available in the UK. Co-cyprindiol, a pill containing ethinylestradiol and cyproterone acetate which used as a treatment for acne and as a contraceptive was included separately.

The newer POP Cerazette© (desogestrel 75mcg) was separated from other POPs; it works in a similar way to COCPs by inhibiting ovulation thus making adherence more straightforward. This study predates the roll out of over-the-counter desogestrel 75mcg; during the study period this was only available in the UK by prescription.

Due to a number of non-specific Read codes for intrauterine contraception (IUC) in IMRD such as 'reinsertion of coil', in many cases it was difficult to ascertain whether the woman had been fitted with a copper intra-uterine device (IUD) or a hormonal intra-uterine system (IUS). Therefore, these two contraceptives were grouped together.

For oral contraceptive pills (OCPs), transdermal contraceptive patches and intravaginal rings, ascertainment of prescription was based on the electronic prescribing records in IMRD. For long-acting reversible contraception (LARC), ascertainment of prescription was based on not only electronic prescribing records, but also medical records (history, examination findings, differential diagnoses and other consultation notes) and additional health data (AHD) records which contain information such as ethnicity, smoking status, blood pressure, weight and height measurements and vaccination records. This approach was taken because LARC methods must be initiated with a procedure which is often recorded in the AHD records or medical notes in place of the device or drug being logged in the prescribing history.

3.3.4 Additional demographics

The following data were also captured for each patient

- Age (in five-year bands).

- Country of GP practice
- Social deprivation by Townsend score (1.9.1.2)

3.3.5 Analysis

StataCorp. 2017. *Stata Statistical Software*: Release 15. College Station, TX: StataCorp LLC was used for all analyses.

3.3.5.1 Descriptive analysis of demographics

Descriptive characteristics were summarized using numbers and percentages for categorical variables and medians and interquartile ranges (IQR) for non-normally distributed continuous variables.

3.3.5.2 Descriptive analysis of contraceptive prescribing

The number of women who received each type of contraceptive was captured and this was reported as a proportion (95% CI) of the total number of women in the cohort for each year. A woman could be prescribed multiple types of contraception within one year. Multiple prescriptions of the same method within a year were treated the same as a single prescription. Proportions (95%) CI were then stratified by age group, country and social deprivation.

3.3.6 Patient and public involvement

I did not involve patients and the public in this study

3.3.7 Ethics

IMRD data collection was approved by the NHS South-East Multicentre Research Ethics Committee in 2003. This study was approved by the Scientific Research Committee (SRC) on 11/05/2021 (SRC reference 18THIN082-A1/Appendix 6.2.2).

3.4 Results:

3.4.1 Descriptive characteristics of the source cohort

3,577,421 women (17,826,685 person-years of follow up) were included in the source cohort. 2,514,495 (70.3%) were registered with a GP practice in England, 524,067 (14.7%) Scotland, 418,558 (11.7%) Wales and 120,301 (3.4%) Northern Ireland. Median (IQR) age at cohort entry was 27.5 (20.7-35.5) years and median follow up was 3.4 years (IQR 1.4-7.5). Townsend data were missing for 804,665 (22.5 %) individuals. There were no other missing data (Table 3.2).

When comparing descriptive characteristics of the cohort before and after excluding those with missing Townsend score, there was no change in median age and I found similar proportions of individuals in each country (Table 3.2).

Table 3.2. Descriptive characteristics of the source cohort with and without the inclusion of those with missing Townsend score

	Including those with missing Townsend Score N (%)	Excluding those with missing Townsend score N (%)
Overall	3,577,421	2,772,756
Country		
England	2,514,495 (70.3)	2,041,302 (73.6)
Scotland	524,067 (14.7)	385,857 (13.9)
Wales	418,558 (11.7)	256,760 (9.3)
Northern Ireland	120,301 (3.4)	88,837 (3.2)
Townsend, quintile		
Missing	804,665 (22.5)	N/A
1	594,680 (16.6)	594,680 (21.5)
2	537,158 (15.0)	537,158 (19.4)
3	610,509 (17.1)	610,509 (22.0)
4	594,777 (16.6)	594,777 (21.5)
5	435,632 (12.2)	435,632 (15.7)
Age at cohort entry (median (IQR) years)	27.5 (20.7-35.5)	27.5 (20.5-35.6)

3.4.2 Contraceptive prescriptions

10,834,109 prescriptions for oral contraceptives, 631,947 IUD/IUS/implant insertions and 1,814,652 progesterone only injections were identified (Table 3.3).

Table 3.3. Total prescriptions identified in the source cohort

	Number of prescriptions/administrations/insertions
Second generation COCP	5,929,858
Third generation COCP	1,062,413
Fourth generation COCP	673,637
Co-cyprindiol	526,404
Progestogen-only pill	2,641,797
Transdermal contraceptive patch	7,448
Intravaginal ring	20,084
Progestogen-only injection	1,814,652
Subdermal contraceptive implant	269,148
Intrauterine device/system	362,799

3.4.3 Repeated cross-sectional data

2,705,638 women (15,251,805 person-years) contributed cross-sectional data. Nineteen cross-sections were identified, one for each calendar year. There was minimal difference in

mean (SD) age between cross sections (Table 3.4). For this comparison, mean age was substituted in place of median age. This is because 'median age' was either 32.5 or 33.5 for all years (all 'DOBs' in IMRD are on 1st July. Therefore, age can only be described to the nearest year). Using mean age more accurately demonstrates that there was minimal fluctuation in average age of the cohort from year to year.

After exclusion of women with missing Townsend score (561,233 (20.7%)), there was minimal difference in other demographics (Table 3.5). However, there was more missing data for Townsend in the later years of the study. This was because Townsend data were not captured by IQVIA for newer practices contributing towards IMRD. Additionally, in more recent years, fewer practices from England have contributed to IMRD (Table 3.4).

Table 3.4. Characteristics of each yearly cross-section

Year	Cohort size (N)	Mean (SD) age at the start of the year	Missing Townsend data (N (%))	Patients in England (N (%))
2000	458,446	32.4 (8.9)	66,627 (14.5)	370,031 (80.7)
2001	539,984	32.6 (9.0)	75,282 (14.0)	438,792 (81.3)
2002	645,459	32.6 (9.1)	85,761 (13.3)	511,137 (79.2)
2003	751,989	32.6 (9.1)	107,990 (14.4)	575,413 (76.5)
2004	837,090	32.6 (9.2)	131,575 (15.7)	615,745 (73.6)
2005	897,180	32.7 (9.3)	143,369 (16.0)	659,759 (73.5)
2006	927,088	32.7 (9.4)	149,089 (16.1)	680,656 (73.4)
2007	958,352	32.7 (9.5)	160,529 (16.8)	694,077 (72.4)
2008	980,878	32.7 (9.5)	160,591 (16.4)	707,852 (72.2)
2009	983,547	32.8 (9.5)	165,080 (16.8)	701,271 (71.3)
2010	974,538	32.8 (9.6)	167,303 (17.2)	690,417 (70.9)
2011	968,128	32.8 (9.6)	170,489 (17.6)	682,226 (70.5)
2012	995,579	32.7 (9.6)	182,276 (18.3)	669,433 (67.2)
2013	934,560	32.7 (9.6)	182,232 (19.5)	607,238 (65.0)
2014	869,844	32.6 (9.6)	181,560 (20.9)	524,828 (60.3)
2015	728,054	32.6 (9.6)	172,494 (23.7)	377,143 (51.8)
2016	662,687	32.5 (9.6)	175,260 (26.5)	310,915 (46.9)
2017	589,450	32.5 (9.6)	185,130 (31.4)	243,186 (41.3)
2018	548,952	32.5 (9.6)	199,215 (36.3)	201,611 (36.7)

Table 3.5. Descriptive characteristics of women contributing cross-sectional data with and without the inclusion of those with missing Townsend score

	Primary analysis N (%)	Exclusion of women with missing data N (%)
Overall	2,705,638	2,144,405
Country		
England	1,885,015 (69.7)	1,555,734 (72.6)
Scotland	405,013 (15.0)	310,706 (14.5)
Wales	314,468 (11.6)	201,680 (9.4)
Northern Ireland	101,142 (3.7)	76,285 (3.6)
Townsend, quintile		
Missing	561,233 (20.7)	N/A
1	482,529 (17.8)	482,529 (22.5)
2	427,003 (15.8)	427,003 (19.9)
3	470,492 (17.4)	470,492 (21.9)
4	446,378 (16.5)	446,378 (20.8)
5	318,003 (11.8)	318,003 (14.8)
Age at cohort entry (median (IQR years)	28.0 (20.5-35.8)	28.0 (20.5-36.1)
Follow up (years)	4.9 (2.7-9.1)	5.2 (2.9-9.4)

3.4.4 Temporal trends

Owing to the large sample size, the estimates were precise; the confidence intervals of proportions were very narrow for all contraceptives even after stratification by year, country, social deprivation and age group (<1.0% either side in all cases). Therefore, confidence intervals have not been presented for most graphical representations of temporal trends in this study.

3.4.4.1 Overall trends

Between 2000-2018, the proportion of any women receiving a prescription for contraception in general practice fell from 32.9% (95% CI 32.7-33.0) to 29.2% (95% CI 29.1-29.3). However, this was in the context of a rise in prescription of LARC from 4.2% (95% CI 4.1-4.2) to 6.5% (95% CI 6.5-6.6) and POPs from 4.3% (95% CI 4.3-4.4) to 10.8 (95% CI 10.7-10.9) and a fall in prescription of CHCs from 26.2% (95% CI 26.0-26.3) to 14.3 (95% CI 14.2-14.3) (Figure 3.1).

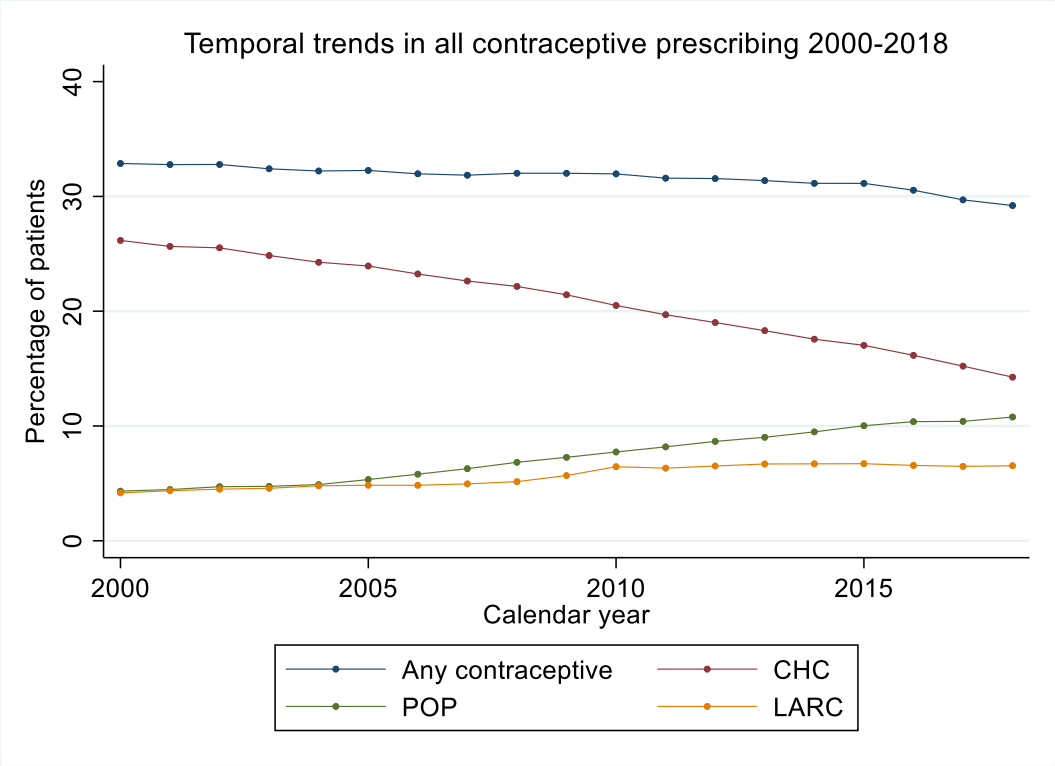


Figure 3.1. Temporal trends in all contraceptive prescribing over the period 2000-2018

3.4.4.2 CHC trends

For the period 2000-2018, the proportion of women receiving a prescription for CHCs fell from 26.2% (95% CI 26.0-26.3) to 14.3% (95% CI 14.2-14.3). Second generation COCP, third generation COCP and co-cyprindiol prescriptions fell from 20.9% (95% CI 20.8-21.0) to 11.0% (95% CI 11.0-11.1), 4.1% (95% CI 4.0-4.1) to 1.7% (95% CI 1.7-1.7) and 2.2% (95% CI 2.2-2.3) to 0.5% (95% CI 0.5-0.5) respectively. Fourth generation COCP prescriptions increased from 0.0% to 1.4% (95% 1.4-1.5) (fourth generation OCPs were available in the UK from 2002). <0.1% of the cohort were prescribed intravaginal rings and contraceptive patches throughout (Figure 3.2).

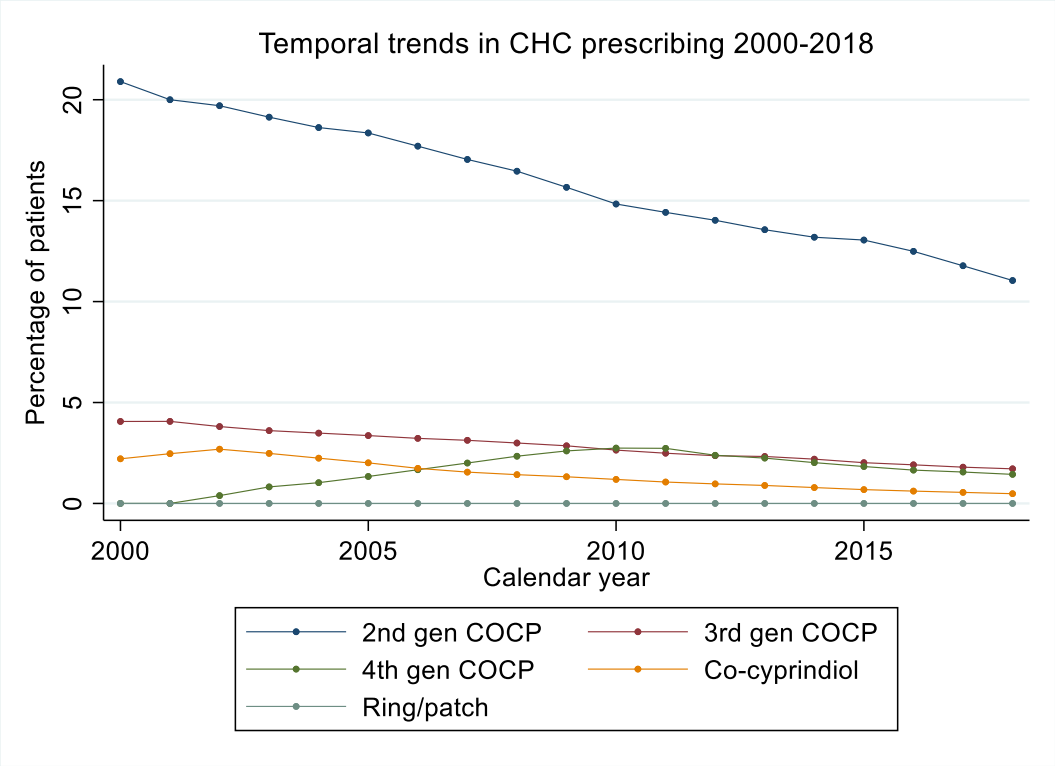


Figure 3.2. Temporal trends in combined hormonal contraception prescribing over the period 2000-2018

3.4.4.3 POP trends

Desogestrel prescriptions increased from 0.0% (95% CI 0.0-0.0) in 2000 to 10.0% (95% CI 9.9-10.1) in 2018 (the desogetrel 75mcg POP was introduced in 2002), whereas prescription of other POPs fell from 4.3% (95% CI 4.3-4.4) to 1.0% (95% CI 0.9-1.0) over the study period. (Figure 3.3).

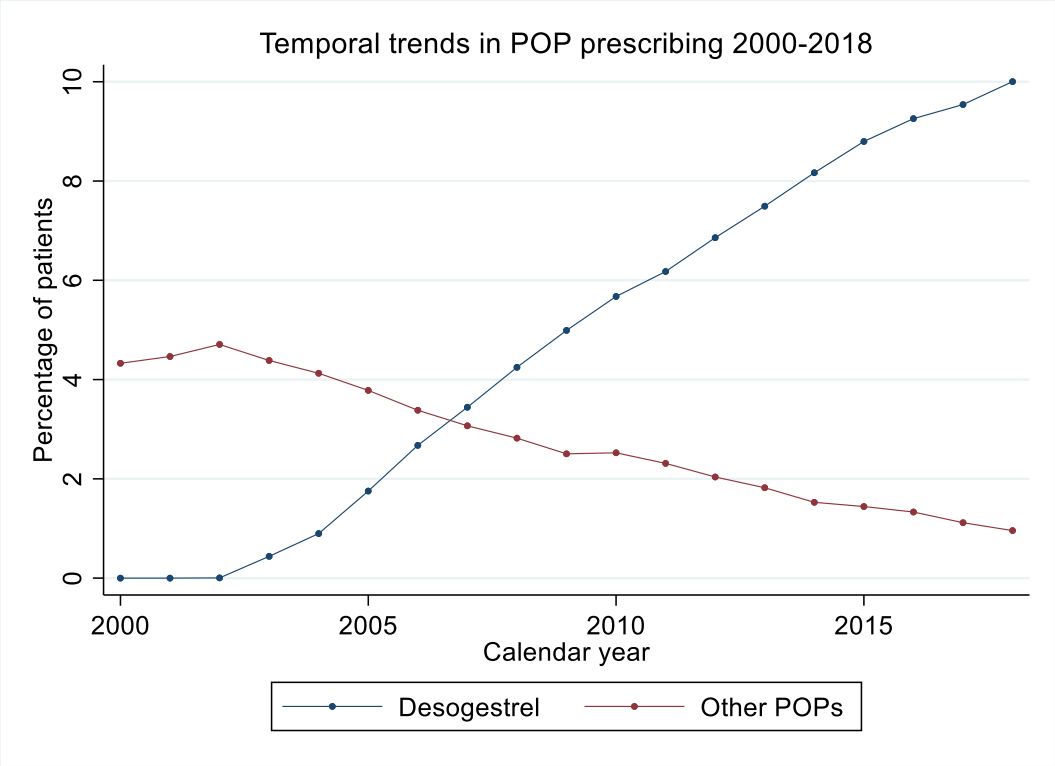


Figure 3.3. Temporal trends in progestogen-only pill prescribing over the period 2000-2018

3.4.4.4 LARC trends

IUD/IUS prescribing increased from 1.2% (95% CI 1.1-1.2) in 2000 to 1.9% (1.9-1.9) in 2018. Implant prescribing increased from 0.0% (95% CI 0.0%-0.0%) to 1.7% (95% CI 1.7-1.8%); of note levonorgestrel implants were discontinued and replaced by etonogestrel implants in 1999. IUD/IUS and implant uptake increased more rapidly in line with LARC linkage to QOF in 2009/2010 and plateaued after this. Injectable contraception prescribing was fairly constant throughout the study period fluctuating from 2.8% (2.8-2.8) to 3.3% (3.3-3.4). However, injectable prescribing fell slightly during the period 2005-2009 when IUD/IUS and implant uptake increased, then rose only marginally when LARC was linked to QOF in 2009. Overall LARC prescribing fell by only 3.0% after linkage to QOF was abolished in 2014/2015 (6.7% (6.6-6.7) in 2013 vs 6.5% (6.5-6.6) in 2018) (Figure 3.4).

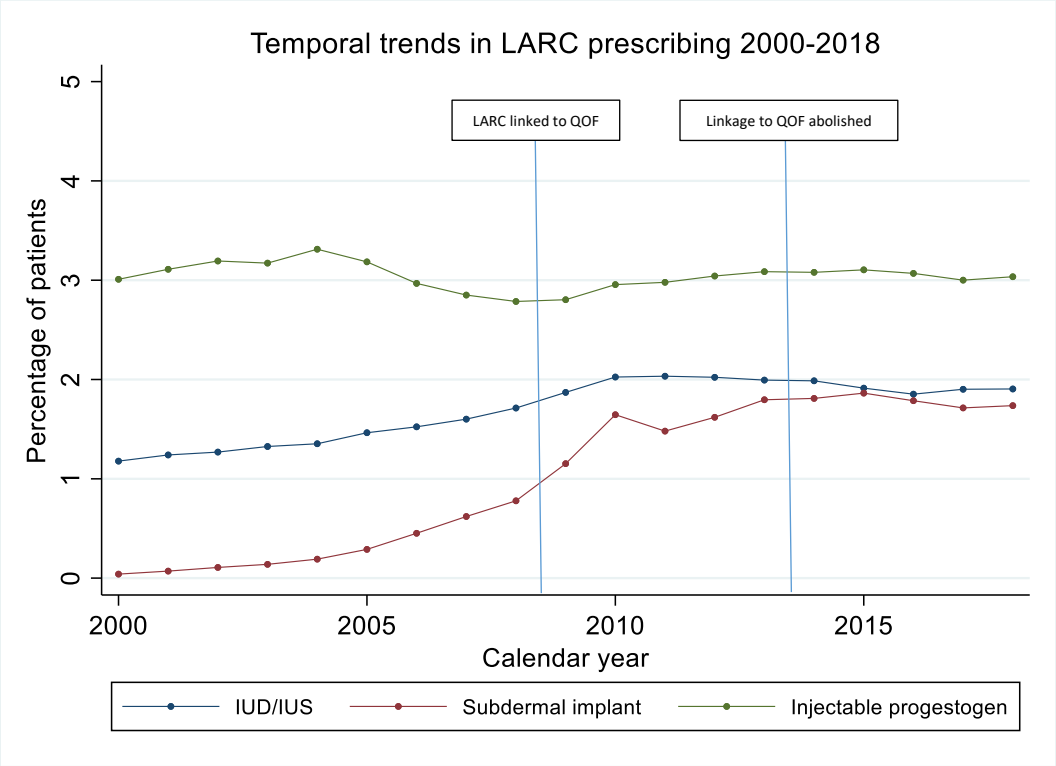


Figure 3.4. Temporal trends in LARC prescribing over the period 2000-2018

3.4.4.5 Geographical trends

Prescribing of CHCs fell in all countries (Figure 3.5). The largest fall in CHC prescribing was seen in England, falling from 26.5% (95% CI 26.3-26.6) to 13.8% (95% CI 13.6-13.9) of women and the smallest fall in uptake in Northern Ireland; 24.8% (95% CI 24.1-25.6) to 16.8% (95% CI 16.4-17.1) of women. Prescribing of POPs rose in all countries, rising the most in Northern Ireland from 3.2% (95% CI 2.9-3.5) to 11.6% (95% CI 11.3-11.9) (Figure 3.6).

At the start of the study period, LARC prescribing was similar in all countries (3.6-4.6%). All countries saw a rise in uptake of LARC over the study period; the largest in Scotland from 4.6% (95% CI 4.4 to 4.8) to 8.0% (95% CI 7.9 to 8.2) and the smallest in Northern Ireland from 3.6% (95% CI 3.3 to 3.9) to 4.8% (95% CI 4.6 to 5.0) (Figure 3.7).

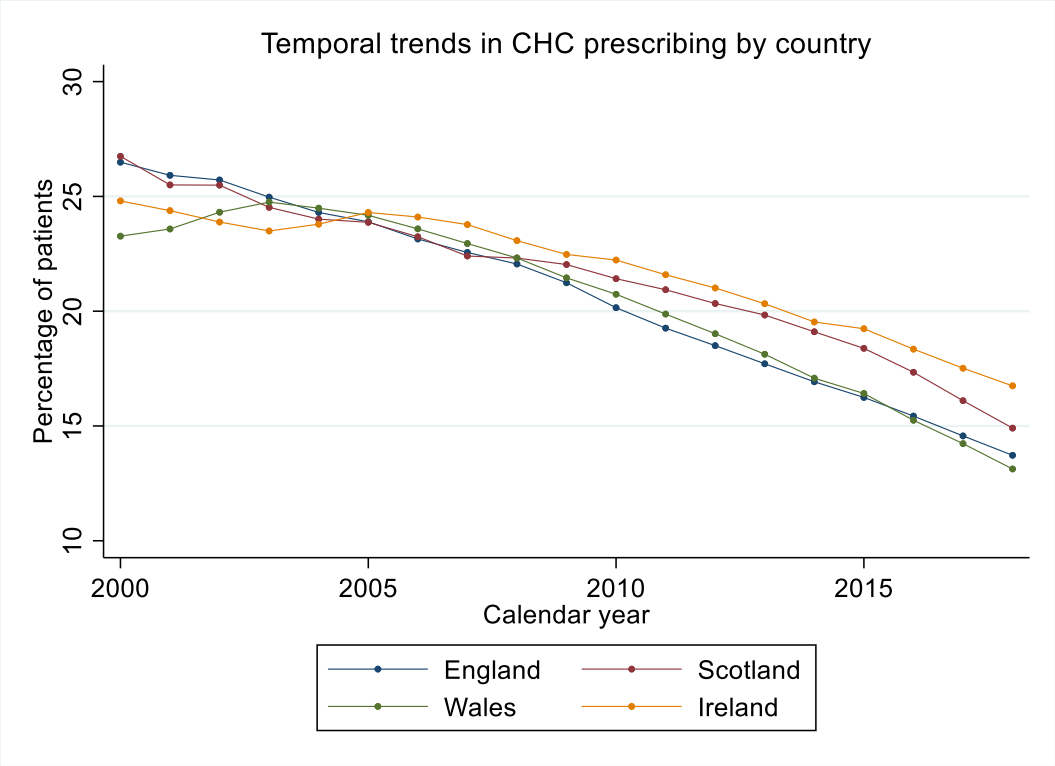


Figure 3.5. Temporal trends in combined hormonal contraception prescribing by country over the period 2000-2018

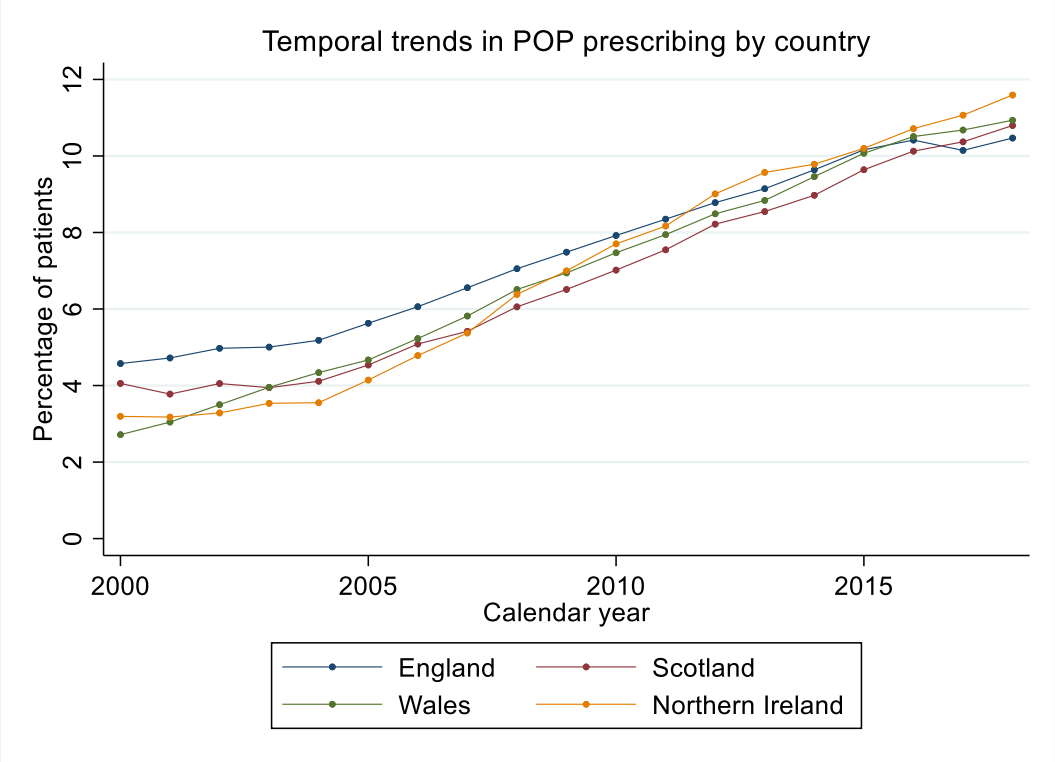


Figure 3.6. Temporal trends in progestogen-only pill prescribing by country over the period 2000-2018

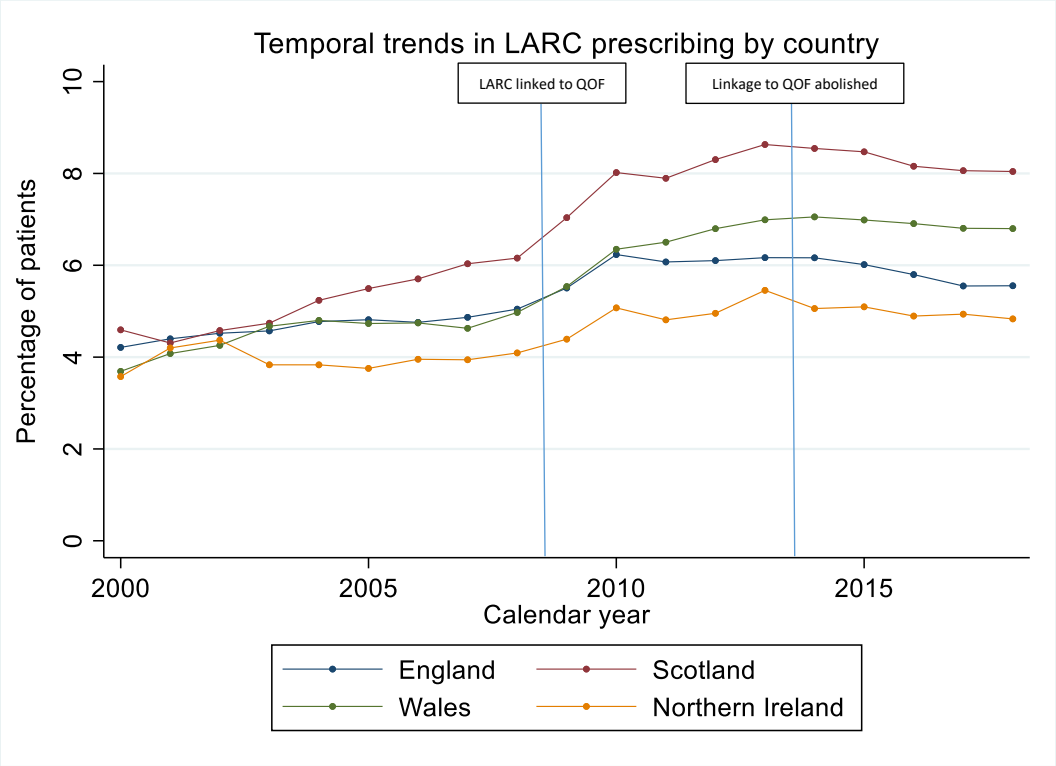


Figure 3.7. Temporal trends in LARC prescribing by country over the period 2000-2018

3.4.4.6 Trends relating to social deprivation

User-dependant methods (CHC and POP) were more commonly prescribed in less socially deprived areas; 26.5% (95% CI 26.2-26.9) in the least deprived areas and 21.2 (95% CI 20.9–21.5) in the most deprived areas in 2018. However, LARC was more commonly prescribed in areas of greater social deprivation 5.6% (5.4 to 5.8) and 7.7% (7.5-7.9) for least deprived vs most deprived respectively in 2018. There was a decline in the prescribing of CHCs across all sociodemographic groups. However, the decline in prescribing was smallest in the least deprived areas falling from 29.2 (95% CI 28.9-29.5) to 26.5% (95% CI 26.2-26.9) in the least deprived compared to 28.2 (95% CI 27.7-28.6) to 21.2 (95% CI 20.9– 21.5) in the most deprived (Figure 3.8). A similar increase in POP and LARC prescribing was observed across all socioeconomic groups (Figure 3.9/Figure 3.10).

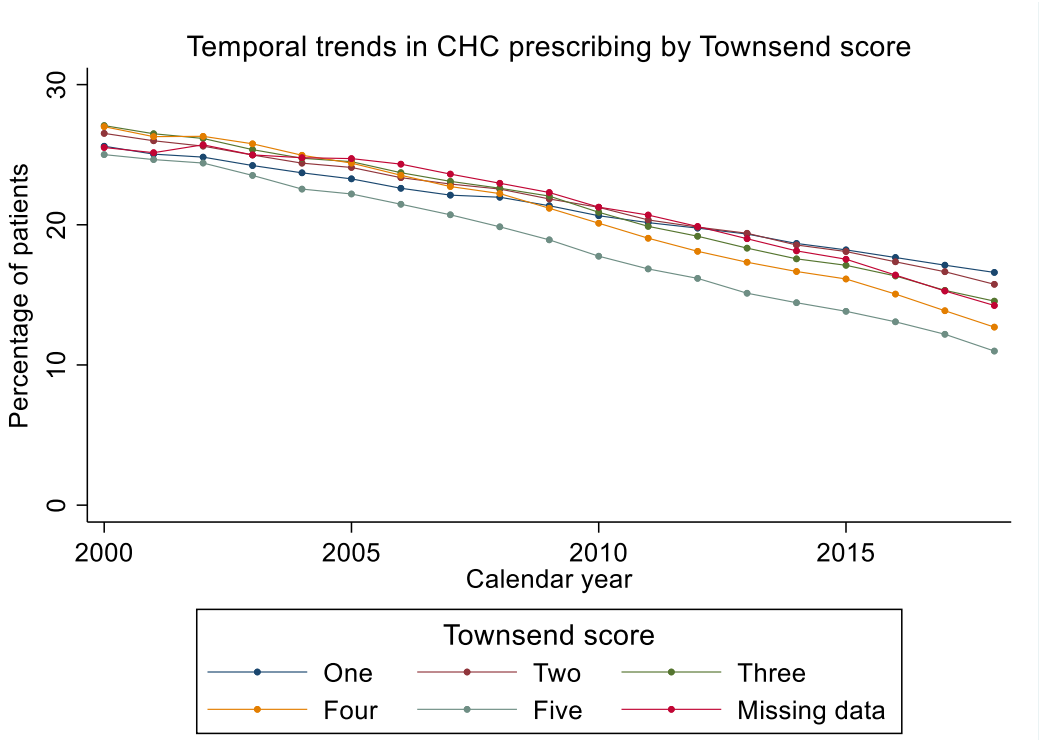


Figure 3.8. Temporal trends in CHC prescribing by social deprivation quintile over the period 2000-2018

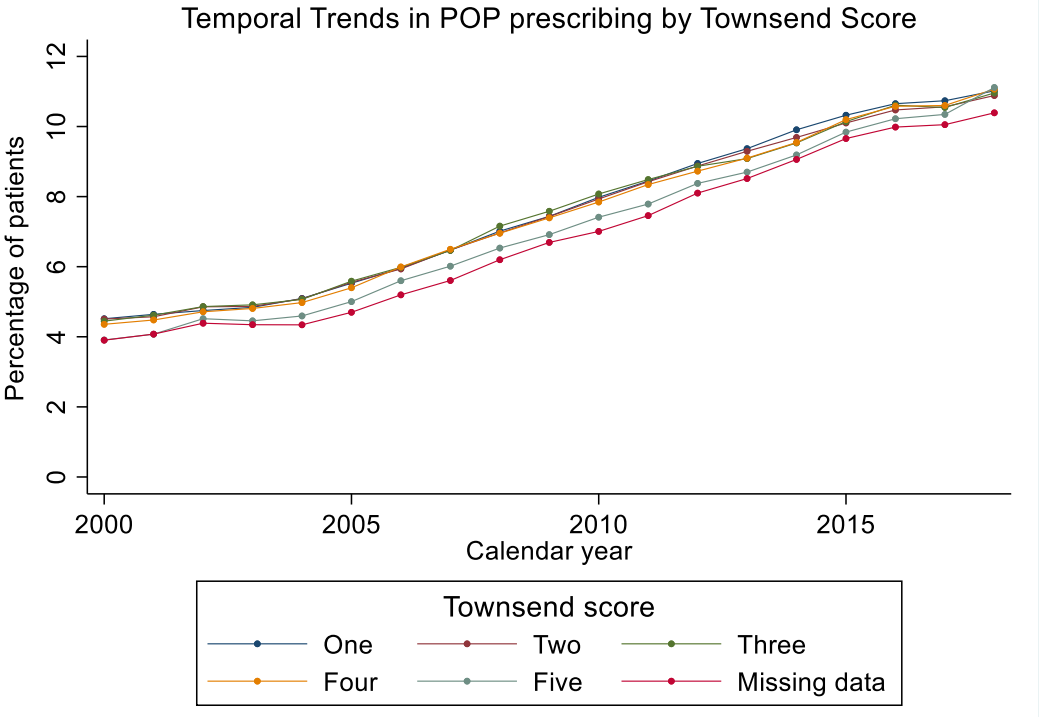


Figure 3.9. Temporal trends in POP prescribing by social deprivation quintile over the period 2000-2018

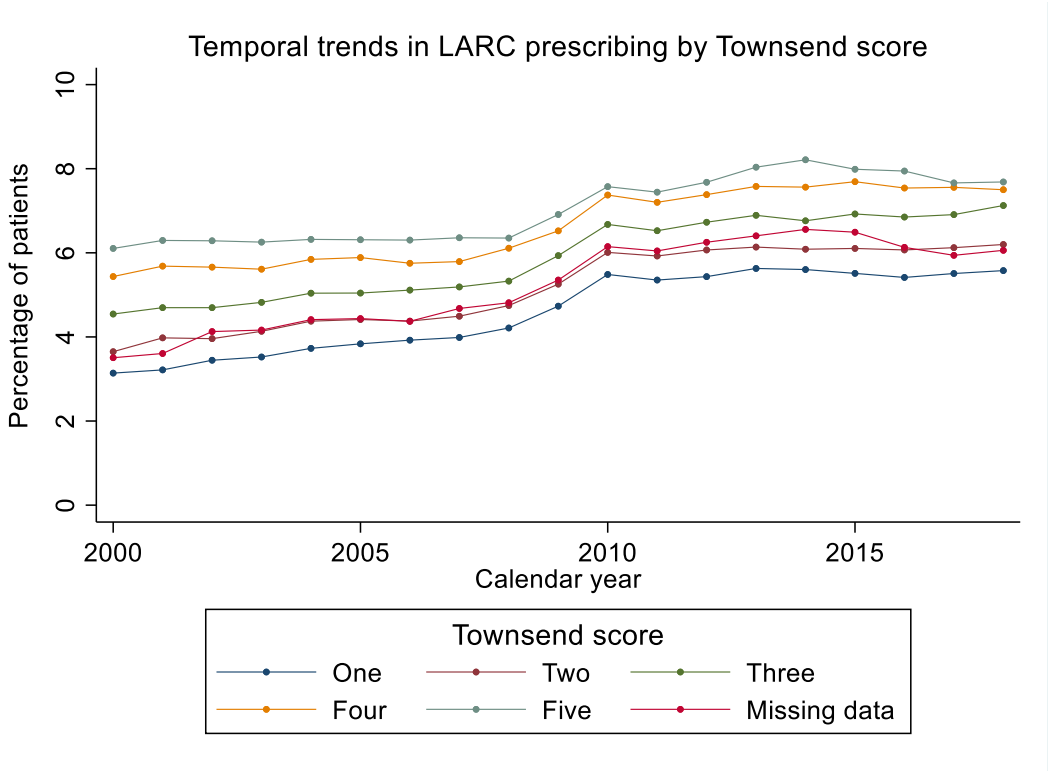


Figure 3.10. Temporal trends in LARC prescribing by social deprivation quintile over the period 2000-2018

3.4.4.7 Age-related trends

CHCs were more commonly prescribed in younger age groups. Women in their twenties saw the most dramatic reduction in CHC prescribing over the study period, falling from 47.0% (95% CI 46.6-47.5) to 25.2% (95% CI 24.9-25.5) in those aged 20-24 years and 42.8% (95% CI 42.4-43.2) to 20.0% (95% CI 19.7-20.3) in those aged 25-29 years (Figure 3.11). POPs were less commonly prescribed in young people and adolescents. All age groups saw a similar increase in POP prescribing over the study period (Figure 3.12). Adolescents aged 15-19 years and women aged 20-24 years saw the biggest increase in LARC update between 2000 and 2013; from 3.9% (95% CI 3.7-4.1) to 6.8% (95% CI 6.6-7.0) and 6.1% (95% CI 5.9-6.3) to 8.9% (95% CI 8.7-9.0) respectively (Figure 3.13). The only age group to see a reduction in LARC prescription after linkage to QOF was abolished was adolescents aged 15-19 years, falling from 6.8% (95% CI 6.6-7.0) in 2013 to 5.6% (95% CI 5.4-5.8) in 2018 (Figure 3.14).

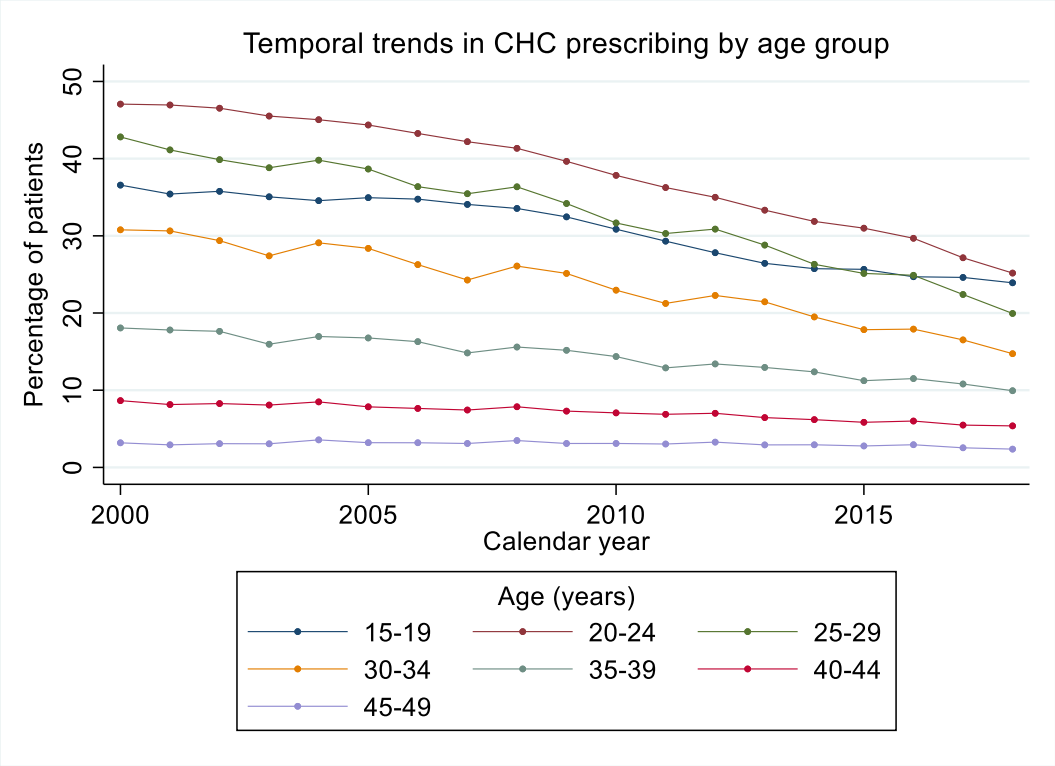


Figure 3.11. Temporal trends in CHC prescribing by age group over the period 2000-2018

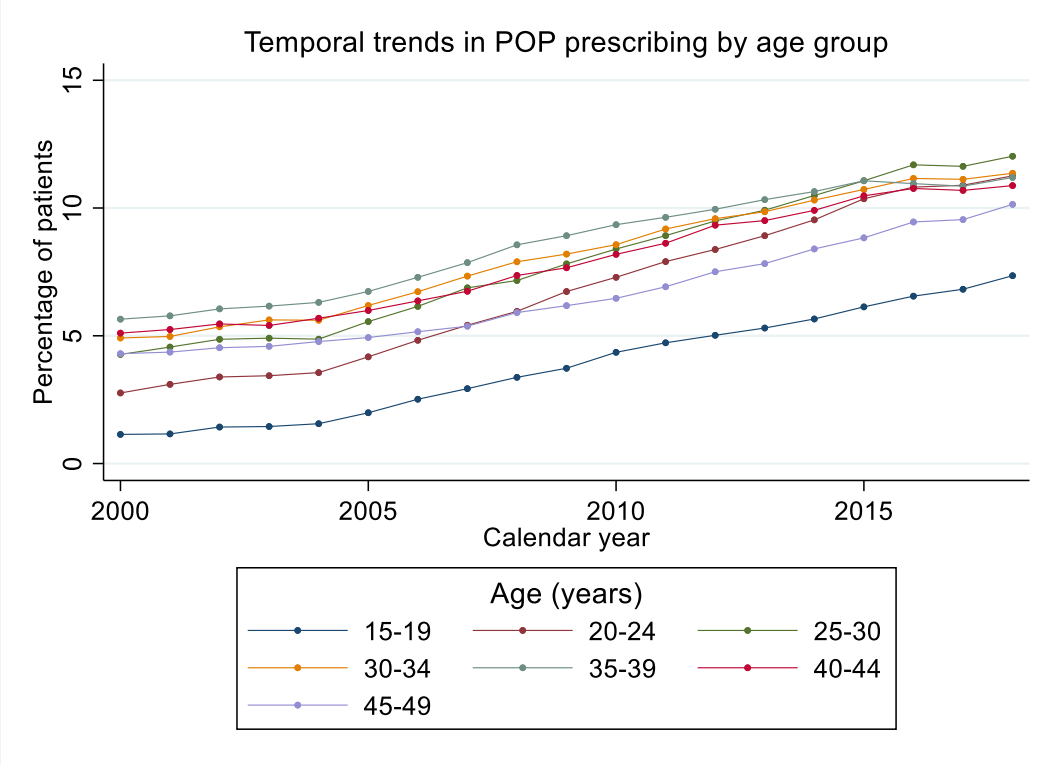


Figure 3.12. Temporal trends in POP prescribing by age group over the period 2000-2018

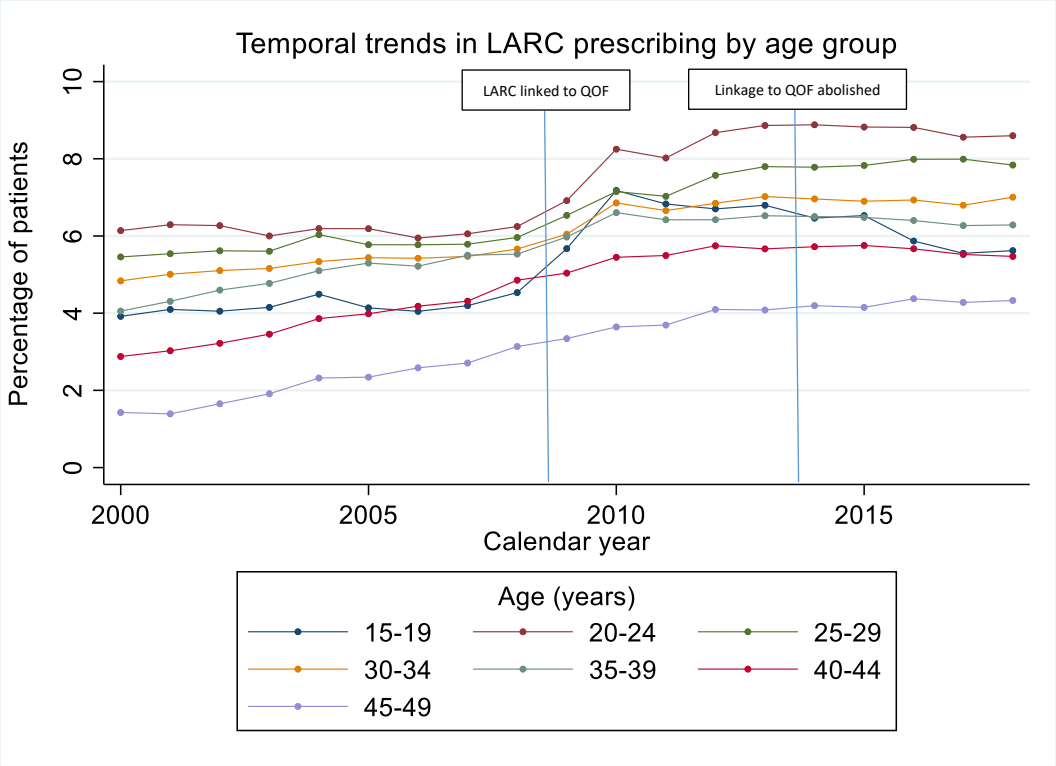


Figure 3.13. Temporal trends in LARC prescribing by age group over the period 2000-2018

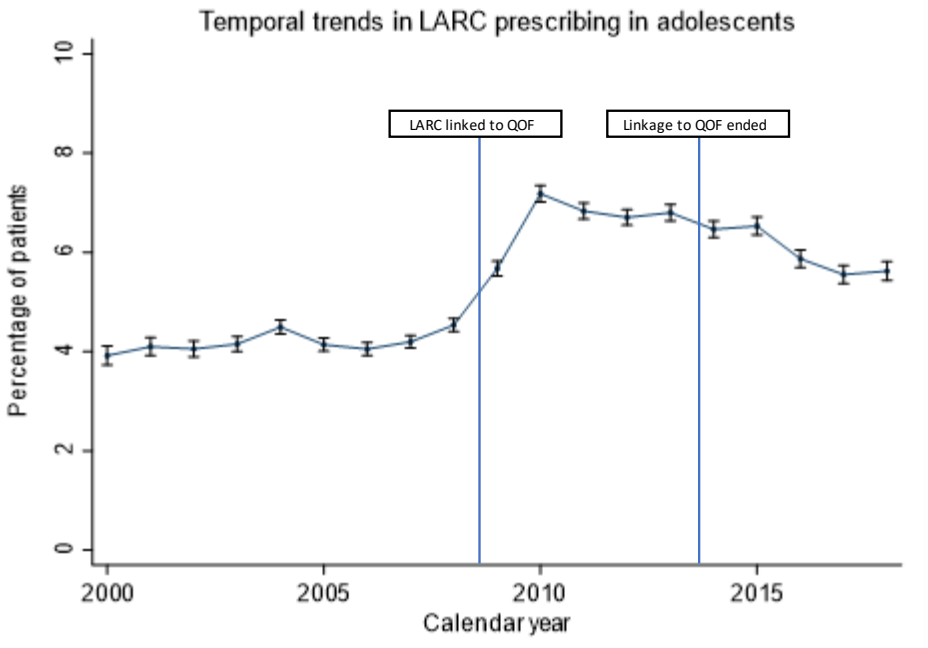


Figure 3.14. Temporal trends in LARC prescribing in adolescents over the period 2000-2018. Vertical bars represent 95% CI

As there was a reduction in the proportion of contributing English practices in the final years of the study (Table 3.4), I was concerned this could compromise generalisability. Given the

clinical and public health implications of a fall in adolescent LARC uptake after withdrawal of QOF, trends in LARC prescribing amongst adolescents were also stratified by country. All countries except Wales saw a fall in LARC prescribing after linkage to QOF was ended in 2014 (Figure 3.15).

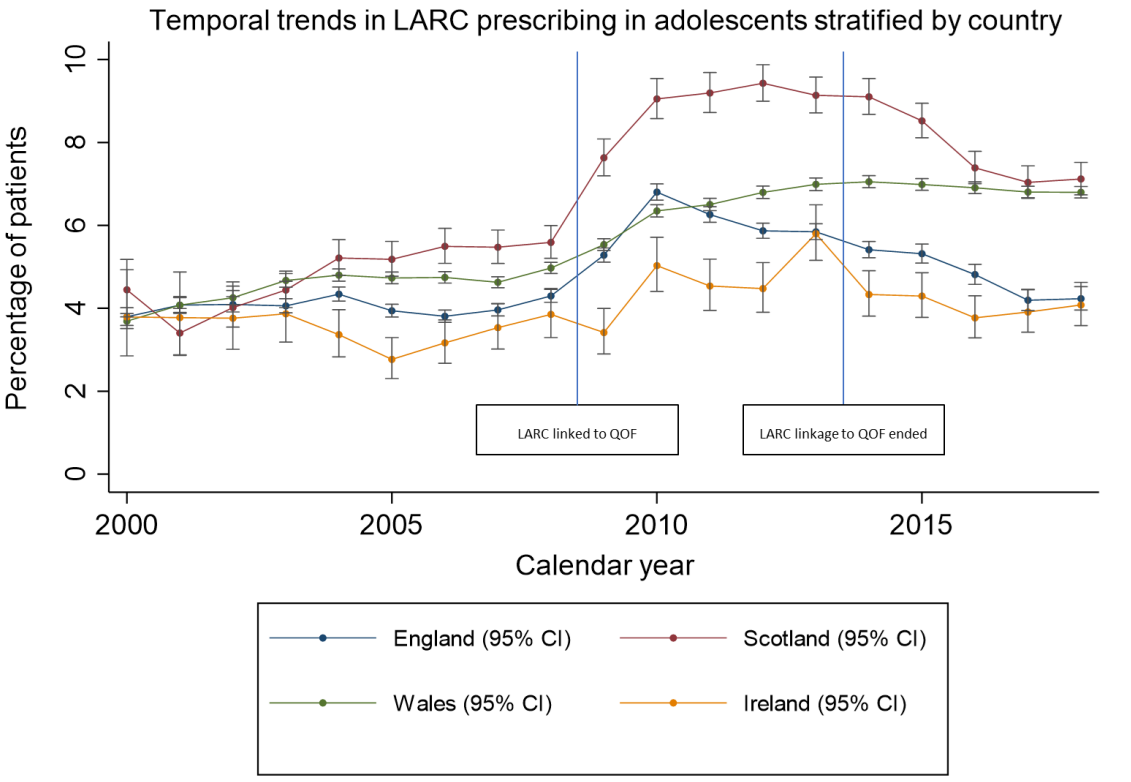


Figure 3.15. Temporal trends in LARC prescribing in adolescents stratified by country over the period 2000-2018. Vertical bars represent 95% CI

3.5 Discussion

3.5.1 Overall

This is the largest study to describe time trends in contraceptive prescribing in the UK. Over a 19-year period, use of COCPs fell by 46% but a 2.5-fold increase in the use of POPs was found. LARC prescription increased with the introduction of the National Institute for Health and Care Excellence (NICE) LARC guidance in 2005, with a further increase following linkage

to QOF in 2009. Adolescents saw an 18% fall in LARC uptake after the QOF indicator was withdrawn in 2014. However, in other age groups, LARC prescribing did not decrease.

3.5.2 Strengths

A strength of this study is the large sample size and the use of a database shown to be generalisable to the UK population. Unlike survey studies which rely on self-reporting of historic contraceptive use, this data is based on detailed prospectively collected electronic prescribing records, thus avoiding recall bias (5.3.2).

3.5.3 Limitations

There are a number of limitations to this study. First, contraceptive prescriptions obtained from sexual and reproductive health (SRH) services were not included. Additionally, some GPs do not offer implant or IUC insertion and women will have to obtain these elsewhere. Therefore, the results are likely to be an underestimate of actual contraceptive uptake across the country, but still an accurate representation of prescribing in primary care. Second, although I was able to capture IUD/IUS and implant insertions, some of these devices can remain in situ for up to ten years and their presence may not be recorded in IMRD if they were inserted prior to GP registration or elsewhere. Therefore, I was not able to provide reliable estimates of prevalent use for these methods. Third, it is acknowledged that a proportion of women will have been prescribed methods for non-contraceptive reasons (e.g. IUS for menorrhagia). Fourth, this study may have been affected by selection bias. This is because in order to contribute to a yearly cross-section, a woman had to be registered with the GP for at least one calendar year from 1st January to 31st December. This will have selected out those women who move more frequently such as students, which

may have compromised study generalisability. Finally, although IMRD has been shown to be generalisable to the UK population overall, when stratifying by country or calendar period contributing practices are not necessarily generalisable to the specific region or time period.

3.5.4 Comparisons with existing literature

Similarly to the USA, Ireland, Australia and Canada, OCPs were the most commonly prescribed contraceptives (216-219). My estimates of contraceptive prescribing are consistent with findings from similar UK studies. Compared to a smaller cohort study performed in THIN for period 01/01/2008-31/12/2008, my estimate for injectable prescribing during 2008 was similar (2.8% vs 2.4% of the cohort). However, my estimate of OCP use was higher (22.2% vs 16.2% for COCPs and 6.8% vs 5.6% for POPs) (104). This is likely to be explained by the fact in their study, a woman could contribute prevalence data to no more than one contraceptive during the year, which was not the case in my study. Additionally, they only included women who had been registered with the contributing practice for five years prior to cohort entry. This will have selected out certain populations such as more geographically mobile women and reduced the generalisability of their results.

My estimates of contraceptive prescribing in Northern Ireland were very similar to a population-based cohort study using the Enhanced Prescribing Database and SP Patient Registration Index for the period 2010-2016; (20.2% vs 16.6% for COCPs) and (9.4% vs 8.0% for POPs). The small difference in estimates of prevalence (mine being slightly higher) could be explained by the fact that they were unable to link 11% of dispensed contraceptives to individuals and thus these were not counted. However, in my study, all prescriptions were linked to patients.

In comparison to a study focusing on the impact of QOF on LARC uptake in CPRD, my estimates of LARC uptake were higher (5.7 vs 3.0 for 2009 and 6.7 vs 3.9 for 2014) (98). This may be explained by differences in the definition of LARC uptake; they classified LARC uptake as 'a branded or generic prescription for LARC' whereas I additionally included documented evidence of LARC insertion in the medical records. Using prescriptions alone, my estimates were closer to their study 4.8% vs 3.0% for 2009 and 5.6 vs 3.9 for 2014. I observed similar trends in LARC uptake before and during the period that LARC was linked to QOF. However, my study provides novel evidence that LARC uptake in general practice may have only fallen by approximately 3.0% since the QOF indicator was abolished in 2015.

In comparison to NHS digital data, I observed similar temporal trends in contraceptive prescribing patterns, with an increase in LARC and POP prescriptions and a decrease in CHC prescriptions (100). However, my prevalence data were not comparable; women attending SRH services represent a highly selected population, the overwhelming majority of whom are taking contraception.

3.5.5 CHCs and POPs

An increase in prescribing of POPs and a reduction in use of COCPs was expected. The introduction of the new POP Cerazette© (desogestrel 75mcg) in 2002 has had a large impact as it works in a similar way to COCPs but has far fewer contraindications (220). Another reason for an increase in POP prescribing could be the shift away from doctors prescribing contraceptives to the administration of medications via patient group direction (PGD); non-medical prescribers in primary care commonly report a 'cautious approach' to prescribing

and may be more likely to supply medications with fewer risks and contraindications (221). Additionally, a Medicines and Healthcare products Regulatory Agency (MHRA) alert regarding venous thromboembolic risk and drospirenone containing COCPs was released in 2011 (222). This is likely to account for the observed fall in fourth generation COCP prescribing. Of note, my data suggests that in 2018, POPs were being prescribed to the same proportion of women as first line COCPs (second generation pills such as Microgynon 30© (levonorgestrel + ethinylestradiol)).

3.5.6 Co-cyprindiol

I observed an expected reduction in the prescribing of Co-cyprindiol (ethinylestradiol + cyproterone acetate); guidelines for prescribing have now become stricter (primary indication should be for management of PCOS/hirsutism/acne unresponsive to topical agents) and the duration of use is restricted (223). At present, fourth generation COCPs are generally being prescribed instead for women with acne; the anti-androgenic properties of drospirenone can reduce sebaceous secretions (224).

3.5.7 Long-acting reversible contraception

The largest increase in LARC uptake over the study period was observed in young people and adolescents. Additionally, this was the only age group where a fall in uptake of LARC was observed after linkage to QOF was abolished. This might suggest that young people were the group who benefitted most from the pay-for-performance scheme. However, it is important to note that there were a number of other national interventions targeted at young people that may have impacted contraceptive uptake during the study period. The Teenage Pregnancy Strategy was launched in 1999 and ran for ten years (95), national

clinical guidance on LARC was published in 2005 (of note we observed an increase in uptake of IUS/IUD and implants and a decrease in use of injectable contraceptives around this time (Figure 3.4)) and the government campaign 'Contraception. Worth Talking About' aimed at improving contraceptive awareness amongst young people which was launched in 2009.

An explanation for the fact that adolescents were the only age group to see a fall in LARC uptake after linkage to QOF was withdrawn could be the fact that they are more likely to be new users of contraception; new users may be more likely to take up LARC when offered than women already established on contraception that works for them. Young women are the most at risk of unplanned pregnancy (225), and if LARC uptake in adolescents has fallen then this is a concern. A study assessing rates of unplanned pregnancies in relation to withdrawal of the QOF indicator would a useful piece of work. This could guide decision making regarding re-implementation of the incentive or the introduction of new interventions.

3.5.8 Geographical trends

There was considerable variation in the increase in LARC prescribing when stratifying by country; the proportion of women who received a LARC prescription in Scotland was nearly twice that of Northern Ireland at the end of the study period. Additionally, Northern Ireland was the only country with no fall in the use of OCPs overall. Heterogeneity in patterns of contraceptive use between Northern Ireland the rest of the UK were not unexpected; there are cultural and social differences in approach to family planning, many of which impact on sexual health policies. For example, until 2019, abortion was only legal under limited

circumstances (226) and until 2009, the legal age of consent was 17 (one year older than the rest of the UK) (227).

Wales was the only country not to see a fall in adolescent LARC uptake after withdrawal of the QOF pay-for-performance indicator in 2014. This may be due to an increase in the effort to tackle unplanned pregnancy in Wales. Teenage conception rates in Wales are amongst the highest in Western Europe and reducing teenage pregnancy was one of the major goals of the Welsh Government as part of their "Our Healthy Future 2010-2020" initiative (228). In 2010 the Welsh government published "The Sexual Health and Wellbeing Action Plan for Wales 2010-2015" (229), and in response, Public Health Wales published "Providing seamless services for the sexual health needs of people living in Wales" (2011). In 2012, The All Wales Medicines Strategy Group published the "Initiating Contraception in Primary Care" guideline (230). This document clearly outlines that LARC must be considered as a first line option for those initiating contraception and if LARC is unacceptable then OCPs can be substituted.

3.5.9 Trends relating to social deprivation

In keeping with published data from Canada, Ireland and the UK, LARC was more commonly prescribed in more socially deprived areas and CHC and POPs were more commonly prescribed in less socially deprived areas (98, 216, 218). These trends are likely to be influenced by educational and social inequalities. Contraceptive failure rates have been shown to be higher across all methods in low-income groups (231). Additionally, in England and Wales, the rate of abortion in the most deprived decile is more than double the rate in the least deprived (232). These factors could generate prejudice amongst GPs when

selecting appropriate contraception. Additionally, women from less deprived groups may be more likely to decline LARC as they have better access to online resources and may have undertaken more background reading about the potential unwanted side effects of LARC such as unscheduled bleeding and complications of IUC insertion such as vasovagal shock and uterine perforation. Unlike in the study undertaken in CPRD (98), I observed a similar increase in LARC uptake over time across all socio-economic groups. This would support an argument that the LARC pay-for-performance scheme had a similar impact on women across different socioeconomic backgrounds.

3.5.10 Conclusion

Over a 19-year period, prescribing of CHCs fell by 46%. However, POP prescribing more than doubled. Use of LARC increased in line with linkage to QOF and plateaued after 2010. Adolescents saw an 18% reduction in the prescribing of LARC after withdrawal of the QOF pay-for-performance indicator.

This study highlights a wide range of temporal and sociodemographic trends in contraceptive uptake across the UK. Prescribers will need to be attuned to changes in demand for contraceptive choices as the model for care undergoes change.

Chapter 4: Use of contraceptives and development of inflammatory bowel disease: a nested case-control study

4.1 Introduction

Changes in the epidemiology of inflammatory bowel disease (IBD) across geographical location and time suggest that environmental risk factors, either alone or by gene-environmental interactions, play a major role in disease development (49).

An increased risk of development of IBD in association with oral contraceptive pill (OCP) exposure has been shown in numerous studies (108, 109, 138). However, the precise biological mechanism remains unknown. A number of proposed theories exist, largely relating to the effect of increased exogenous oestrogen and decreased endogenous testosterone on immunomodulation, intestinal wall function, gut microbiome and hypercoagulability (the increased tendency of blood to clot) (1.8.1).

How hormone formulation, dose and duration of OCP exposure relate to IBD risk is poorly characterised. Additionally, there is a paucity of literature on how progestogen-only and parenteral preparations of contraception affect IBD risk.

4.2 Hypothesis

Combined hormonal contraception (CHC) causes an increase in circulating exogenous oestrogen and has anti-androgenic properties. Progestogen-only contraception does not have these effects. In my IBD incidence study, I observed a gender-time interaction, with IBD incidence falling by 1.3% per year in women and 0.6% per year in men (2.4.8) (1). Over the same period, prescription of CHC has nearly halved whereas progestogen-only pill (POP)

prescription has more than doubled (3.4.4) (2). I hypothesise that CHC increases risk of IBD, whereas progestogen-only contraception does not.

4.3 Aims and objectives

4.3.1 Aims

The purpose of this work was to quantify associations between various types of contraception and risk of IBD, adjusting for available confounding factors. I was particularly interested in the impact of OCP hormone formulation, dose and duration of therapy on risk of subsequent development of IBD.

4.3.2 Objectives

The specific objectives using IQVIA™ Medical Research Data (IMRD) data were as follows:

1. To describe the incidence of Crohn's disease (CD) and ulcerative colitis (UC) in a cohort of women of reproductive age for the period 01/01/2000 – 31/12/2018.
2. To derive odds ratios for development of IBD by a range of contraceptive exposures.
3. To derive odds ratios for development of IBD by dose and duration of OCP exposure.
4. To investigate interactions between smoking and OCP exposure on IBD risk (in a large US cohort of 232,452 women, it was found that the association between OCPs and UC was exclusive to smokers (157)).

4.4 Methods

4.4.1 Study design

A nested case-control study using electronic UK general practice (GP) records from the IMRD database (4.4.3.1).

4.4.2 Study population

4.4.2.1 Source cohort

A source cohort of women aged 15-49 years who were registered with study practices contributing to IMRD for the period 01/01/2000-31/12/2018 was identified. This was a dynamic cohort (2.3.2.2). 15-49 years was selected because it is the World Health Organisation (WHO) definition of 'women of reproductive age' (215).

4.4.2.1.1 Cohort entry

Cohort entry was the latest date of:

- Date of registration with the GP practice plus nine months to avoid misclassifying prevalent IBD as incident disease (182) (2.3.2.2.1.1)
- The start of the study period (01/01/2000)
- The date the patient turned 15 years old
- The date the practice achieved published measures of acceptable mortality recording (2.3.2.2.1.2)
- The date the practice achieved published measures of acceptable computer usage (2.3.2.2.1.2)

4.4.2.1.2 Cohort exit

Cohort exit was defined as the earliest date of the following:

- De-registration with the GP practice contributing data
- The date the practice stopped contributing data to IMRD
- The end of the study period (31/12/2018)
- The date the patient turned 50 years old
- The first recording of any medical event which would usually preclude future use of contraception (hysterectomy, bilateral salpingo-oophorectomy or sterilisation) (Appendix 6.3.9)
- The first prescription for post-menopausal hormone replacement therapy (HRT) (Appendix 6.4.1)
- Diagnosis of 'any IBD' (including CD, UC, inflammatory bowel disease unclassified (IBDU) and unspecified IBD)
- Death

4.4.3 Outcomes

The main outcome of interest was the diagnosis of CD or UC. The definition of 'diagnosis of CD/UC' was the same as used in chapter two (2.3.3).

4.4.3.1 Nested case-control design

Within the cohort, I designed two nested case-control studies, one for CD and one for UC. The nested case control design was selected because it allowed me to explore associations between incident IBD and a range of different contraceptive exposures whilst not losing any of the available cases and compromising study power or generalisability (233).

Cases were those diagnosed with incident CD or UC during study follow up. Eligible cases were required to have at least one year of prescribing history prior to the date of diagnosis. One year was selected because prescriptions for OCPs are typically not longer than one year in length.

Each case was individually matched with up to six controls by year of birth and GP practice using the *sttocc* command in Stata to perform incidence density sampling. Incidence density sampling involves matching each case to study participants from the source cohort who are at risk at the time of case occurrence (234). I.e. controls are women in the source cohort who have not developed IBD at the time of diagnosis for their matched case. When using incidence density sampling, it is possible that controls may later become cases (if they were to develop IBD at a later time-point in the source cohort). If this were to happen then that subject would be included in the study twice; once as a control and then later as a case.

Each control was allocated an index date which was the date of diagnosis for their matched case. Each control was required to have the same (or greater) prescribing history prior to the index date as their matched case. Any additional prescribing history that a control may have had did not contribute towards the analysis (i.e. all controls contributed the same amount of prescribing history as their matched cases over the same calendar period). The lookback period was defined as the period between the start of the prescribing history for cases (or matched date for controls) and the IBD diagnosis date (or matched index date for controls). Prescribing history during time periods when practices had not met acceptable standards of data quality were not included (2.3.2.2.1.2/Figure 4.4/Figure 4.5).

4.4.4 Sample size calculation

If we assume that approximately 30% of women of reproductive age were being prescribed hormonal contraception by their GP during the study period (chapter three) and that the odds ratio of exposure in cases relative to controls is 1.24 for CD and 1.30 for UC (109), then I would require 961 CD cases and 640 UC cases matched to controls at a 1:4 ratio to detect a difference of this size or greater significant at the 95% threshold with 80% power. Although this would be easily achievable in IMRD, I wanted to stratify exposure by the different classes of contraception (second generation COCPs, Newer COCPs, progestogen-only pills (POP) and long-acting reversible contraception (LARC)). Therefore, I wanted to maximise sample size without introducing bias. This could be achieved by matching more controls to each case.

In case-control studies, increasing the number of controls per case to more than around four is often inappropriate due to the diminishing returns that more controls add statistically, the cost involved in recruiting more participants and the bias that may be introduced when adding more controls who are 'not as good a match' as the first control (235, 236). However, given that data for all patients are available in IMRD, cost becomes a moot point. Additionally, the large pool of patients available allows for appropriate selection of controls when only matching by a few variables.

When adding more controls than six per case, this made little difference statistically. For example, for UC and 'any contraception', when matching 6:1, I would require 596 controls per case and matching 7:1, I would require 583 controls per case to detect an OR of greater than 1.30, significant at the 95% threshold with 80% power. In this study, I was able to

match 5.95 appropriate controls to each case when attempting to match 6:1. I was concerned that when attempting to match more than six controls per case, cases from smaller practices (which may be more rural) would be matched to fewer controls and this may introduce bias. Therefore, I matched controls to cases at a 6:1 ratio.

4.4.5 Exposures

Exposure to contraceptives was based on prescribing history for the total lookback period. COCPs were subdivided by pill generation (Table 1.2). Co-cyprindiol, was also included. First generation pills were not included. POPs were included separately. LARC methods that were included were: intrauterine devices (IUD), intrauterine systems (IUS), subdermal implants and intra-muscular/subcutaneous progestogen injections. Transdermal contraceptive patches and intravaginal rings were not included as I was able to identify <6 users amongst all cases and controls. '<6' has been quoted as due license agreements with IQVIA^{TM}, I am unable to present results for less than six individual patients. This to ensure that all patients in the database remain non-identifiable, despite having rare or unique characteristics.

For OCPs, ascertainment of prescription was based on the electronic prescribing records in IMRD. For LARC, ascertainment of prescription was based on not only electronic prescribing records, but also medical records and additional health data (AHD) records. This is because these methods must be initiated with a procedure which is often recorded in the AHD records or medical notes in place of the device or drug for injection being logged in the prescribing history. As per chapter three, due to a number of non-specific Read codes for IUD/IUS such as 'reinsertion of coil', these two contraceptives were grouped together (3.3.3).

Specifically for OCPs, women were classed as current users if their most recent prescription would finish <=28 days before (or any time after) the index date. Twenty-eight days was selected because OCPs are packaged in strips which last 28 days (one typical menstrual cycle). For injectables, to be classified as a current user, the last injection was required to be given within 16 weeks of the IBD diagnosis/index date with no subsequent prescription for a new contraceptive. For implants and IUS/IUD, to be classified as a current user, the device was required to be inserted within three years of the diagnosis/index date and five years of the diagnosis/index date respectively, with no evidence of subsequent device removal or prescription for a different method of contraception.

4.4.5.1 Primary analysis

For the primary analysis, women were categorised based on their contraceptive use during the entire lookback period and 'current use' was not considered (Table 4.1).

Table 4.1. Categorisation of contraceptive exposures for the primary analysis

User type	**Criteria**
Non-contraceptive users	No prescribed contraceptive use during the lookback period
Second generation COCP users	Only 2nd generation COCP prescriptions during the entire lookback period
Newer generation COCP users	Any mixture of third generation COCP, fourth generation COCP and co-cyprindiol prescriptions during the lookback period but no other contraception
POP users	Only POP prescriptions during the lookback period
Parenteral (LARC) users	Any evidence of IUS/IUD, implant or progestogen injection use during the lookback period but no other contraception
Mixed contraceptive users	Any combination of COCPs, POPs and parenteral methods during the lookback period

4.4.5.2 Current contraceptive use

As previous studies have shown current OCP use is more strongly associated with development of IBD than former use (109), I conducted a sub-analysis whereby exposure was stratified by current contraceptive use at the time of IBD diagnosis/index date (as opposed to the primary analysis where contraception throughout the lookback period contributed). Those patients not using contraception at IBD diagnosis/index date were classified as either non-users (no prescriptions for contraception in the lookback period) or past users (any previous prescriptions for contraception in the lookback period but not using contraception at time of diagnosis/index date).

4.4.5.3 Oestrogen strength

I conducted another sub-analysis where current COCP users were categorised by the oestrogen content of the COCP they were using at the time of index date. Pills were categorised into low strength (<30mcg ethinylestradiol) and standard strength (>=30mcg ethinylestradiol) oestrogen. For those pills containing mestranol, I treated 50mcg mestranol as bioequivalent to 35mcg ethinylestradiol (237). For those pills containing estradiol I treated 200mcg estradiol as bioequivalent to 1mcg ethinylestradiol (238, 239).

4.4.5.4 Duration of OCP exposure

'Average months of OCP exposure per year of prescribing history' was calculated by summing the total single-cycle packs of OCPs prescribed during the lookback period then dividing by the total number of years during the lookback period. If a woman was prescribed more pills than should be taken during the lookback period under normal circumstances, then she was classified as taking 'continuous OCP throughout'. For the purposes of this

study ‘continuous OCP throughout’ was defined as 21 COCPs/month or 28 POPs/month (1.7.2.1.1/1.7.2.2). ‘Average months of OCP exposure per year of prescribing history’ was treated as both a continuous variable and separately as categorical variable in quantiles of three months per year to check for evidence of non-linearity with development of IBD. This was done separately for COCPs and POPs.

4.4.5.5 Average daily dose of oestrogen

‘Average daily dose of oral oestrogen over the lookback period’ was calculated by summing the oestrogen content of all prescribed COCPs over the lookback period and dividing by the number of days during the lookback period. If a woman was prescribed more oestrogen containing pills than are typically taken under normal circumstances (twenty-one 50mcg ethinylestradiol pills per cycle or equivalent) then this ‘maximum dose’ (1,050mg ethinylestradiol/month) was used. ‘Average daily dose of oral oestrogen over the lookback period’ was similarly analysed as both a continuous variable and a categorical variable in quantiles of 5mcg ethinylestradiol per day (or equivalent).

4.4.6 Causal inference and confounding

Causal inference is the examination of associations between variables to explore whether there is a causal effect of an exposure on an outcome. Causal inference is often applied in observational research to answer questions about the aetiology of disease. For example, ‘does alcohol cause coronary artery disease?’ or ‘does caffeine intake improve asthma?’.

In observational studies, causal inference requires careful consideration of confounders. A confounder is an additional variable (not the exposure or the outcome) which is associated

with the exposure, is a cause of the outcome and does not reside on the causal pathway between the exposure and outcome (240). If confounders are not appropriately adjusted for, this can introduce bias. For example, in a study looking at associations between coffee intake and lung cancer, it would be important to adjust for smoking. This is because coffee drinkers may be more likely to smoke and smoking causes lung cancer. In this example, if smoking were not adjusted for, it may lead to false rejection of the null hypothesis of no association (type one error).

It is important when identifying confounders that directions of causality are considered. Directions of causal effects can determine whether an external variable represents a potential confounder or something entirely different such as a 'mediator' or a 'collider'.

4.4.6.1 Directed acyclic graphs

Directions of causal effects can be explored using directed acyclic graphs (DAGs). DAGs are diagrams which contain variables joined together by arrows. The arrows represent the direction of causality (i.e. if a change in variable A causes a change in variable B, an arrow would be drawn from A to B). For example, we know that smoking increases risk of lung cancer, so in a DAG containing these variables, an arrow would be drawn from 'smoking' to 'lung cancer' but not the other way around. For some variables, the relationship goes both ways. For example, 'BMI' and 'contraception'. Increased BMI might preclude the use CHC so an arrow would be drawn from 'BMI' to 'contraception'. However, some women report weight gain on contraceptives such as injectables, so an arrow would also be drawn from 'contraception' to 'BMI'.

DAGs are useful tools when designing hypothesis driven observational studies. Studies of causal inference often have many important external variables which can have relationships with one another as well as the exposure and the outcome. A very simple DAG using the example of smoking as a confounder of the relationship between coffee and lung cancer is shown in Figure 4.1A.

4.4.6.2 Mediators

A mediator is a variable that lies along the causal path and mediates the association between exposure and outcome. For example, one could hypothesise that 'gut dysbiosis' might be a mediator between OCP exposure and IBD (Figure 4.1B) (1.8.1). Therefore, if 'gut dysbiosis' is adjusted for, this could close some of the causal path between OCP exposure and IBD, preventing a causal association to be observed between exposure and outcome (type two error). It is therefore important that mediators are not adjusted for in studies of causal inference.

4.4.6.3 Colliders

A collider is a different sort of variable which has two plausible causes that lie within a pathway of interest. A collider can be caused by the outcome and by the exposure (i.e. the direction of causal effect points the other way from a confounder). A plausible example of a collider in a study of causality between OCPs and IBD might be 'nausea' as nausea can be caused by both OCPs and IBD (Figure 4.1C). Mistakenly adjusting for nausea might introduce a confounding pathway (an alternative path between exposure and outcome) and introduce bias.

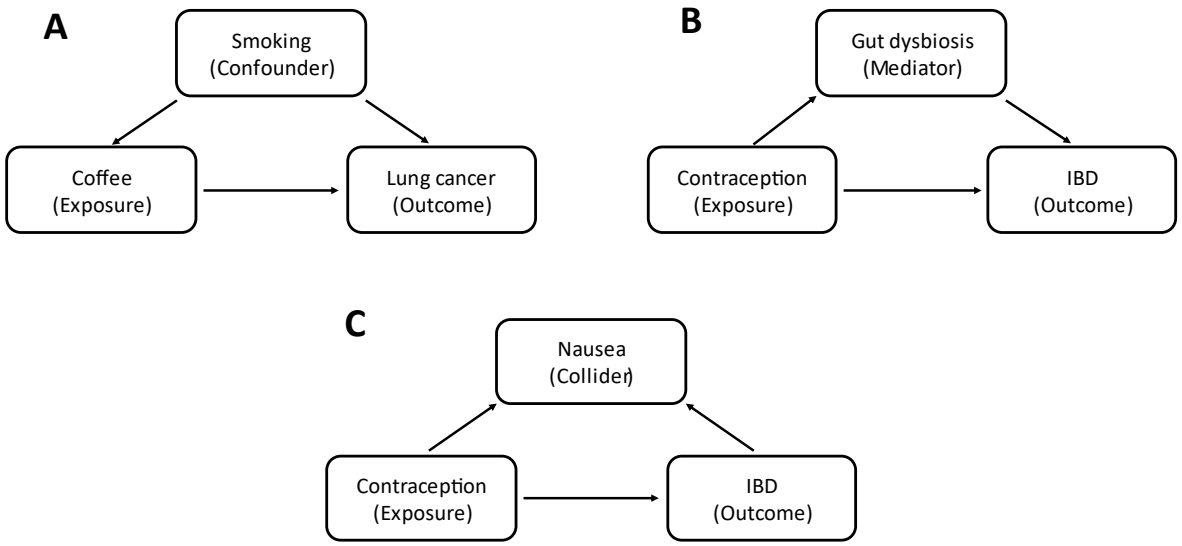


Figure 4.1 Directed acyclic graphs showing examples of confounding (A), mediation (B), collision (C)

4.4.6.4 Included covariates in this study

I adjusted for smoking status treating smoking as a categorical variable with the levels 'never smoker', 'ex-smoker' and 'current smoker' (Appendix 6.3.8). Smoking was included as it is an established risk factor for CD and may decrease risk of developing UC (55). Additionally, smoking is a relative contraindication to the prescription of OCPs due to increased risk of cardiovascular complications and VTE (82, 241, 242).

I adjusted for body mass index (BMI) as a categorical variable using the levels 'underweight' (BMI <18), 'normal weight' (BMI 18-25), 'overweight' (BMI 25-30) and 'obese' (over 30). BMI was included as pooled results of a meta-analysis identified obesity as a risk factor for CD (243) and BMI is an important factor to consider when choosing appropriate contraception; raised BMI is a relative contraindication to the prescription of OCPs due to risk of VTE and

injectable contraceptives are avoided in those with low BMI due to the impact on bone health (82). I also adjusted for BMI as a continuous variable in a sensitivity analysis (4.4.8.8.5). However, it is acknowledged that the relationship between BMI and risk of CD was found to be non-linear in a previous meta-analysis (243)

History of endometriosis, acne and polycystic ovarian syndrome (PCOS) were included as covariates because they are all commonly treated with OCPs and are also potentially linked to development of IBD (6.3.4/6.3.5/6.3.6). Increased risk of IBD has been shown in women with endometriosis in a nationwide Danish cohort study (244). Severe acne is a feature of IBD in some individuals (245, 246). Additionally, in an undiagnosed patient, other cutaneous manifestations of IBD could masquerade or be misdiagnosed as acne. PCOS has been shown to be associated with reduced biodiversity in the gut microbiome. In particular, a lower abundance of bacteria that synthesize short-chain fatty acids (SCFA) (247). Decreased levels of gut *Odoribacter* and *Roseburia* have been associated with IBD, potentially by increasing host inflammatory response via reduced SCFA production (248, 249).

Social deprivation as measured by Townsend score (250) was included as I found there to be an association between Townsend score and risk of UC in my incidence study (2.4.6) (1). Additionally, in my cross-sectional study, I found OCP uptake to be lower in more deprived socio-economic groups (3.4.4.6) (2).

Evidence of pregnancy during follow up was included as a yes/no binary variable (Appendix 6.3.7); pregnancy would usually preclude the use of contraception and women may be less likely to conceive if they are unwell and developing a chronic inflammatory illness.

Additionally, if my hypothesis regarding oestrogen containing contraception is true, then one could hypothesise that increases in systemic endogenous oestrogen during pregnancy may affect IBD risk.

Directions of causal inference between exposure, outcome and covariates were explored using DAGs (Figure 4.2) (240). This was done to ensure that all covariates included could plausibly represent confounders as opposed to introducing bias through other mechanisms.

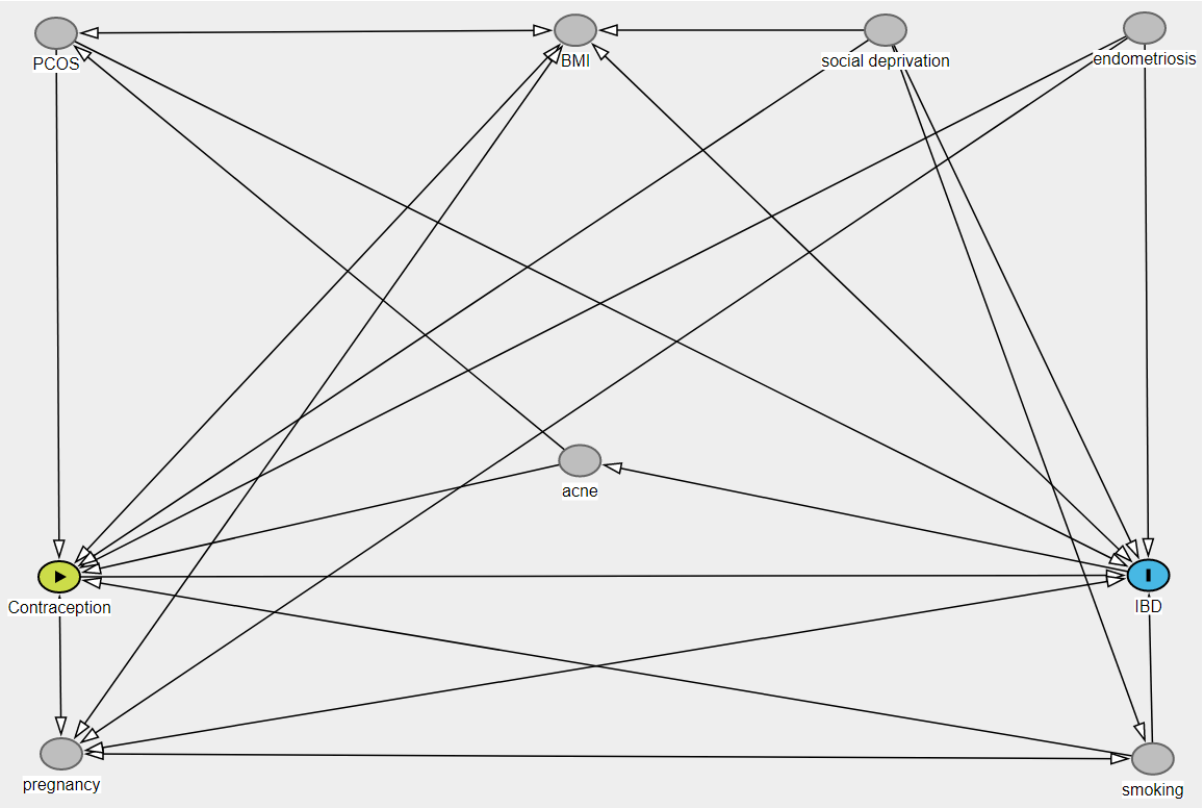


Figure 4.2. Directed acyclic graph exploring directions of causal inference between exposure, outcome and covariates. Image made using the R package 'dagitty' (251). Available at www.dagitty.net

Data on BMI and smoking were captured using the earliest value recorded during the lookback period. If data were missing during this period, then the latest value recorded prior to the start of the lookback period was substituted. Covariate assessment windows were explored in a sensitivity analysis (4.4.8.8.6).

4.4.7 Graphical depictions of the study

For clarity, I have included some graphical depictions of the study (Figure 4.3/Figure 4.4/Figure 4.5) (252).

Figure 4.3 is the graphical overview of the study. Analysis time is on the x-axis moving left to right and the black vertical lines represent 'temporal anchors' in time for the patients (252) . The period of time between the 'start of the prescribing history' and 'end date' is the 'lookback period'. The coloured horizontal bars represent windows for assessment of exposure, covariates and exclusion criteria.

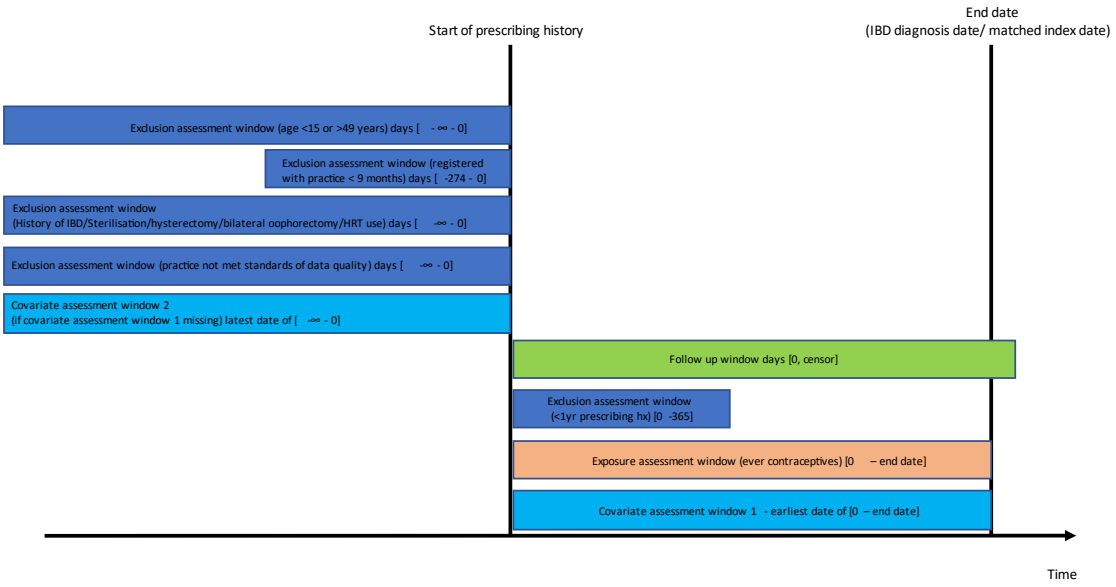


Figure 4.3. Graphical overview of the study

Figure 4.4 and Figure 4.5 show example IBD cases and their matched controls. Calendar time is shown on the x-axis. The dotted vertical lines represent the IBD diagnosis date (or matched index date for controls), the start of the prescribing history for the IBD case (or

matched start date for controls) and the date the GP practice met acceptable standards of data quality (ACU/AMR date). The orange horizontal bars represent periods of contraceptive exposure. The lookback period or 'exposure window' is shown at the top of the figures. These figures demonstrate how changes in the lookback period (in this case due to a later ACU/AMR date in Figure 4.5) can result in differences in observed exposure status. In Figure 4.4 the lookback period is longer and the IBD case is classed as 'exposed'. In Figure 4.5 the lookback period is shorter and the IBD case is classed as 'unexposed'.

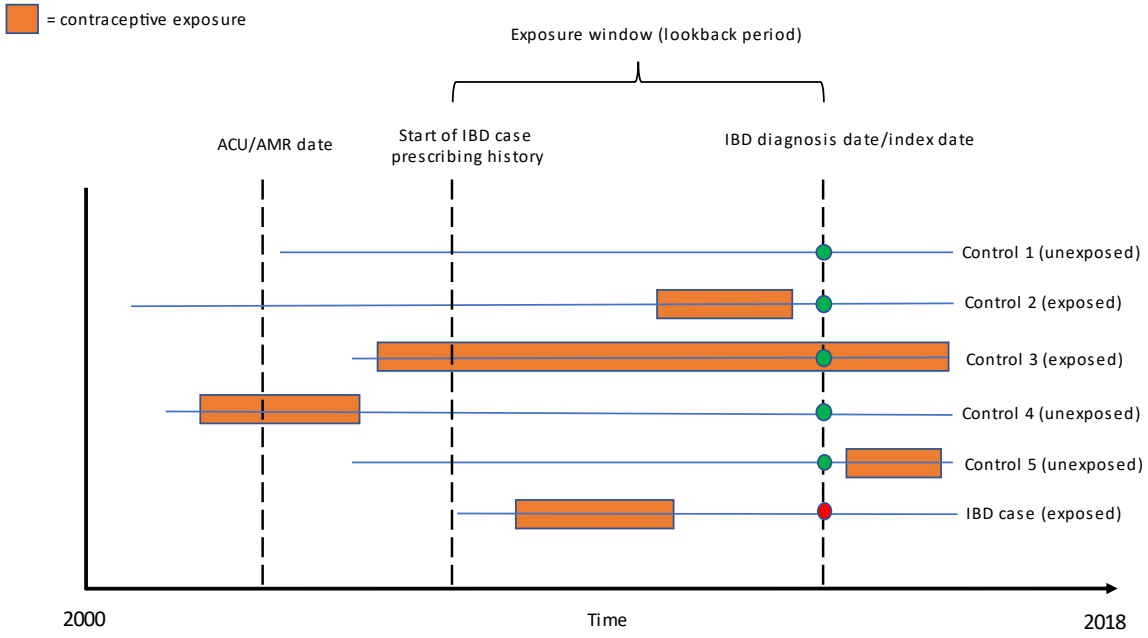


Figure 4.4. Lookback periods for individual matched cases and controls within a GP practice with an historical ACU/AMR date

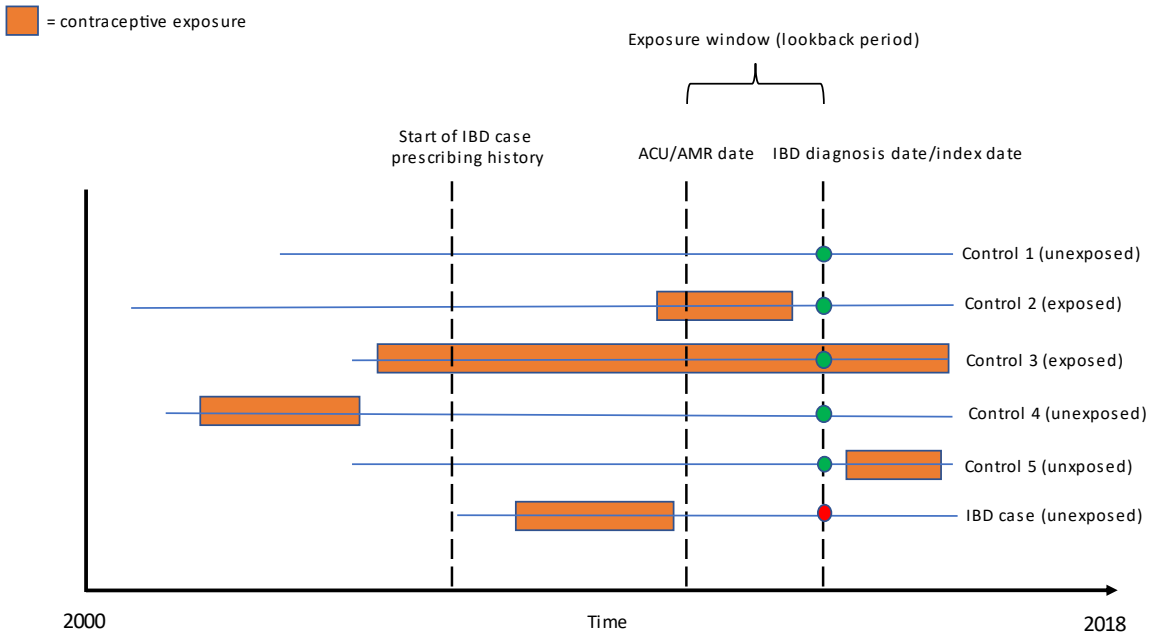


Figure 4.5. Lookback periods for individual matched cases and controls within a GP practice with a recent ACU/AMR date

4.4.8 Analysis:

4.4.8.1 Statistical software

StataCorp. 2017. *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC was used for all analyses.

4.4.8.2 Descriptive analysis of demographics

Descriptive characteristics were summarized using numbers and percentages for categorical variables, means and standard deviations (SD) for normally distributed continuous variables and medians and interquartile ranges (IQR) for non-normally distributed continuous variables.

4.4.8.3 Descriptive analysis of temporal trends

Crude incidence estimates per 100,000 person-years at risk were calculated for the source cohort by dividing the total number of cases by the total number of person-years of follow up then multiplying by 100,000. 95% CI were calculated assuming a Poisson distribution.

4.4.8.4 Analysis of nested-case control data

Conditional logistic regression was used to analyse the nested-case control studies and obtain odds ratios for each exposure with 95% confidence intervals. The Wald test was used to test for significance of exposures and categorical variables in the regression model and to test for multiplicative interactions.

4.4.8.5 Interactions

In a large US cohort of 232,452 women, it was found that the association between the OCP and UC was exclusive to smokers (157). The authors hypothesised that an interaction between smoking and OCP exposure could be mediated by the synergistic effect of oestrogen and cigarettes on either hypercoagulability or TH-2 mediation. Therefore, I was particularly interested in an interaction between OCP exposure and smoking. I explored this by including a smoking/OCP exposure interaction term in my regression models. This was done using smoking as a categorical variable and 'average months per year of OCP exposure' as a continuous variable.

4.4.8.6 Secular trends

To check for secular trends, I stratified ORs for OCP exposure by calendar period of IBD diagnosis date/index date using five-yearly quantiles.

4.4.8.7 Handling missing data

Missing data was dealt with by including 'missing' as a level to categorical variables and complete case analysis for the continuous variable BMI in a sensitivity analysis.

4.4.8.8 Sensitivity analyses

I conducted seven sensitivity analyses.

4.4.8.8.1 Sensitivity analysis one: Exclusion of OCP switchers

For this analysis, I excluded women who switched contraceptive pill in the year preceding diagnosis/index date. 'Switching' was defined as two or more prescriptions for different OCPs within the year. I also counted the number of OCP prescriptions per patient and the number of OCP switches in the year preceding diagnosis/index date across both cases and controls.

This sensitivity analysis was performed because I hypothesized that women may switch contraception more frequently in the period leading up to a diagnosis of IBD. I theorised that undiagnosed IBD symptoms such as abdominal or pelvic pain might be put down to contraceptive side effects thus resulting in a switch and an additional new prescription. if IBD cases have more frequent prescriptions for contraceptives in the period leading up to an IBD diagnosis, this could result in overestimation of exposure in this group and bias results towards rejection of the null hypothesis.

4.4.8.8.2 Sensitivity analysis two: Additional levels to the exposure variable

For the primary analysis, contraceptives were separated into four groups: second generation COCPs, newer COCPs, POPs and parenteral (LARC) contraception. This sensitivity analysis was conducted to explore the association between individual types of contraception and development of IBD, with the acknowledgement that the 'mixed contraceptives' group would likely be inflated as women could switch between a greater number of different types of contraception. I used the following levels to the contraceptive exposure variable:

- Non-contraceptive users (no prescribed contraceptive use during the lookback period)
- Second generation COCP users
- Third generation COCP users
- Fourth generation COCPs users
- Co-cyprindiol users
- POP users
- IUD/IUS users
- Contraceptive implant users
- Contraceptive injection users
- Mixed contraceptive users (any combination of the above methods during the lookback period)

4.4.8.8.3 Sensitivity analysis three: Excluding cases with less than five years of prescribing history

In the primary analysis, I anticipated that some of the IUD/IUS and implant exposure would be uncaptured in those case-control pairs contributing less than five years of prescribing history. This is because most indwelling contraceptive devices can remain in situ for 3-5 years (i.e. devices inserted at a previous GP would be missed in those participants with shorter analysis time). Therefore, I performed a sensitivity analysis excluding those case control pairs contributing less than five years of prescribing history. However, it was acknowledged that study power would be heavily compromised using this methodology.

4.4.8.8.4 Sensitivity analysis four: Restricting analysis time to a five-year lookback period

Previous studies have shown that current OCP exposure increases risk of IBD more than past exposure (109). Therefore, I anticipated that contraceptive exposure in the period leading up to diagnosis could potentially be more relevant than historical use. In the primary analysis, I calculated odds ratios for 'average months per year' of OCP exposure over the whole of follow up. However, case-control pairs contributed a wide range of analysis times in my study ranging from 1-19 years. The case-control pairs contributing longer analysis times would be an older cohort at IBD diagnosis, but the 'average months of OCP use per year' would be over a far greater period with more 'historical OCP use' contributing. This might underestimate the effect of OCPs on IBD risk in older women (who by definition are more likely to have longer prescribing histories) and overestimate the effect in younger women.

Firstly, I calculated odds ratios for 'months per year of COCP use' as a continuous linear variable separately for each calendar year for 1-10 years prior to IBD diagnosis/index date and plotted odds ratios (Figure 4.11). I then performed a sensitivity analysis restricting the lookback time to five years prior to IBD diagnosis/index date across all case control pairs (all other prescribing history was disregarded). Five years was selected so to capture as many parenteral contraception insertions as possible (4.4.8.8.3).

4.4.8.8.5 Sensitivity analysis five: Treating BMI as a continuous variable and using a complete case analysis

I adjusted for BMI as a continuous linear variable in this sensitivity analysis and excluded those with missing BMI status. This was done to help assess for bias that may have been introduced by categorising and including a 'missing' level to this variable (approach used in the primary analysis).

4.4.8.8.6 Sensitivity analyses 6a & 6b: Changes to covariate assessment windows

I conducted two sensitivity analyses exploring different ways of capturing data on BMI and smoking.

4.4.8.8.6.1 Sensitivity analysis 6a: Adding an additional covariate assessment window

As the data included in IMRD are not collected for research purposes, it was anticipated that many patients would have missing data related to smoking status and BMI (5.3.8). Therefore, I conducted a sensitivity analysis whereby an additional covariate assessment window was added after the index date should data be missing earlier (Figure 4.6). For this sensitivity analysis the following approach was used to capture covariate information:

"Data on covariates (BMI and smoking) were captured using the earliest value recorded during the lookback period. If data were missing during this period then the latest value recorded prior to the start of the lookback period was substituted. If data were missing during this period then the earliest date recorded after the index data was substituted".

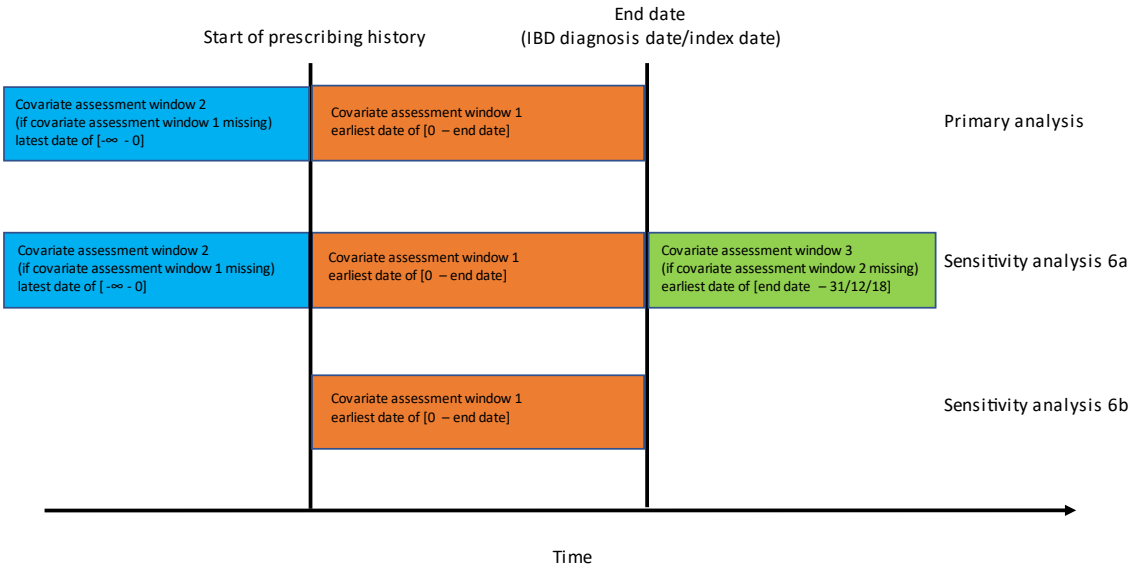


Figure 4.6. Graphical depiction of study comparing covariate assessment windows for primary analysis and sensitivity analyses 6a and 6b

4.4.8.8.6.2 Sensitivity analysis 6b: Removing a covariate assessment window

For the primary analysis, the lookback period for cases started at the beginning of the prescribing history and ended at the diagnosis date. Controls were allocated an index date (the same date as the IBD diagnosis date for their matched case) and also allocated a 'start date' which was the same date as the start of the prescribing history for their matched case. This allowed the 'lookback period' (also covariate assessment window one) to be exactly the same in calendar time for cases and controls. However, many controls were registered with their GP for longer than their matched cases prior to the 'start date'. This period (covariate

assessment window two) was therefore longer for controls than cases in several instances. To assess bias that this may have introduced, I conducted a sensitivity analysis where information on covariates was only assessed during covariate assessment window one (Figure 4.6). i.e. “Data on covariates (BMI and smoking) were captured using the earliest value recorded during the lookback period. If data were missing during this period, then the data were recorded as ‘missing’”.

4.4.9 Ethical approval

The contribution of patient level data to IMRD was approved by the NHS South-East Multicentre Research Ethics Committee in 2003. Under this approval, anonymised patient data can be provided to researchers following independent scientific review without the need for additional Research Ethics Committee approval. For this study, independent ethical approval was sought from the Scientific Research committee. Approval was obtained on 29/09/2018 (SRC reference 18THIN082 – Appendix 6.2.1).

4.4.10 Patient and public involvement:

I involved representatives from the University College Hospitals NHS Foundation Trust IBD Patient Panel in refining the research question and designing the study protocol (2.3.8).

4.5 Results:

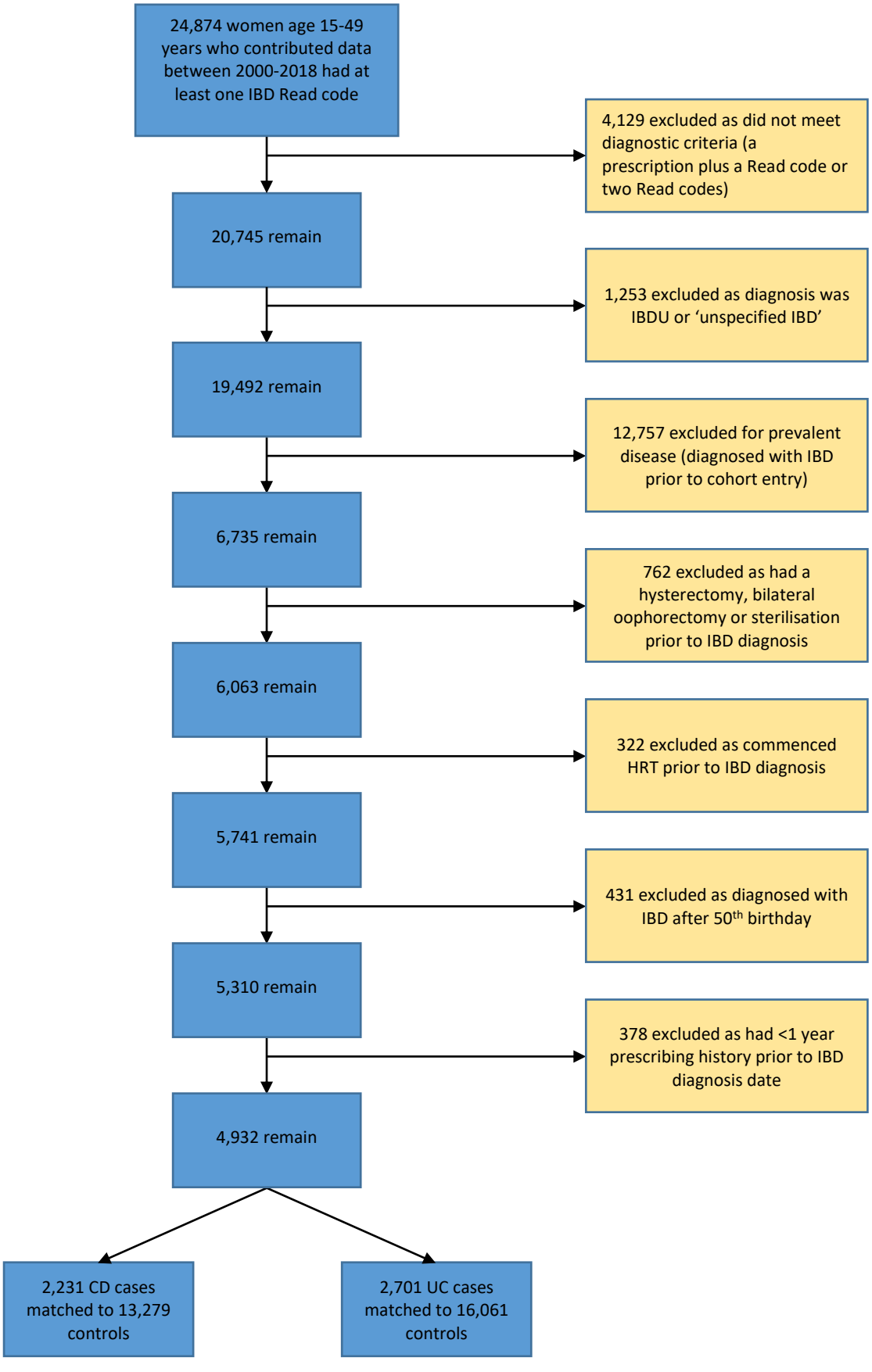
4.5.1 Source cohort

A source cohort of 3,202,575 women contributing 16,300,866 person-years of follow up was identified. Median (IQR) age at cohort entry was 28.2 (21.1-36.1) years. Overall incidence

was 14.7 (95% CI 14.1 -15.3) and 17.8 (95% CI 17.2-18.5) per 100,000 person-years for CD and UC respectively.

4.5.2 IBD cases and exclusions

After exclusions, 4,932 IBD cases were eligible for inclusion (Figure 4.7).



4.5.3 Demographics of cases and controls

2,231 incident cases of CD were matched to 13,279 controls and 2,701 incident cases of UC were matched to 16,061 controls. Median lookback period (IQR) was 5.4 (3.0-8.7) years in the CD study and 5.2 (2.9-8.8) years in the UC study. Median age (IQR) was 29.8 (22.9-38.3) for CD and 33.2 (26.4-40.1) for UC. Smoking was more common amongst cases than controls in the CD study (30.9% vs 22.4%) and less common amongst cases than controls in the UC study (20.8% vs 22.1%). Median BMI was similar across cases and controls for both studies (23.1-23.9) (Table 4.2).

Table 4.2. Patient demographics for cases and controls in the primary analysis

	Crohn's disease		**Ulcerative colitis**	
	cases (n= 2,231) (%)	**controls (n= 13,279) (%)**	**cases (n=2,701) (%)**	**controls (n=16,061) (%)**
Median age (IQR) (diagnosis/index date)	29.8 (22.9-38.3)	29.8 (22.9-38.3)	33.2 (26.4-40.1)	33.2 (26.4-40.1)
Townsend				
1	412 (18.5)	2,670 (20.1)	567 (21.0)	3,385 (21.1)
2	382 (17.1)	2,353 (17.7)	526 (19.5)	2,934 (18.3)
3	401 (17.8)	2,387 (18.0)	481 (17.8)	2,981 (18.6)
4	354 (15.9)	2,096 (15.8)	394 (14.6)	2,496 (15.5)
5	268 (12.0)	1,522 (11.5)	251 (9.3)	1,704 (10.6)
Missing	414 (18.6)	2,251 (17.0)	482 (17.9)	2,561 (16.0)
Body mass index				
Median (IQR)	23.6 (21.0-27.6)	23.8 (21.2-27.9)	23.1 (20.8-26.4)	23.9 (21.3-28.0)
Normal (18-25)	1,042 (46.7)	5,532 (41.7)	1,436 (53.2)	7,119 (44.3)
Overweight (25-30)	428 (19.2)	2,252 (17.0)	476 (17.6)	3,050 (19.0)
Obese (>30)	310 (13.9)	1,874 (14.1)	294 (10.9)	2,313 (14.4)
Underweight (<17)	81 (3.6)	358 (2.7)	91 (3.4)	380 (2.4)
Missing	370 (16.6)	3,263 (24.6)	404 (15.0)	3,199 (19.9)
Smoking				
Non-smoker	968 (43.4)	6,480 (48.8)	1,384 (51.2)	8,078 (50.3)
Ex-smoker	238 (10.7)	1,112 (8.4)	395 (14.6)	1,505 (9.4)
Smoker	690 (30.9)	2,980 (22.4)	563 (20.8)	3,552 (22.1)
Missing	335 (15.0)	2,707 (20.4)	359 (13.3)	2,926 (18.2)
Polycystic ovarian syndrome	56 (2.5)	328 (2.5)	58 (2.2)	464 (2.9)
Endometriosis	37 (1.7)	148 (1.1)	35 (1.3)	215 (1.3)

Pregnancy	630 (28.2)	3,553 (26.8)	867 (32.1)	4,606 (28.7)
Acne	341 (15.3)	2,333 (17.6)	491 (18.2)	2,710 (16.9)

4.5.4 Missing data

Amongst the 34,272 cases and controls, 5,708 (16.6%), 7,236 (21.1%) and 6,327 (18.5%) had missing data for Townsend score, BMI and smoking respectively. There were no other missing data. Missing data for Townsend score was similar across cases vs controls and exposed vs unexposed groups in both studies. However, IBD cases and patients exposed to contraceptives were more likely to have data recorded for BMI and smoking status (Table 4.3).

Table 4.3. Missing data overall and with respect to exposure and outcome across CD and UC studies

	Missing Townsend data	**Missing BMI data**	**Missing smoking data**
CD study			
Overall (n=15,510)	2,665 (17.2)	3,633 (23.4)	3,042 (19.6)
Cases (n=2,288)	414 (18.6)	370 (16.6)	335 (15.0)
Controls (n=13,279)	2,251 (17.0)	3,263 (24.6)	2,707 (20.4)
Exposed to any contraception during follow up (n=9,647)	1,685 (17.5)	1,486 (15.4)	1,117 (11.6)
Unexposed to any contraception during follow up (n=5,863)	980 (16.7)	2,147 (36.6)	1,925 (32.8)
UC study			
Overall (n=18,762)	3,043 (16.2)	3,603 (19.2)	3,285 (17.5)
Cases (n=2,701)	482 (17.9)	404 (15.0)	359 (13.3)
Controls (n=16,061)	2,561 (16.0)	3,199 (19.9)	2,926 (18.2)
Exposed to any contraception during follow up (n=11,198)	1,749 (15.6)	1,329 (11.9)	1,159 (10.4)
Unexposed to any contraception during follow up (n=7,564)	1,294 (17.1)	2,274 (30.1)	2,126 (28.1)

There was little difference in the other covariates across cases and controls after all individuals with any missing data were excluded (Table 4.4).

Table 4.4. Descriptive characteristics of cases and controls before and after exclusion of those with missing data

	Primary analysis		Excluding those with missing Townsend, BMI or smoking	
	cases (n= 4,932) (%)	**controls (n= 29,340) (%)**	**cases (n=3,055) (%)**	**controls (n=14,670) (%)**
Median age (IQR) (diagnosis/index date)	31.7 (24.7-39.4)	31.8 (24.7-39.4)	33.3 (26.4-40.4)	32,4 (25.7-40.3)
Polycystic ovarian syndrome	114 (2.3)	792 (2.7)	82 (2.7)	478 (3.3)
Endometriosis	72 (1.5)	363 (1.2)	56 (1.8)	198 (1.4)
Pregnancy	1,497 (30.4)	8,159 (27.8)	1,006 (32.9)	4,682 (31.9)
Acne	832 (16.9)	5,043 (17.2)	542 (17.7)	2,800 (19.1)

4.5.5 Case validation

Amongst the 4,932 IBD cases, 4,917 (99.7%) had at least one additional event supportive of the diagnosis recorded in the GP records (a prescription for IBD drugs, gastrointestinal symptoms in keeping with IBD, a referral to a gastroenterologist, an endoscopy) with 4,642 (94.1%) having at least two supporting events (Table 4.5) (Appendix 6.3.12/6.3.13/6.4.2).

Table 4.5. Algorithm for IBD cases accompanied by clinically relevant supporting events

Supporting event, n (%)	**Crohn's disease (%) n=2,231**	**Ulcerative colitis (%) n= 2,701**
Symptoms	1,975 (88.5)	2,274 (84.2)
Referral to gastroenterology	1,025 (45.9)	1,191 (44.1)
Endoscopy	1,545 (69.3)	1,617 (59.9)
Treatment with IBD drugs	2,059 (92.3)	2,661 (98.5)
Number of supporting events		
None	10 (0.4)	5 (0.2)
One	117 (5.2)	158 (5.8)
Symptoms	33 (28.2)	8 (5.1)
Referral to gastroenterology	1 (0.9)	2 (1.3)
Endoscopy	7 (6.0)	3 (1.9)
Treatment with IBD drugs	76 (65.0)	145 (91.8)
Two	481 (21.6)	704 (26.1)
Symptoms + referral to gastroenterology	19 (4.0)	7 (1.0)
Symptoms + endoscopy	45 (9.4)	5 (0.7)
Symptoms + treatment with IBD drugs	299 (62.2)	492 (69.9)
Referral to gastroenterology + treatment with IBD drugs	26 (5.4)	51 (7.2)
Referral to gastroenterology + endoscopy	3 (0.6)	0 (0.0)
Endoscopy + treatment with IBD drugs	89 (18.5)	149 (21.2)
Three	967 (43.3)	1,159 (42.9)
Symptoms + referral to gastroenterology + endoscopy	54 (5.6)	10 (0.9)
Symptoms + referral to gastroenterology + treatment with IBD drugs	222 (23.0)	374 (32.3)

Symptoms + endoscopy + treatment with IBD drugs	647 (66.9)	703 (60.7)
Referral to gastroenterology + endoscopy + treatment with IBD drugs	44 (4.6)	72 (6.2)
Four – Symptoms + referral to gastroenterology + endoscopy + use of IBD drugs	656 (29.4)	675 (25.0)

4.5.6 Crohn's disease:

Use of COCPs was associated with an increased risk of CD (OR 1.60 (95% CI 1.41-1.82). The increased risk was higher for second generation COCPs than newer COCPs when compared to non-use (OR 1.69 (95% CI 1.48-1.93) vs 1.25 (95% CI 1.01-1.57) respectively). Use of POPs and parenteral contraceptive methods were not associated with an increased risk of CD compared to non-use (OR 1.09 (95% CI 0.84-1.40) and 1.15 (95% CI 0.99-1.47) respectively) (Table 4.6/Figure 4.8).

The risk of CD went up with increasing duration of exposure to COCPs (Figure 4.9). When treating 'average months of COCP exposure per year' as a continuous linear variable, each additional month per year of COCP exposure, increased risk of CD by 6.4% (95% CI 5.1-7.7) compared to non-users. When treating average daily dose of oral oestrogen over follow up as a continuous linear variable, CD risk increased by 3.1% (95% CI 2.5-3.7) per mcg/day of ethinylestradiol (or equivalent) compared to non-users. Longer durations of exposure to POPs had no effect on CD risk (OR 0.99 (95% CI 0.97-1.02)).

The risk of CD was increased further amongst current users of COCPs (OR 2.12 (95% CI 1.83-2.44) & 1.64 (95% CI 1.33-2.01) for second generation and newer COCPs respectively). However, amongst current COCP users, there was no difference in CD risk for those using low strength oestrogen pills compared to standard strength oestrogen pills (OR 1.16 (95% CI 0.74-1.80)).

Table 4.6. Adjusted odds ratios for Crohn's disease and ulcerative colitis by contraceptive exposure in the primary analysis

	Crohn's disease			Ulcerative colitis		
	Cases n(%) n=2,231	Controls n(%) n=13,279	Adjusted odds ratio (95% CI) †	Cases n(%) n=2,701	Controls n(%) n=16,061	Adjusted odds ratio (95% CI) †
Non-user	659 (29.5)	5,204 (39.2)	1 (reference)	921 (34.1)	6,643 (41.4)	1 (reference)
2nd gen user	622 (27.9)	2,819 (21.2)	1.69 (1.48-1.93)	573 (21.2)	3,008 (18.7)	1.27 (1.12-1.44)
Newer gen user	117 (5.2)	728 (5.5)	1.25 (1.01-1.57)	165 (6.1)	822 (5.1)	1.38 (1.14-1.67)
POP user	81 (3.6)	537 (4.0)	1.09 (0.84-1.40)	138 (5.1)	760 (4.7)	1.25 (1.03-1.53)
Parenteral method user	150 (6.7)	879 (6.6)	1.21 (0.99-1.47)	195 (7.2)	1,166 (7.3)	1.17 (0.98-1.39)
Mixed user	602 (27.0)	3,112 (23.4)	1.50 (1.30-1.72)	709 (26.3)	3,662 (22.8)	1.31 (1.15-1.48)

†Adjusted for social deprivation by Townsend score, smoking status, BMI, history of PCOS, history of endometriosis, history of acne, history of pregnancy. All odds ratios are generated using non-use as the reference group

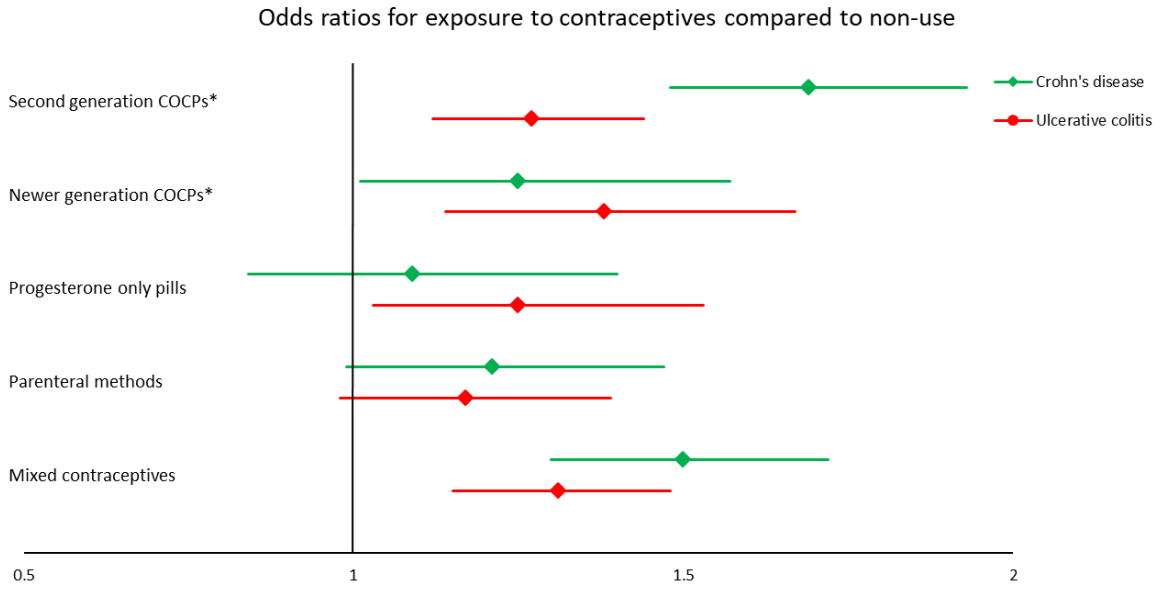


Figure 4.8. Adjusted odds ratios for Crohn's disease and ulcerative colitis exposed to contraceptives compared with non-use in the primary analysis. Odds ratios with 95% confidence intervals are adjusted for Townsend score, body mass index, smoking status and history of polycystic ovarian syndrome, endometriosis, acne and pregnancy

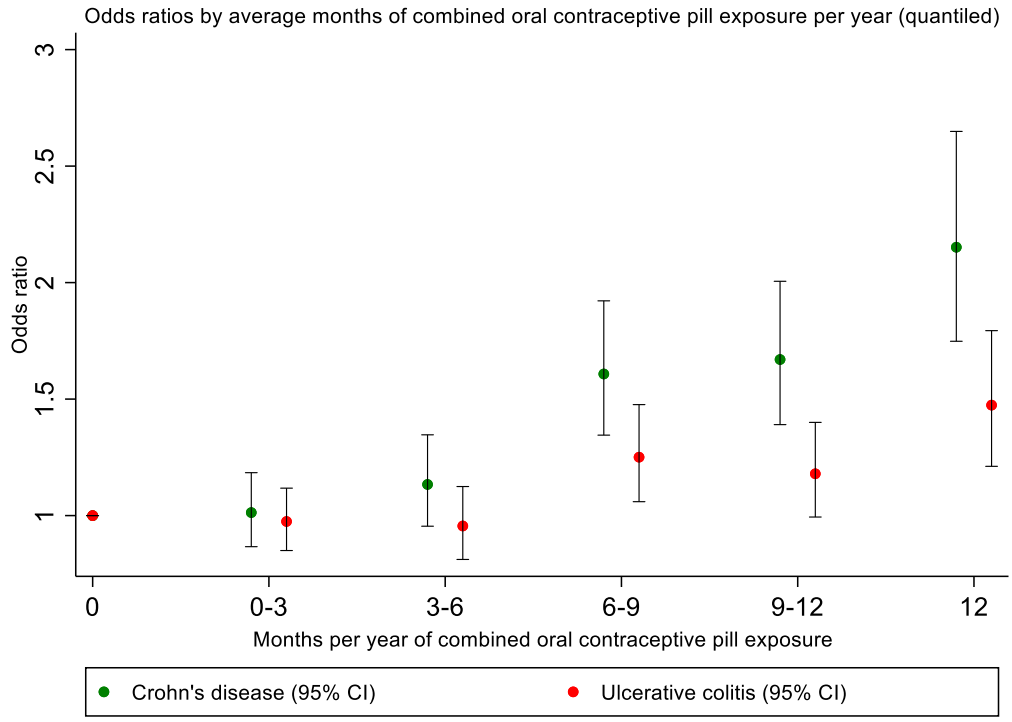


Figure 4.9. Adjusted odds ratios for Crohn's disease and ulcerative colitis exposed to combined oral contraceptive pills (COCPs) compared to non-use in the primary analysis. Average months per year of exposure to COCPs is stratified in three-monthly quantiles. Odds ratios and 95% confidence intervals are adjusted for Townsend score, body mass index, smoking status and history of polycystic ovarian syndrome, endometriosis, acne and pregnancy

4.5.7 Ulcerative colitis

I found use of all types of OCPs to be associated an increase in risk of UC; OR 1.27 (95% CI 1.12-1.44) for second generation COCPs, 1.38 (95% CI 1.14-1.67) for newer generation COCPs and 1.25 (95% CI 1.03-1.53) for POPs. Parenteral methods had no effect on UC risk (OR 1.17 (95% CI 0.98-1.39)) (Table 4.6/Figure 4.8).

When treating 'average months of COCP exposure per year' as a continuous linear variable, each additional month per year of COCP exposure, increased risk of UC by 3.3% (95% CI 2.1-4.4) compared to non-users, equating to an additional 1.7% (95% CI 1.1-2.2) increase in risk per mcg/day of ethinylestradiol (or equivalent) (Figure 4.9). However, a similar dose-response relationship was not observed with POPs (OR 1.02 (95% CI 1.00-1.04).

Risk of UC increased for all types of OCP amongst current users; OR 1.48 (95% CI 1.29-1.69) for second generation COCPs, 1.62 (95% CI 1.34-1.95) for newer generation COCPs and 1.35 (95% CI 1.12-1.64) for POPs (Table 4.7). Amongst current COCP users, there was no difference in UC risk for those using low strength oestrogen pills compared to standard strength oestrogen pills (OR 1.33 (95% CI 0.81-2.18)).

Table 4.7. Numbers, proportions and adjusted odds ratios for Crohn's disease and ulcerative colitis by current contraceptive exposure

	Crohn's disease			Ulcerative colitis		
	Cases n(%) n=2,231	Controls n(%) n=13,279	Adjusted odds ratio (95% CI) †	Cases n(%) n=2,701	Controls n(%) n=16,061	Adjusted odds ratio (95% CI) †
Non-user	659 (29.5)	5,204 (39.2)	1 (reference)	921 (34.1)	6,643 (41.4)	1 (reference)
Current second gen COCP user	544 (24.4)	1,993 (15.0)	2.12 (1.83-2.43)	458 (17.0)	2,033 (12.7)	1.48 (1.29-1.69)
Current newer gen COCP user	155 (7.0)	751 (5.7)	1.64 (1.33-2.01)	187 (6.9)	763 (4.8)	1.62 (1.34-1.95)
Current POP user	107 (4.8)	633 (4.8)	1.21 (0.96-1.52)	156 (5.8)	778 (4.8)	1.35 (1.12-1.64)
Current parenteral method user	225 (10.1)	1,304 (9.8)	1.23 (1.04-1.47)	295 (10.9)	1,608 (10.0)	1.25 (1.07-1.45)
Mixed past contraceptive user	541 (24.3)	3,394 (25.6)	1.19 (1.04-1.36)	684 (25.3)	4,236 (26.4)	1.09 (0.97-1.23)

†Adjusted for social deprivation by Townsend score, smoking status, BMI, history of PCOS, history of endometriosis, history of acne, history of pregnancy. All odds ratios are generated using non-use as the reference group

4.5.8 Interactions

I found the association between COCP exposure and UC to be greater in non-smokers (p=0.03) (Table 4.8). I observed no other interactions between OCP exposure and smoking on development of either CD or UC (Table 4.9/Table 4.10).

Table 4.8. Interaction coefficients (adjusted OR†) for smoking & combined oral contraceptive pill exposure interactions

Smoking status	**CD (95% CI) p= 0.35**	**UC (95% CI) p= 0.03**
Never smoker	1.05 (1.04-1.07)	1.04 (1.02-1.05)
Ex-smoker	1.07 (1.04-1.10)	1.01 (0.99-1.04)
Current smoker	1.07 (1.05-1.09)	1.01 (0.99-1.04)
Missing	1.08 (1.05-1.11)	1.07 (1.04-1.10)

†Adjusted for social deprivation by Townsend score, smoking status, body mass index, history of polycystic ovarian syndrome, history of endometriosis, history of acne, history of pregnancy

Table 4.9. Interaction coefficients (adjusted OR†) for smoking & progestogen-only pill exposure interactions

Smoking status	CD (95% CI) p= 0.12	UC (95% CI) p=0.13
Never smoker	0.98 (0.94-1.02)	1.00 (0.97-1.04)
Ex-smoker	0.98 (0.91-1.06)	1.00 (0.94-1.05)
Current smoker	0.99 (0.95-1.04)	1.06 (1.01-1.10)
Missing	1.10 (1.00-1.19)	0.98 (0.88-1.09)

† Adjusted for social deprivation by Townsend score, smoking status, body mass index, history of polycystic ovarian syndrome, history of endometriosis, history of acne, history of pregnancy

Table 4.10. Interaction coefficients (adjusted OR†) for smoking & 'any oral contraceptive pill' exposure interactions

Smoking status	CD (95% CI) p= 0.17	UC (95% CI) p= 0.11
Never smoker	1.05 (1.03-1.06)	1.03 (1.02-1.05)
Ex-smoker	1.06 (1.03-1.09)	1.01 (0.99-1.04)
Current smoker	1.06 (1.04-1.08)	1.03 (1.00-1.05)
Missing	1.08 (1.05-1.12)	1.06 (1.03-1.09)

†Adjusted for social deprivation by Townsend score, smoking status, body mass index, history of polycystic ovarian syndrome, history of endometriosis, history of acne, history of pregnancy

4.5.9 Secular trends

I found no evidence of temporal changes in the relationship between OCPs and CD or UC (Table 4.11).

Table 4.11. Adjusted odds ratios for Crohn's disease and ulcerative colitis by any OCP exposure. Results are stratified by calendar period in five-yearly quantiles

	Crohn's disease			Ulcerative colitis		
Year	**Cases n(%) n=2,231**	**Controls n(%) N=13,279**	**Adjusted odds ratio (95% CI) †**	**Cases n(%) n=2,701**	**Controls n(%) n=16,061**	**Adjusted odds ratio (95% CI) †**
2000-2004	427 (19.1)	2,538 (19.1)	1.51 (1.15-1.95)	524 (19.4)	3,134 (19.5)	1.29 (1.02-1.63)
2005-2009	749 (33.6)	4,470 (33.7)	1.62 (1.30-2.00)	856 (31.7)	5,107 (31.8)	1.20 (0.99-1.46)
2010-2014	710 (31.8)	4,214 (31.7)	1.36 (1.09-1.70)	858 (31.8)	5,075 (31.6)	1.30 (1.06-1.58)
2015-2018	345 (15.5)	2,057 (15.5)	1.38 (0.99-1.95)	463 (17.1)	2,745 (17.1)	1.40 (1.05-1.87)

†Adjusted for social deprivation by Townsend score, smoking status, BMI, history of polycystic ovarian syndrome, history of endometriosis, history of acne, history of pregnancy. All odds ratios are generated using non-use as the reference group

4.5.10 Sensitivity analyses

4.5.10.1 Sensitivity analysis one: Exclusion of OCP switchers in the year prior to IBD diagnosis/index date

For the CD study, the mean number of OCP scripts per patient in the year preceding the diagnosis/index was 1.08 for cases and 0.75 for controls. 104 (4.7%) cases switched OCP during this time period (switch was defined as two or more prescriptions for different OCPs within the year) and 532 (4.0%) switched amongst controls. In the UC study, the average number of OCP scripts in the year preceding diagnosis/index date was 0.85 for cases and 0.64 for controls. 110 (4.1%) cases and 483 (3.0%) controls switched OCP during the same time period.

Following exclusion of those who switched OCP in the year prior to the index date/diagnosis date, when treating 'months of COCP exposure per year' as a continuous linear variable, there was little change in the association with IBD in comparison to the primary analysis (OR 1.07 (95% CI 1.05-1.08) vs 1.06 (95% CI 1.05-1.08) for CD and OR 1.03 (95% CI 1.02-1.04) vs 1.03 (95% CI 1.02-1.04 for UC). I found no evidence of a non-linear relationship between exposure and outcome following exclusion of switchers (Figure 4.10).

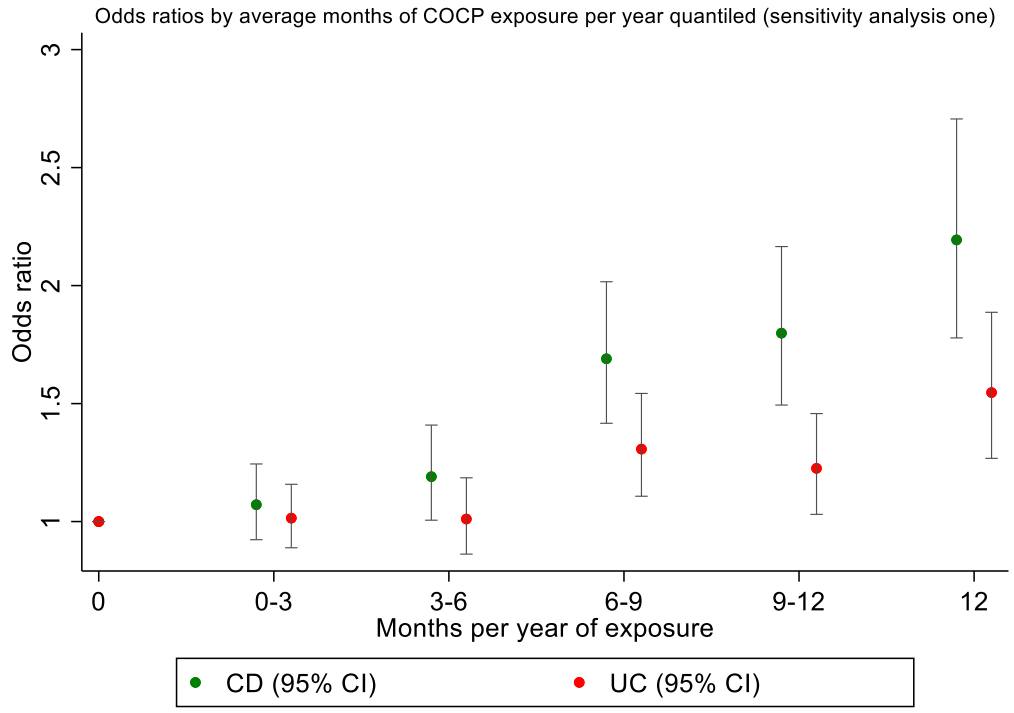


Figure 4.10. Adjusted odds ratios for Crohn's disease and ulcerative colitis exposed to combined oral contraceptive pills (COCPs) compared to non-use with the exclusion of those who switched OCP in the year preceding diagnosis. Average months per year of exposure to COCPs is stratified in three-monthly quantiles. Odds ratios and 95% confidence intervals are adjusted for Townsend score, body mass index, smoking status and history of polycystic ovarian syndrome, endometriosis, acne and pregnancy

4.5.10.2 Sensitivity analysis two: Stratifying contraceptive exposure using more levels

When stratifying COCPs and parenteral contraception by more levels (splitting up newer generation COCPs and LARC into individual types of contraception), more patients were classed as 'mixed users' which impacted sample size for individual methods. ORs between the various subtypes of newer COCPs were wider and crossed the null value. The only new finding was a modest association between IUD/IUS and CD (OR 1.40 (95% CI 1.08-1.81) (Table 4.12).

Table 4.12. Numbers, proportions and adjusted odds ratios for Crohn's disease and ulcerative colitis by contraceptive exposure (sensitivity analysis two: Stratifying exposure by more levels)

	Crohn's disease			Ulcerative colitis		
	Cases n(%) n=2,231	**Controls n(%) n=13,279**	**Adjusted odds ratio (95% CI) †**	**Cases n(%) n=2,701**	**Controls n(%) n=16,061**	**Adjusted odds ratio (95% CI) †**
Non-user	659 (29.5)	5,204 (39.2)	1 (reference)	921 (34.1)	6,643 (41.4)	1 (reference)
2nd gen COCP user	622 (27.9)	2,819 (21.2)	1.69 (1.48-1.93)	573 (21.2)	3,008 (18.7)	1.28 (1.13-1.45)
3rd gen COCP user	60 (2.7)	332 (2.5)	1.34 (1.00-1.81)	85 (3.2)	406 (2.5)	1.42 (1.11-1.83)
4th gen COCP user	26 (1.2)	117 (0.9)	1.74 (1.12-2.72)	24 (0.9)	149 (0.9)	1.09 (0.70-1.71)
Co-cyprindiol user	20 (0.9)	196 (1.5)	0.84 (0.52-1.36)	34 (1.3)	178 (1.1)	1.42 (0.97-2.08)
POP user	81 (3.6)	537 (4.0)	1.09 (0.84-1.40)	138 (5.1)	760 (4.7)	1.22 (1.10-1.48)
Injectable contraceptive user	45 (2.0)	281 (2.1)	1.06 (0.75-1.48)	57 (2.1)	321 (2.0)	1.25 (0.93-1.69)
Implant user	12 (0.5)	116 (0.9)	0.79 (0.43-1.46)	18 (0.7)	129 (0.8)	0.99 (0.60-1.65)
IUD/IUS user	82 (3.7)	424 (3.2)	1.40 (1.08-1.81)	106 (3.9)	651 (4.1)	1.11 (0.89-1.38)
Mixed user	602 (27.0)	3,112 (23.4)	1.48 (1.29-1.71)	745 (27.6)	3,816 (23.8)	1.32 (1.16-1.49)

†Adjusted for social deprivation by Townsend score, smoking status, BMI, history of PCOS, history of endometriosis, history of acne, history of pregnancy. All odds ratios are generated using non-use as the reference group

4.5.10.3 Sensitivity analysis three: Exclusion of those case-control pairs with less than five years of prescribing history

2,292 (46.5%) cases and 13,717 (46.8%) controls were excluded. There was minimal change to the odds ratios relating to parenteral contraception after exclusions (1.27 (0.96-1.68) vs 1.21 (0.99-1.47) for CD and 1.25 (0.98-1.59) vs 1.17 (0.98-1.39) for UC) (Table 4.13).

Table 4.13. Numbers, proportions and adjusted odds ratios for Crohn's disease and ulcerative colitis by contraceptive exposure

	Crohn's disease			Ulcerative colitis		
	Cases n(%) n=1,220	**Controls n(%) n=7,234**	**Adjusted odds ratio (95% CI) †**	**Cases n(%) n=1,420**	**Controls n(%) n=8,389**	**Adjusted odds ratio (95% CI) †**
Non-user	258 (21.2)	2,185 (30.2)	1 (reference)	357 (25.1)	2,704 (32.2)	1 (reference)
2nd gen user	318 (26.1)	1,553 (21.5)	1.62 (1.33-1.98)	294 (20.7)	1,589 (18.9)	1.29 (1.07-1.55)
Newer gen user	55 (4.5)	330 (4.6)	1.30 (0.93-1.80)	72 (5.1)	360 (4.3)	1.37 (1.03-1.83)
POP user	43 (3.5)	251 (3.5)	1.27 (0.89-1.82)	53 (3.7)	347 (4.1)	1.13 (0.82-1.54)
Parenteral method user	82 (6.7)	477 (6.6)	1.27 (0.96-1.68)	105 (7.4)	611 (7.3)	1.25 (0.98-1.59)
Mixed user	464 (38.0)	2,438 (33.7)	1.47 (1.22-1.78)	539 (38.0)	2,778 (33.1)	1.36 (1.15-1.61)

†Adjusted for social deprivation by Townsend score, smoking status, BMI, history of PCOS, history of endometriosis, history of acne, history of pregnancy. All odds ratios are generated using non-use as the reference group

4.5.10.4 Sensitivity analysis four: Restricting analysis time to a shorter lookback period

When calculating odds ratios for 'months per year of COCP use' as a continuous linear variable separately for each calendar year for 1-10 years prior to IBD diagnosis/index date, exposure closer to diagnosis date was more strongly associated with IBD for both CD and UC (Figure 4.11). I conducted a sensitivity analysis restricting lookback time to five years across all case-control pairs. Additional prescribing history was discounted. Case-control pairs with less than five years of prescribing history were excluded.

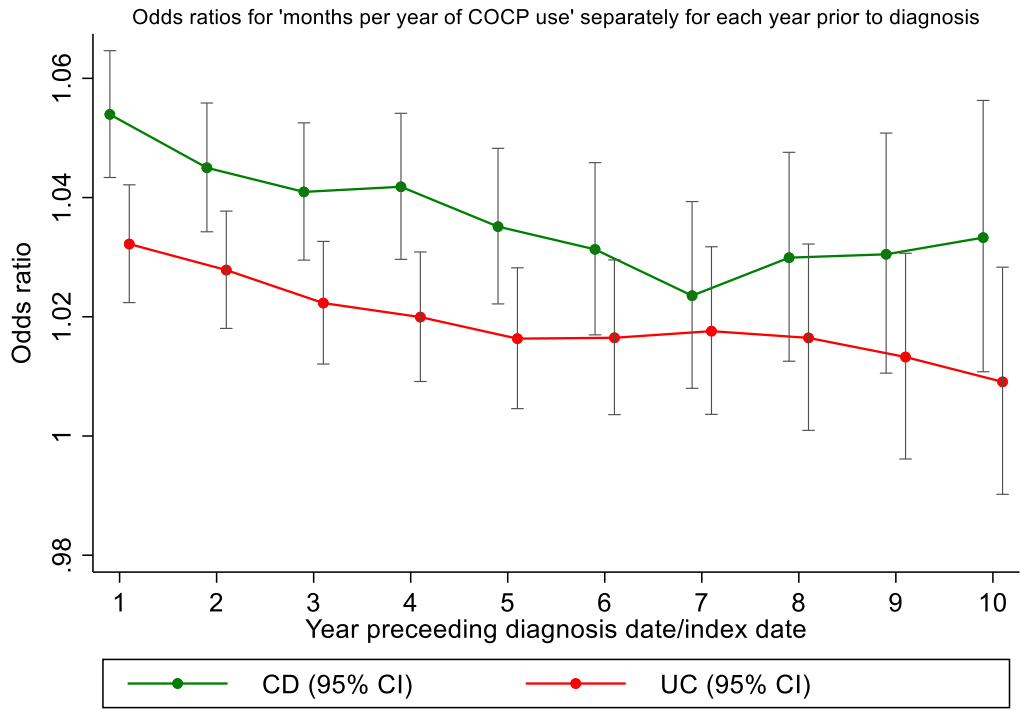


Figure 4.11. Adjusted odds ratios for CD and UC by 'months per year of COCP use' (treated as a continuous linear variable) calculated separately for each year prior to diagnosis/index date. Reference value is 'non-use'. Odds ratios and 95% confidence intervals are adjusted for Townsend score, body mass index, smoking status and history of polycystic ovarian syndrome, endometriosis, acne and pregnancy

Table 4.14. Numbers, proportions and adjusted odds ratios for Crohn's disease and ulcerative colitis by contraceptive exposure (sensitivity analysis four: Exclusion of those case-control pairs with less than five years of prescribing history and restriction of lookback time to five years)

	Crohn's disease			Ulcerative colitis		
	Cases n(%) n=1,220	**Controls n(%) n=7,234**	**Adjusted odds ratio (95% CI) †**	**Cases n(%) n=1,420**	**Controls n(%) n=8,389**	**Adjusted odds ratio (95% CI) †**
Non-user	368 (30.2)	2,834 (39.2)	1 (reference)	497 (35.0)	3,590 (42.8)	1 (reference)
2nd gen COCP user	314 (25.7)	1,443 (20.0)	1.62 (1.33-1.98)	277 (19.5)	1,468 (17.5)	1.29 (1.07-1.55)
Newer gen COCP user	75 (6.2)	348 (4.8)	1.30 (0.93-1.80)	92 (6.5)	381 (4.5)	1.37 (1.02-1.83)
POP user	62 (5.1)	396 (5.5)	1.27 (0.89-1.82)	94 (6.6)	487 (5.8)	1.13 (0.82-1.55)
Parenteral method user	100 (8.2)	648 (9.0)	1.27 (0.96-1.68)	142 (10.0)	815 (9.7)	1.25 (0.98-1.59)
Mixed user	301 (24.7)	1,565 (21.6)	1.47 (1.22-1.78)	318 (22.4)	1,648 (19.6)	1.36 (1.15-1.61)

†Adjusted for social deprivation by Townsend score, smoking status, BMI, history of PCOS, history of endometriosis, history of acne, history of pregnancy. All odds ratios are generated using non-use as the reference group

2,292 (46.5%) cases and 13,717 (46.8%) controls were excluded. After exclusions, the only discernible difference from the primary analysis (aside from generally wider 95% CIs due to reduction in study power), was that there was no longer an association between POPs and UC (1.13 (95% CI 0.82-1.55) vs 1.25 (95% CI 1.03-1.53) (Table 4.14).

4.5.10.5 Sensitivity analysis five: Treating BMI as a continuous variable and excluding those with missing BMI

When treating BMI as a continuous variable and excluding those with missing BMI, 774 (15.7%) cases and 6,462 (22.0%) controls were excluded. Results were similar to the primary analysis across all methods of contraception for both CD and UC. However, confidence intervals were wider and crossed the null value for CD and newer generation COCPs (Table 4.15).

Table 4.15. Numbers, proportions and adjusted odds ratios for Crohn's disease and ulcerative colitis by contraceptive exposure (Sensitivity analysis five: women with missing BMI excluded and BMI treated as a continuous variable)

	Crohn's disease			Ulcerative colitis		
	Cases n(%) n=1,861	Controls n(%) n=10,016	Adjusted odds ratio (95% CI) †	Cases n(%) n=2,297	Controls n(%) n=12,862	Adjusted odds ratio (95% CI) †
Non-user	496 (26.7)	3,220 (32.2)	1 (reference)	712 (31.0)	4,578 (35.6)	1 (reference)
2nd gen COCP user	523 (28.1)	2,259 (22.6)	1.57 (1.34-1.83)	500 (21.8)	2,534 (19.7)	1.24 (1.08-1.42)
Newer gen COCP user	99 (5.3)	608 (6.1)	1.11 (0.87-1.44)	149 (6.5)	713 (5.5)	1.31 (1.06-1.61)
Progestogen-only pill user	71 (3.8)	456 (4.6)	0.96 (0.73-1.26)	125 (5.4)	680 (5.3)	1.27 (1.03-1.58)
Parenteral method user	129 (6.9)	757 (7.6)	1.06 (0.85-1.33)	175 (7.6)	1,018 (7.9)	1.15 (0.95-1.38)
Mixed user	543 (29.2)	2,716 (27.1)	1.37 (1.16-1.60)	636 (27.7)	3,339 (26.0)	1.23 (1.07-1.41)

†Adjusted for social deprivation by Townsend score, smoking status, BMI, history of polycystic ovarian syndrome, history of endometriosis, history of acne, history of pregnancy. All odds ratios are generated using non-use as the reference group.

4.5.10.5.1 Sensitivity analyses 6a & 6b: Changes to covariate assessment windows

4.5.10.5.1.1 Sensitivity analysis 6a: Adding an additional covariate assessment window

When adding an additional covariate assessment window after the index date/diagnosis date, missing data for BMI and smoking was reduced compared to the primary analysis (21.1% vs 13.4% for BMI and 18.5% vs 5.8% for smoking) (Table 4.16). Compared to the primary analysis, there was minimal difference in results across all methods of contraception when adding the additional covariate assessment window (Table 4.17).

4.5.10.5.1.2 Sensitivity analysis 6b: Removing a covariate assessment window

When removing a covariate assessment so that information on BMI and smoking was only ascertained during the lookback period, missing data was dramatically increased. Missing data for BMI increased by 58.9% from 774 (15.7%) to 1,230 (24.5%) amongst cases and by 94.2% from 6,462 (22.0%) to 12,553 (42.8%) amongst controls. Missing data for smoking increased by 38.8% from 694 (14.1%) to 963 (19.5%) amongst cases and by 66.4% from 5,633 (19.2%) to 9,374 (31.9%) amongst controls (Table 4.16). Odds ratios were closer to

unity with an observed reduction in the association between contraception and IBD across all methods (Table 4.17). The only OR which did not cross the null value in this sensitivity analysis was the association between second generation COCPs and CD (OR 1.39 (95% CI 1.21-1.59)).

Table 4.16. Comparison of missing data for primary analysis and sensitivity analyses 6a & 6b

	Missing BMI data			Missing smoking data		
	Primary analysis	**Analysis 6a**	**Analysis 6b**	**Primary analysis**	**Analysis 6a**	**Analysis 6b**
CD study						
Overall (n=15,510)	3,633 (23.4)	2,288 (14.8)	6,296 (40.6)	3,042 (19.6)	915 (5.9)	4,645 (30.0)
Cases (n=2,231)	370 (16.6)	211 (9.2)	560 (25.1)	335 (15.0)	61 (2.7)	446 (20.0)
Controls (n=13,279)	3,263 (24.6)	2,077 (15.6)	5,736 (43.2)	2,707 (20.4)	854 (6.4)	4,199 (31.6)
Exposed to any contraception during follow up (n=9,647)	1,486 (15.4)	865 (9.0)	2,643 (27.4)	1,117 (11.6)	219 (2.3)	1,738 (18.0)
Unexposed to any contraception during follow up (n=5,863)	2,147 (36.6)	1,423 (24.3)	3,653 (62.3)	1,925 (32.8)	696 (11.9)	2,907 (49.6)
UC study						
Overall (n=18,762)	3,603 (19.2)	2,366 (12.6)	7,487 (39.9)	3,285 (17.5)	1,059 (5.6)	5,692 (30.3)
Cases (n=2,701)	404 (15.0)	232 (8.6)	670 (24.8)	359 (13.3)	76 (2.8)	517 (19.1)
Controls (n=16,061)	3,199 (19.9)	2,134 (13.3)	6,817 (42.4)	2,926 (18.2)	983 (6.1)	5,175 (32.2)
Exposed to any contraception during follow up (n=11,198)	1,329 (11.9)	834 (7.4)	2,889 (25.8)	1,159 (10.4)	238 (2.1)	2,028 (18.1)
Unexposed to any contraception during follow up (n=7,564)	2,274 (30.1)	1,532 (20.3)	4,598 (60.8)	2,126 (28.1)	821 (10.9)	3,664 (48.4)

Table 4.17. Adjusted odds ratios for Crohn's disease and ulcerative colitis by contraceptive exposure. Comparing primary analysis to sensitivity analysis 6a & 6b

	Crohn's disease Adjusted odds ratio (95% CI) †			**Ulcerative colitis** Adjusted odds ratio (95% CI) †		
	Primary analysis	**Analysis 6a**	**Analysis 6b**	**Primary analysis**	**Analysis 6a**	**Analysis 6b**
Non-user	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
2nd gen user	1.69 (1.48-1.93)	1.74 (1.53-1.99)	1.39 (1.21-1.59)	1.27 (1.12-1.44)	1.27 (1.13-1.44)	0.97 (0.86-1.10)
Newer gen user	1.25 (1.01-1.57)	1.30 (1.04-1.62)	1.04 (0.83-1.30)	1.38 (1.14-1.67)	1.37 (1.14-1.66)	1.07 (0.88-1.31)
POP user	1.09 (0.84-1.40)	1.10 (0.86-1.42)	0.89 (0.68-1.15)	1.25 (1.03-1.53)	1.28 (1.05-1.56)	0.99 (0.81-1.22)
Parenteral method user	1.21 (0.99-1.47)	1.24 (1.01-1.51)	1.05 (0.85-1.28)	1.17 (0.98-1.39)	1.18 (0.99-1.40)	0.99 (0.83-1.17)
Mixed user	1.50 (1.30-1.72)	1.54 (1.34-1.77)	1.20 (1.04-1.39)	1.31 (1.15-1.48)	1.33 (1.17-1.50)	1.00 (0.88-1.14)

†Adjusted for social deprivation by Townsend score, smoking status, BMI, history of PCOS, history of endometriosis, history of acne, history of pregnancy. All odds ratios are generated using non-use as the reference group

4.6 Discussion:

4.6.1 Overall summary

This is the first study to describe IBD diagnosis in relation to a range of different contraceptives including progestogen-only methods. I observed an increase in risk of CD and a more modest increase in risk of UC with increasing durations of exposure to COCPs. IBD diagnosis was higher amongst current users of COCPs than past users. There was no association between POP exposure and CD, but UC risk was slightly increased amongst POP users. However, the association was not greater with increasing durations of exposure. There was no association between use of parenteral progestogen-only contraception and IBD. Although there were inconsistencies, these findings are broadly in accordance with the hypothesis that oestrogen-containing contraception is associated with development of IBD.

4.6.2 Strengths

Study strengths include the large number of included cases and controls and the use of electronic health care records from a database which has been shown to be generalisable to

the general UK population. Unlike other studies that have relied on self-reporting of historic contraceptive use which is a potential source of recall bias (5.3.2), these data are based on prospectively collected electronic prescribing records which include detailed information on treatment duration, formulation and dosage. In comparison to other case-control studies, where controls have been peer-nominated or recruited from clinic, all women aged 15-49 years from IMRD were eligible for inclusion, thus minimising selection bias (5.3.3).

4.6.3 Limitations

4.6.3.1 Misclassification of exposure to contraceptives:

Although the vast majority of women in the UK obtain OCPs from primary care, this study does not capture those contraceptives obtained from sexual and reproductive health (SRH) services. In the UK, 5% of females aged 13 to 54 years used an SRH service for reasons of contraception between 01/04/2019 and 31/03/2020 (100). Additionally, although IMRD includes robust and detailed prescribing data, we were unable to capture information on patient adherence. It has been reported that up to 52% of women miss their OCP once or more per month with 14% missing twice or more per month (253). These factors could potentially result in a shift in the odds ratios towards unity and an underestimate in the effect of contraceptives on IBD risk. On the other hand, in some cases I may have underestimated oestrogen exposure. This could occur when a woman takes packs of COCPs back-to-back, without a seven-day break to avoid a withdrawal bleed. In this study it was presumed that COCPs were taken as standard (21 days per month with a seven-day break). If oestrogen exposure has been underestimated then this could lead to an overestimate in the effect of oestrogen on IBD risk.

4.6.3.2 Sample size

Although our sample size was large, we lacked statistical power to analyse newer classes of COCPs separately; third generation, fourth generation and co-cyprindiol were grouped together, as were parenteral (LARC) methods.

4.6.3.3 Misclassification of IBD

I was not able to confirm the cases with radiological, endoscopic or histological findings. Therefore, it is possible that a small number were misclassified. As per chapter two, linkage of patients to Hospital Episode Statistics (HES) data may have assisted in the validation of coding for IBD in primary care.

4.6.3.4 Timing of IBD diagnosis date

Although a validation paper has shown that the median time between IBD diagnosis and the electronic recording in the primary care records is only eight days (80), there are bound to be delays in IBD diagnosis for a myriad of other reasons such as hesitancy in seeking medical attention, misdiagnosis, or extended wait times for colonoscopy and gastroenterology outpatient appointments. Additionally, it has been shown in another primary care database (CPRD) that there is an excess of GI symptoms up to five years before diagnosis of IBD compared to the background population which may be attributable to undiagnosed disease (254). This could introduce bias if I have included contraceptive exposure after a woman has already developed IBD; Developing a new chronic illness is likely to influence contraceptive uptake. This could be because women who are unwell, may be less likely to have sex and do not require contraception. Alternatively, women being worked up for a chronic disease may

feel that this is an important time to avoid pregnancy, thus ensure they are covered with contraception.

4.6.4 Comparisons with existing literature

In keeping with published literature, I found an association between OCP use and risk of IBD (108, 109, 138). My overall odds ratios for OCP exposure in relation to IBD were very similar to a meta-analysis including 20 studies published in 2017; 1.51 (95% CI 1.34-1.71) vs 1.32 (95% CI 1.17-1.49) for CD and 1.29 (95% CI 1.15-1.44) vs 1.30 (95% CI 1.13-1.49) for UC (109). In comparison to a smaller nested-case control study from the Asia-Pacific region, I observed similar odds ratios for newer generations of OCPs (1.25 (95% CI 1.01-1.57) vs 1.31 (95% CI 0.55-1.99) for CD and 1.38 (95% CI 1.14-1.67) vs 1.20 (95% CI 0.70-1.70) for UC) (159). However, they concluded that these associations were non-significant which could be explained by insufficient study power. In keeping with the small number of previous studies looking at duration of OCP exposure, I found that risk of IBD increased with longer periods of exposure. I observed a more than doubling in risk of CD in those taking COCPs continuously throughout follow up.

4.6.5 Novel findings

No previous studies have looked at IBD risk specifically in relation to progestogen-only contraceptive methods and our finding that increased CD risk was isolated to oestrogen containing contraception is novel. Of note, a study exploring associations between OCPs and disease outcomes in CD found that there was an increased risk of surgery in those taking COCPs but not progestogen-only methods (136). Although I found no difference in IBD risk between users of low strength and standard strength oestrogen containing COCPS, it should

be noted that differences in oestrogen content amongst most OCPs are small (usually containing 20-35mcg ethinylestradiol or equivalent). This is not true for historic first-generation pills which contained higher doses of sex hormones and were not included in this study.

I identified no effect of parenteral contraception on IBD risk. This could support an argument that OCPs may be having a local effect on the gut wall or gut microbiota to drive disease pathogenesis. However, it is important to note the parenteral contraceptive users in this study represent a mixed and relatively small group, some using methods that primarily act locally such as the IUS and others that work systemically such as injectable progestogens and implants. Importantly, all of the parenteral contraceptives included were progestogen-only or non-hormonal methods.

4.6.6 Interactions

I found no interaction between smoking and OCP exposure on CD risk. Contrary to a large US cohort study (157), I found that development of UC was slightly more associated with non-smokers taking COCPs (Table 4.8). However, I did not observe this effect for POPs or OCPs overall (Table 4.9/Table 4.10). It has been hypothesised that an interaction between smoking and OCP exposure could be mediated by the synergistic effect of oestrogen and carbon monoxide on TH-2 mediation (157). However, my findings would not support this hypothesis. I was unable to identify a plausible biological mechanism for my finding and as the association was small ($p=0.03$), it is likely to be represented by chance.

4.6.7 Sensitivity analyses

4.6.7.1 Sensitivity analysis one: Exclusion of OCP switchers in the year prior to IBD diagnosis/index date

Slightly more patients switched OCP amongst cases than controls in the year preceding the IBD diagnosis date/index date across both studies (104 (4.7%) vs 532 (4.0%) for CD and 110 (4.1%) vs 483 (3.0%) for UC). However, after exclusion of these 'switchers', minimal difference in the association between OCP exposure and development of IBD was observed. This would not support an argument that increased switching of contraceptives amongst IBD cases biased results.

4.6.7.2 Sensitivity analysis two: Stratifying contraceptive exposure using more levels

When stratifying the exposure by more levels, the only new finding was a modest association between IUD/IUS and (OR 1.40 (95% CI 1.08-1.81). As this effect was small, it may be a chance finding. It would be particularly interesting to unpick associations for the newer types of COCPs. Although my study sample was large, too few women were exposed to these methods to analyse separately; there were 145 third generation users, 50 fourth generation users and 54 co-cyprindiol users amongst IBD cases across both studies. A way to overcome this could be pooling data from multiple electronic GP databases. But this was outside the budget of this project.

4.6.7.3 Sensitivity analysis three: Exclusion of those case-control pairs with less than five years of prescribing history

After exclusion of case control pairs with less than five years of prescribing history, we did not capture a higher proportion of parenteral method users and the results had no meaningful impact on my conclusions.

4.6.7.4 Sensitivity analysis four: Restricting analysis time to a shorter lookback period

When restricting analysis time to five years, there was minimal change in results aside from wider confidence intervals; the association between POPs and UC was no longer significant at the 95% threshold.

4.6.7.5 Sensitivity analysis five: Treating BMI as a continuous variable and excluding those with missing BMI

When treating BMI as a continuous variable and excluding those with missing BMI, results were similar to the primary analysis across all methods of contraception for both CD and UC. The fact that there was little difference when using both complete case analysis and categorisation as an approach to the handling of missing BMI data is reassuring.

4.6.7.6 Sensitivity analyses 6a & 6b: Changes to covariate assessment windows

4.6.7.6.1.1 Sensitivity analysis 6a: Adding an additional covariate assessment window

After the addition of an additional covariate assessment window, missing data were reduced. However, results were very similar to the primary analysis.

I did not use this method of capturing covariates for the primary analysis because I felt that

capturing information on lifestyle factors after the diagnosis of a chronic disease was more likely to introduce bias than replacing the status with 'missing' (as per the primary analysis). This is because BMI and smoking are highly likely to be influenced by being diagnosed with IBD. For example, weight loss is a presenting feature of Crohn's disease. Alternatively, a patient with recently diagnosed colitis may be on high doses of steroids which could cause them to gain weight. Additionally, smoking habits are likely to change because of an IBD diagnosis. Smoking has been shown to alter the course of IBD (209) and particularly for CD, smokers will be strongly encouraged to quit by their specialist gastroenterologist. By this logic, I concluded that if covariates are assessed after IBD has been diagnosed, then they cannot be true confounders of the association between exposure and outcome.

4.6.7.6.1.2 Sensitivity analysis 6b: Removing a covariate assessment window

Missing covariate data was dramatically increased when removing a covariate assessment window and this was differential across cases and controls; controls now having 42.8% and 31.9% missing data for BMI and smoking respectively. Odds ratios shifted towards unity across all methods of contraception. An explanation for this could be that including such a large 'missing' group essentially reduced the amount of adjustment and introduced considerable bias. Both BMI and smoking represent important biologically plausible confounders (4.4.6.4) are highly significant covariates in the regression models across both studies ($p < 0.00001$). Due to the large increase in missing data, this approach was not used for the primary analysis.

4.6.8 Comparisons with genetic literature

Although a number of studies have associated oestrogens with IBD pathogenesis, GWAS have not implicated genetic determinants of circulating oestrogen levels (variants in/near CYP19A1, FAM9B, Xq27.3, TRIM4, CYP11B1/B2 (255)) as at risk loci for IBD (256) and a Mendelian randomisation analysis has found that genetically predicted 17β-estradiol reduced low-grade systemic inflammatory markers in women (257). However, it is important to note that COCPs do not work by slightly increasing background levels of endogenous oestrogen, they provide exogenous hormones which have several inhibitory effects on the pituitary and hypothalamus to prevent ovulation and anti-androgenic properties.

4.6.9 Clinical implications and conclusion

The benefits of contraceptives greatly outweigh the risk of developing IBD in the vast majority of individuals. However, our results may be useful to those women seeking contraception who have a strong family history of IBD. Importantly, our research does begin to shed some light on the potential biological mechanisms involved in the pathogenesis of these two diseases, highlighting the importance of future studies focusing on specific exogenous sex hormones.

Chapter 5: Discussion

5.1 Introduction

In this chapter, the key findings from the previous studies are summarised, the strengths and limitations of the work are discussed, implications for clinical practice, patients and public health are addressed with suggestions for future research proposed.

5.2 Summary of key findings

5.2.1 Incidence and prevalence of recorded inflammatory bowel disease in UK primary care: a cohort study

In this UK cohort study over the period 2000-2018, I identified 65,700 cases of inflammatory bowel disease (IBD), of which, 22,560 were incident cases diagnosed during follow up. Overall, I observed some of the highest reported global incidence and prevalence rates for IBD. Ulcerative colitis (UC) incidence is falling, largely driven by a reduction in the number of new diagnoses in older adults. However, Crohn's disease (CD) incidence is comparatively more stable. UC incidence was higher in people from the least deprived areas whereas there was minimal association between social deprivation and CD. CD incidence was highest in Scotland and Northern Ireland, whereas UC incidence was highest in East England. Despite overall incidence of IBD falling, paediatric IBD is on the rise with a 94% increase in new diagnoses in adolescents aged 10-16 years. The prevalence of IBD continues to rise with a 59.1% increase in disease burden since the turn of the century.

5.2.2 Time trends in contraceptive prescribing in UK primary care: a repeated cross-sectional study

In this study of contraceptive prescribing from 2000-2018, I identified 13,280,708 prescriptions for contraceptives. Oral contraceptive pill (OCP) prescribing was higher in women from the least deprived areas, whereas long-acting reversible contraception (LARC) prescribing was higher in women from the most deprived areas. There were considerable differences in contraceptive prescribing between countries; in 2018, the proportion of women who were prescribed LARC in Scotland was nearly twice that of Northern Ireland. Over the study period, prescribing of combined hormonal contraceptives (CHCs) nearly halved whereas progestogen-only pill (POP) prescribing more than doubled. LARC prescribing increased in line with the introduction of The National Institute for Health and Care and Excellence (NICE) guidelines and again following the introduction of a Quality and Outcomes Framework (QOF) pay-for-performance incentive related to the provision of LARC information. After withdrawal of the pay-for-performance incentive in 2014, LARC prescribing plateaued in all age groups apart from adolescents who saw an 18% reduction in LARC uptake.

5.2.3 Use of contraceptives and development of inflammatory bowel disease: a nested case-control study

In this nested case-control study including 4,932 IBD cases matched to 29,340 controls, I found that CD, and to a lesser extent UC, was associated with exposure to CHC. IBD risk increased with longer durations of exposure; in women taking continuous CHC throughout follow up, risk of CD was double that of the unexposed group. POPs were not associated with CD but there was a modest association with UC which did not increase amongst those

exposed to POPs for longer time periods. Parenteral progestogen-only contraception was not associated with development of CD or UC. Aside from a modest association between POPs and UC which demonstrated no 'dose-response' effect, the findings of this study are consistent with a hypothesis that oestrogen-containing contraception, not progestogen-only methods, are associated with increased risk of IBD.

5.3 Strengths and limitations of the data source in the context of this project

Although primary care databases represent powerful tools for health researchers, inherent limitations arise when conducting observational research using routine electronic health records. In this section, I will discuss the strengths and limitations of IQVIA™ Medical Research Data (IMRD) in the context of my studies.

5.3.1 Sample size

An important strength of IMRD is the size of the dataset; IMRD holds the records of over 18.3 million patients. This makes IMRD a powerful tool when using the entire dataset for epidemiological studies and can give precise estimates of incidence and prevalence of relatively rare conditions. However, even in such a large dataset, limitations arise when analysing smaller extractions of data. For example, in my case-control study, I lacked study power to examine newer formulations of combined oral contraceptive pills (COCPs) separately. This would be important piece of research as the progestogens in 4th generation COCPs have the greatest anti-androgenic potential and one could hypothesise that they might increase the risk of IBD the most due to reductions in levels of endogenous testosterone (1.8.1).

In a number of my sensitivity analyses, nearly half the case-control pairs were excluded, which made results difficult to interpret due to reduction in sample size. This could be overcome by combining results from IMRD with an extraction from another electronic primary care database such as QResearch or alternatively using Clinical Practice Research Datalink (CPRD) which now incorporates data from both VISION and EMIS GP IT systems. Combining results from multiple primary care databases is an approach which has been taken in other nested-case control studies to overcome sample size issues (133).

5.3.2 Recall bias

Recall bias is a systematic error that occurs when study participants are more or less likely to recall information on exposure depending on their outcome status, or more or less to recall information relating to their outcome dependant on their exposure status (258). In retrospective study designs such as case-control studies, the accuracy of historic reporting is often influenced by the outcome. To give a simple example, in a study exploring associations between oesophageal cancer and smoking, a person who has developed oesophageal cancer may be more able to provide a detailed smoking history than a healthy control. Factors other than the outcome may also influence recall such as age, social deprivation and education. Additionally, 'unhealthy' lifestyle factors such as smoking and excessive alcohol consumption may be underreported in certain groups. A strength of IMRD is that all records are collected prospectively. To put this in the context of my nested case-control study, when compared to other observational retrospective studies which have relied on participants to provide accurate contraceptive histories and covariate information, all of this information has been collected in IMRD prospectively and prior to development of IBD, thus minimising recall bias.

5.3.3 Selection bias

Many case-control studies are prone to selection bias. Selection bias occurs when selected controls differ from the population of interest, thus leading to a systematic error in association. For example, inviting neighbours of cases or colleagues of researchers to participate can introduce bias as they may not be representative of the background population. Studies using large scale data sources can also be susceptible to selection bias. For example, the UK biobank (a cross sectional study which recruited over 500,000 individuals between 2006 and 2010) received only a 5% response rate for participation. This resulted in a highly selected population which is not representative of the UK (259). A strength of IMRD is that it has been shown to be generally representative of the UK and thus selection bias can be minimised by choosing controls from the entire database. Selecting controls from the entire electronic database also negates the possibility of refusal to participate or non-response (self-selection bias).

5.3.4 Generalisability

A strength of IMRD is that overall it has been shown to be representative of the UK in terms of age, gender, geographical location, smoking prevalence and the prevalence of a number of chronic conditions. However, subgroups of patients from IMRD are not necessarily generalisable to the wider UK population when stratifying by other factors such as country, age group, social deprivation or calendar period. In my repeated cross-sectional study of contraceptive prescribing, I found that geographical location of GP practices varied considerably from year to year (Table 3.4). In the final year of this study (2018), only 36.7% of women were registered with a GP practice in England compared to 72.2% ten years prior in 2008. This is clearly not geographically representative of the UK, as in reality, England

makes up 86.4% of the UK population. The reason for this is because IMRD relies on GP practices to use Vision computer software in their clinics. In recent years there has been a move away from English GPs using Vision software and thus IMRD has become smaller. As a result, the devolved nations of the UK are over-represented. Given that I observed considerable geographical variation in IBD incidence overall (Figure 2.7), one could argue that the incidence and prevalence estimates for IBD earlier in my first study may be more accurate than the last 5-6 years where England is under-represented. Researchers must consider the generalisability of their data source when reporting temporal trends in epidemiology using electronic primary care databases.

This work could have been strengthened by using an alternative data source; CPRD instead of IMRD. This is because CPRD includes GP practices which use EMIS software in addition to Vision. Therefore, more English GP practices contribute and in terms of geographical distribution, it is more representative of the UK. Additionally, CPRD is larger (39.5 million patients) and has the benefit of more complete area-level deprivation data, which was unavailable in my studies for patients who began contributing to IMRD after 2016. Unfortunately, access to CPRD including linkage to small area level data and HES data was outside of the budget for this project.

5.3.5 Validation

Although the Read code hierarchical coding system provides an extensive library of codes which can be added to and updated, there are considerable variations in coding style over time and from practice to practice. Some GPs may record as much as possible using Read codes, whereas others may rely more heavily on free text (which I was unable to access for

my studies); this impacts on missing data (5.3.8). Additionally, many Read codes are non-specific and their meaning is subject to interpretation. For example, one could argue that "ZRh4.00 - Reasons for smoking scale" could refer to a smoker or an ex-smoker. As most of the Read code lists used by primary care researchers are unvalidated, this can result in inconsistences in reporting between research teams. A good example of this would be the disparity in incidence rates between my cohort study and two other studies using the same data source which used different Read code lists in addition to different diagnostic algorithms (2.5.5) (200, 201). As a quality filter, I reviewed my Read code lists with a panel of clinicians and researchers and compared my Read code lists to those used in previous studies. This ensured that any discrepancies were resolved in the early stages of the project.

5.3.6 Confounding

Demonstrating causal inference in observational study designs is challenging due to a range of biases including confounding. Confounding occurs when a separate variable or 'confounder' influences both the exposure (independent variable) and the outcome (dependant variable). If confounders are not properly adjusted for, this can lead to an underestimate or overestimate in the effect of interest (4.4.6).

Randomised controlled trials (RCTs) are the gold-standard to quantify the effect of pharmacological interventions. This is because through prospectively randomising participants, important sources of bias including known and unknown confounding can be minimised or even eliminated. However, RCTs are not always feasible or ethical. To answer the research question 'does contraception increase risk of CD?', this randomised controlled trial would be:

a) Unfeasible due to the huge sample size and long follow up period that would be required: If we assume a background CD incidence of 14.7 per 100,000 person-years in women of reproductive age (4.5.1) and an odds ratio of 1.51 for CD and OCP exposure (4.5.6), then 106,901 participants (1:1 exposed/unexposed ratio) would need to be followed up over five years to calculate a difference of this size or greater, significant at the 95% threshold with 80% power.
b) Unethical because one cannot randomise women to 'contraception' or 'no contraception'. It might be possible to conduct a head-to-head RCT comparing two different methods of contraception (e.g. 2nd generation vs 4th generation COCPs). However, due to unfeasibility issues, this study would not be appropriate.

Therefore, an observational study was performed. In my study, I identified confounders *a priori* based on theoretical knowledge/potential biological mechanisms and explored these using directed acyclic graphs (DAGs) (Figure 4.2). I also explored exposure-covariate-outcome relationships by using the Wald test to quantify significance of variables in regression models and to test for multiplicative interactions. However, although IMRD includes information for some important confounders such as smoking and body mass index (BMI), a lot of demographic information (particularly relating to lifestyle and education) is simply not recorded. For example, in a large US cohort study they were able to adjust for additional reproductive factors such as 'age at menarche' and 'parity' (157). Alternatively, in a questionnaire-based study, other factors such as education level, diet, physical activity and sexual history and could be determined. Where possible, I used proxy-variables such as pregnancy (yes/no) to provide some information on parity, Townsend Score to broadly categorise deprivation and BMI which correlates to an extent with variations in diet and

exercise. However, this is clearly not ideal, particularly for diet which may represent an important confounder for the observed relationship between COCP use and IBD; diet has been strongly implicated in IBD pathogenesis (1.4.4.2) and body mass and bone health (which are directly influenced by diet) are important factors to consider when selecting appropriate contraception. IMRD contains minimal information on potential 'non-medical' confounders such as diet, exercise and level of education, which represents an inherent limitation of the data source.

5.3.7 Temporal bias

Temporal bias occurs in case-control studies where the study period is not representative of the data available to clinicians during the diagnostic process (i.e. there is a mismatch between the study time period and the 'real-life' time period) (260). This can become problematic when this mismatch relates to the date of the outcome and exposure/covariate information is collected around this time. This is because the exposures and covariates are often influenced by the outcome. For example, in a case-control study exploring associations between weight gain and development of type-2 diabetes, an overweight patient may make efforts to lose weight when diagnosed with diabetes. Therefore, if measurements of weight are used during the peri-diagnostic period, this could underestimate measurements of weight in cases and subsequently inflate the observed association between weight gain and diabetes.

Case-control studies using IMRD are subject to temporal bias because there are unavoidable delays between disease onset and the recording of Read codes in the electronic patient record. This is particularly true for diseases which may have an insidious onset, are prone to

diagnostic delays or are diagnosed in secondary care such as IBD. One way around this might be to use the 'date of onset of IBD symptoms' as the outcome as opposed to the 'date of recording of IBD'. However, unlike a number of other chronic diseases such as Parkinson's disease which have relatively specific presenting features, IBD largely presents with non-specific gastrointestinal (GI) symptoms which are very common presenting complaints in primary care (e.g. abdominal pain, watery bowel movements or fatigue). Therefore, it would be difficult to pinpoint which pre-diagnostic symptoms relate to IBD and which relate to another premorbid condition such as infective gastroenteritis or irritable bowel syndrome (IBS). Furthermore, Patients with IBD have been shown to have an excess of GI symptoms up to five years before diagnosis (254). So if 'date of symptom onset' were used as the outcome, there would be very little analysis time for the majority of cases in my study. To minimise the effect of temporal bias in my study, I captured covariate information as close to the beginning of the prescribing history as possible (Figure 4.3).

Although there is an inevitable delay between the development of IBD and the recording of the diagnosis in the medical records, this is unlikely to have dramatically affected the results of my incidence study. This was a large cohort study including 78,985,977 person-years of follow up. As IBD is a relatively rare diagnosis, a time lag as large as months, or even a year (which would be unlikely in most cases), would not have resulted in a measurable underestimate in IBD incidence.

5.3.8 Missing data

The primary use of the software contributing to IMRD is for patient management purposes and not research. Thus, information recorded will often only reflect what is deemed

relevant to the patient's care. Therefore, missing data can be problematic and introduce bias. There are a number of ways of handling missing data including: complete-case analysis, categorisation, single and multiple imputation. Missing data are typically grouped into three categories:

a) Missing completely at random (MCAR) – 'missingness' is unrelated to the observed data and the unobserved data. i.e. There are no systemic differences between patients with missing data and those with complete records.
b) Missing at random (MAR) – missing data is systemically related to the observed data but not the unobserved data. i.e. the 'missingness' can be explained by other factors which have been measured in the study.
c) Missing not at random (MNAR) – the 'missingness' is systemically related to the unobserved data. i.e. it is the value of the variable that is missing that is related to the reason it is missing. For example, smokers may be more likely to have their smoking status recorded than non-smokers.

In my case-control study, there was 18.5% missing data for smoking and 21.1% missing data for BMI. This is important because smoking and abnormal BMI represent relative contraindications to contraception. Therefore, women initiating or established on contraception are more likely to be asked about smoking and have their BMI recorded than unexposed women. Additionally, women who become unwell and are being worked up for a chronic disease may be more likely to be asked about smoking and weighed, particularly given that weight loss can be a presenting feature of IBD.

In this study, data on BMI and smoking were unavailable for a larger proportion of controls than cases, and for a larger proportion of unexposed individuals than exposed individuals (Table 4.3). From this I can conclude that 'missingness' is related to both exposure and outcome and data were not MCAR. I do not feel that an adequate amount of covariate information was captured to accurately impute results for BMI and smoking. Moreover, smoking data has been shown to be MNAR in primary care datasets; those who have no record of smoking status are more likely to be non-smokers or ex-smokers than current smokers (261). Additionally, I suspect that obese or underweight patients are more likely to be weighed than patients of normal weight. As multiple imputation largely relies on data MAR, I did not use this approach in my analyses.

5.4 Implications for clinical practice, health policy, and patients:

Since the start of the COVID-19 pandemic, descriptive epidemiology has gained increasing attention due to its application in modelling disease trajectory and planning service delivery. In this project, I carried out two descriptive epidemiological studies and one hypothesis-driven piece of research. Although the hypothesis-driven study was a more complex and in-depth piece of work, the results of the descriptive studies have a wider range of implications for clinical practice and public health. This highlights the importance of descriptive, hypothesis-generating research in modern epidemiology.

In this section, I discuss the impact of my studies on clinical practice, service delivery, people living with IBD and women of reproductive age seeking contraception. I also discuss the wider public health and policy implications of my findings.

5.4.1 Incidence and prevalence of inflammatory bowel disease

Prior to commencing this PhD, there was a paucity of contemporary literature relating to the epidemiology of IBD in the UK. In very recent years, the epidemiology of IBD has become an attractive subject to research given the wider implications of rising prevalence on cost and service delivery. My descriptive study provides detailed time trends in incidence and prevalence which may assist in the distribution of resources to ensure that the needs of people living with IBD continue to be met in the future.

5.4.1.1 Compounding IBD prevalence and an ageing demographic

Prevalence of IBD in the UK will continue to rise until incidence approximates mortality in absolute numbers, provided there are no dramatic changes in migration patterns of people living with IBD. Given the current IBD cohort is younger than the background population, it has been predicted that prevalence equilibrium will not be reached until roughly 2050 in developed countries and IBD prevalence will be as high as 1% in many regions by 2030 (68).

My results have shown a dramatic rise in the prevalence of IBD in older adults. There are huge economic implications associated with any ageing population. Furthermore, there are a number of additional challenges specific to managing IBD in older people, namely: polypharmacy, comorbid disease, frailty and the consequences of long-term IBD therapy. Specific concerns might include:

- Risks associated with endoscopy and surgery.
- Increased risk of bowel malignancy.
- Increased risk of malnutrition.

- The prescription of corticosteroids in patients with comorbidities such as metabolic bone disease and diabetes which may lead to harm. Additionally, the increased risk of gastrointestinal haemorrhage in older adults.
- Mental health and isolation in the context of chronic disease. In older patients with CD, depression and perceived stress are frequently reported (262).
- Pill burden and treatment compliance.
- Drug-drug interactions, of which there are numerous between IBD medications and drugs commonly prescribed in older patients.
- Antibiotic use and *C.difficile* infection.
- Risk/benefit of prescribing drugs which are difficult to tolerate and/or are associated with complications (e.g. patients aged over 60 are at increased risk of severe infection and mortality with anti-TNF therapy (263)).

Older adults are making up an increasing proportion of the UK IBD cohort and this proportion will continue to increase until prevalence equilibrium is reached. Caring for this growing population will have significant cost and service delivery implications. This is in the context of huge financial challenges to the NHS. IBD physicians, allied health professionals and service managers must be prepared to adapt to the complex needs of this group. This could be achieved in part by an increase in interdisciplinary working to manage patients with multimorbidity and polypharmacy.

5.4.1.2 Rising paediatric IBD

The increasing number of new IBD diagnoses in children has resulted in a massive increase in paediatric IBD prevalence, particularly for CD. Since 2000, I observed an increase in IBD

prevalence of 30.2% (from 5 to 7 per 100,000 people) in those aged 0-9 years and 260% (from 30 to 109 per 100,000 people) in those aged 10-16 years.

Given that the reasons behind rising paediatric IBD incidence are unclear (5.6.1), it is difficult to predict if incidence will continue to rise or plateau. If IBD incidence in adolescents plateaus, then paediatric IBD prevalence will plateau relatively quickly as a result (when compared to the phenomenon of compounding prevalence that is observed in adults) (5.4.1.1). This is because the 'endpoint' for most children living with IBD is transition to adult care and not death. Transition to adult care happens at a set point (in most cases at age 18-21 years (264)). This will happen faster than it takes the adult IBD cohort to age and for mortality to increase.

Children with IBD have, by definition, been diagnosed recently. There are a large number of physical and psychological challenges involved in inducing and maintaining clinical remission in this age group. Managing these challenges have significant cost and resource implications over a lifetime of disease. Specific considerations in children include:

- The long-term sequelae of IBD on: micronutrient deficiencies, growth and bone health, lifelong risk of colonic malignancy (265).
- Psychosocial function and stigma associated with IBD. Children with IBD have higher rates of depression/anxiety and report lower quality of life compared with children with other chronic diseases such as cystic fibrosis and diabetes (266). Depressive symptoms in paediatric IBD have been shown to correlate with disease activity (267).
- Absence from school due to illness and impact on educational attainment and future skills.

- Adherence to therapy. In many serious chronic diseases that can affect children such as IBD (268), perinatally-acquired HIV (269) and diabetes (270), adherence to therapy during adolescence is a major challenge.
- Parental stress. When a child is diagnosed with IBD, the entire family is affected and parental stress is strongly linked to childhood illness (271). This can be made worse by the unpredictable nature of IBD (272).

IBD incidence and prevalence in children is rising. Given the advances in modern IBD treatment, most of these patients can be expected to live long and healthy lives. As childhood IBD requires a wide multidisciplinary approach, there are numerous resource and budget considerations that will need to be addressed to care for this at-risk group which is growing in size. The needs of this group could be addressed in part by the recruitment and training of staff to work specifically with adolescents. This may help to strengthen services by supporting patients during the transition from paediatric to adult care.

5.4.2 Contraceptive care delivery

5.4.2.1 Prescribing inequalities

LARC is more commonly prescribed to women from socially deprived backgrounds and OCPs are more commonly prescribed to women from less deprived backgrounds (3.5.9) (2). Although LARC is more effective at preventing pregnancy, disparities in prescribing between economic groups represents health inequality. I hypothesise that this may relate to a preference for practitioners to prescribe LARC to those they feel are at greatest risk of unplanned pregnancy (abortion rates are double in the most deprived decile compared to the least deprived decile (232)) or those who they feel may not be able to adhere to user-

dependant contraception properly (contraceptive failure rates are higher across all methods in low-income groups (231)). Additionally, women from more deprived backgrounds may not have access to online resources which can assist in contraceptive decision making. For example, women who have not been online prior to consultation may not be aware of unwanted LARC side effects such as inter-menstrual bleeding on the contraceptive implant, or pain associated with intra-uterine contraception (IUC) insertion.

Although I certainly do not advocate reducing prescription of LARC, many women prefer OCPs to LARC. It is very important that all women, regardless of social deprivation, are taken through all of the appropriate contraceptive methods, given proper education and allowed to make their own informed decisions. As part of a patient-centred approach to healthcare, all women should be allowed to select contraception based solely on the advantages and disadvantages of the method and their individual needs, rather than external factors related to their economic status, education or GP preference. This study highlights the need to properly educate contraceptive providers to avoid future prescribing inequalities.

5.4.2.2 Adolescent LARC uptake and unplanned pregnancies

One of the most important findings from my descriptive study of contraceptive prescribing was the fall in LARC prescribing amongst adolescents since withdrawal of the QOF pay-for-performance indicator for LARC. Furthermore, this was not found in Wales, where there has been a substantial drive from to government to bring down rates of unplanned pregnancies over the last ten years.

Although LARC prescribing is decreasing in adolescents in primary care, teenage abortion

rates continue to fall across all countries of the UK (273-275). This is clearly multifactorial and can be explained by a wide range of factors such as compulsory sexual education in all schools from age 11 and improvements in access to condoms and emergency contraception. Although rates of unplanned teenage pregnancy are falling, increasing LARC uptake in this age group is still important; this will ensure a continuing (or faster) downward trend in unplanned pregnancies.

Although Wales has seen no fall in LARC uptake, the question remains how this problem should be tackled in England, Scotland and Northern Ireland. A suggestion might be to reintroduce the QOF indicator. However, this carries a substantial cost to the taxpayer and given that LARC prescribing plateaued instead of continuing to rise while the QOF was in place, we may not see a dramatic increase in LARC uptake.

Another suggestion would be to roll out a government campaign encouraging LARC uptake which is specifically aimed at adolescents. In order for LARC uptake in adolescents to increase, a number of things must occur:

1) Access to LARC training must be readily available to practitioners as well as appropriate reimbursement.
2) GP practices must be able to provide LARC to adolescents or signpost to convenient services which can be reached by walking or public transport.
3) LARC should be considered as a ‘first-line’ method of contraception to this age group.
4) Women should be encouraged to enter into a dialogue and question the contraceptive choices offered to them including user-dependant and LARC methods. This could be

done in part by signposting to resources before they attend for a contraception appointment. E.g. https://www.contraceptionchoices.org/

Therefore, any future campaign would do well to target not just adolescents but also primary care services. This could help to debunk some of the myths and misconceptions around LARC that are held by both patients and clinicians (276) (Table 5.1).

Table 5.1. Myths and misconceptions surrounding long-acting reversible contraception

Patient concerns	**Clinician concerns**
IUDs cause abortions	Parental consent is required
LARC will make me gain weight	Adolescents wont reliably check IUD/IUS strings
IUDs cause infections	Teens prefer to use condoms and OCPs
IUDs are painful	Intrauterine contraception is not appropriate for young nulliparous women

Additionally, if GP practices cannot provide LARC, then there must be established referral pathways where LARC can be accessed in a convenient and straightforward manner. If a young woman has struggled to get a GP appointment and now must travel a long distance and 'rejoin the back of the queue' because her local GP does not offer LARC, then this may discourage her from using LARC. Instead, she may settle for another less reliable method that her GP can provide on the day. This highlights the importance of 'joined-up care' between GP practices and specialist centres. The NHS must provide a service that is able to deliver effective healthcare whilst being easy to navigate for patients and healthcare providers alike.

5.4.2.3 Over-the-counter desogestrel POP

How contraceptive care is delivered in UK is currently under a period of transition with closure of multiple sexual and reproductive healthcare (SRH) services and the availability of

over-the-counter POP (desogestrel 75mcg) (214). Results from this study relating to changes in demand for COCPs and POPs can inform service delivery moving forward.

Although COCPs remain the most popular method, prescription of COCPs in primary care has halved in the last 20 years (3.4.4.2). Given that GP appointments are increasingly difficult to obtain, I anticipate that we will see a further drop in CHC prescribing following the roll out of over-the-counter desogestrel 75mg which may be more convenient for some women.

Initiating a woman on over-the-counter desogestrel requires a consultation from a trained health professional to discuss other contraceptive options, risk of pregnancy, mechanism of action, risk/benefit, how to take, missed pill rules etc. Busy pharmacies must be prepared to allocate resources to the increasing demand for over-the-counter POP, including training their staff to take on the detailed and lengthy consultations that are required.

Given that it broadens contraceptive availability, over-the-counter desogestrel is supported by contraceptive providers and generally regarded by SRH physicians, gynaecologists and pharmacists as a positive step forwards (214). However, it is not as effective as LARC. Additionally, it may impact on health inequalities given that it must be paid for. It is hoped that pharmacists will use the opportunity to signpost women, particularly adolescents, to information on LARC and reverse the falling trend in this population.

5.4.3 Oestrogen-containing contraception and risk of IBD

My case-control study suggests that exposure to COCPs is associated with IBD, particularly CD. That being said, COCPs represent a highly effective user-dependant method and have 'more forgiving' missed pill rules than POPs (COCPs can be taken late or even missed whilst maintaining contraceptive protection). COCPs also have a number of other benefits including management of hirsutism and acne and can be used to control abnormal menstrual bleeding patterns.

Given that IBD is relatively rare (incidence 25 per 100,000 person-years and prevalence 725 per 100,000 people (2.4.3/2.4.9)), the benefit of taking a COCP to prevent unwanted pregnancy would greatly outweigh the risk of developing IBD in most women. However, children or siblings of people living with IBD may want to take this into consideration when choosing appropriate contraception. At this stage, we still do not have enough evidence to advise contraceptive prescribers to ask their patients about a personal or family history of IBD - the absolute risk increase would be very small in the background population and it is not clear whether contraception modifies disease course in established IBD. Although my results provide valuable insights into the potential hormonal contribution to IBD pathogenesis, until further research has been undertaken (5.6.3.1/5.6.3.2/5.6.3.3), current contraceptive prescribing practice is unlikely to change.

5.5 Ongoing patient and public involvement

I involved a patient group in the early stages of the project to assist in refining the research question and justifying the importance of the work. However, when conducting the research, there was minimal input from the group due to licence agreements with IQVIA™ regarding data sharing, and the specific computer programming skills that were required.

Since the completion of the studies included in this thesis, I have reached out to the UCLH IBD patient panel and circulated the relevant publications from the work which were well received (1, 3).

I intend to involve the UCLH IBD Patient Panel in assisting with dissemination of the work to patients. This could be achieved in multiple ways; the writing of a lay summary which could be circulated amongst patients and their relatives, the use of social media channels to upload articles, links and blogs about the work, or alternatively through collaboration with charities such as Crohn's and Colitis UK who have recently funded another project on IBD incidence and prevalence using an alternative data source (277).

5.6 Future research directions

There are a number of future research projects that could be undertaken which build on the work produced in this thesis.

5.6.1 Understanding the drivers for an increase in paediatric IBD incidence

My cohort study of IBD epidemiology showed a near doubling in the incidence of paediatric IBD since the year 2000. Three explanations for this include:

1) 'Unmasking' of prevalent IBD (i.e. earlier diagnosis due to improvements in diagnostic tools and access to services).
2) Earlier onset IBD in genetically susceptible individuals due to increased and earlier exposure to environmental triggers.
3) New cases of IBD in children who may have never previously developed IBD due to exposure to new environmental triggers.

Earlier in this thesis, I explain why unmasking of prevalent disease alone is unlikely to cause such a dramatic rise in incidence in adolescents (2.5.7). Therefore, I think it is likely that environmental factors play an important role. Identifying early life risk factors for IBD would be greatly important in guiding the development of primary prevention strategies for those at higher risk.

Several observational studies have explored early life exposures and the risk of IBD in children (278). In adults, environmental factors related to IBD risk have been explored in THIN using a case-control design (135) . A similar study could be conducted in a paediatric population and results could be stratified by calendar period to look for trends over time. Alternatively, a matched cohort design could be used to look at a specific exposure of interest, then patients could be followed up prospectively until development of IBD. These studies would have the advantage of a larger sample size than previous work. Furthermore, unlike studies in adults using primary care databases, studies in children benefit from often having their entire medical history from birth (they are often born within the data collection period).

5.6.2 Contraceptive prescribing during the COVID-19 pandemic

An extension of my repeated cross-sectional study covering the period when the UK was affected by the COVID-19 pandemic would be a useful piece of work. This could provide valuable information on contraceptive availability during the lockdown period and identify which groups of women may have been affected more than others. Unfortunately, I was not able to extend my study; the departmental licence to use IMRD at The Research

Department of Primary Care and Population Health was not renewed after 2018. Therefore, data after 31/12/2018 are not available to researchers within the department.

5.6.2.1 LARC uptake in new users

It has been shown that removal of some QOF pay-for-performance indicators such as lifestyle counselling for patients with hypertension is associated with an immediate decline in performance on quality measures (279). My findings in adolescents could be explored in more depth using a cohort study design in IMRD focusing on new contraceptive initiators. This could be done by entering females who have never been prescribed contraception into a study in their early teenage years then following them up prospectively until the first contraceptive prescription. By adjusting for appropriate covariates in a multivariable regression analysis, sociodemographic and time trends in contraceptive prescribing amongst new users could be explored in a more detailed manner. This could inform public health initiatives aiming to target specific patient groups.

5.6.2.2 LARC prescribing in relation to unplanned pregnancy

An increase in LARC prescribing has been related to reduced rates of abortion during the period of LARC linkage to QOF using an interrupted time series study design in CPRD (98). However, this does not inform us on what happened after the withdrawal of the pay-for performance indicator. An extension of this interrupted time series study would help us better quantify the relationship between reductions in LARC prescribing and abortion following the retirement of the QOF indicator.

5.6.3 Contraception and IBD research

Although the results of my case-control study do not have immediate clinical implications, the finding that oestrogen-containing contraception may drive IBD pathogenesis is novel. Building on the results of my nested case-control study, there are a number of future projects which may yield important results for women living with IBD.

5.6.3.1 Further quantifying the relationship between contraception and IBD risk

A way to further explore the relationship between oestrogen containing contraception and IBD risk would be using Mendelian randomisation. A Mendelian randomisation study uses variations in genes of known function to examine causal relationships between modifiable exposures and development of disease (280). Given certain assumptions are met, Mendelian randomisation studies can provide strong support for causal relationships, because genotypes are randomly assigned at conception and cannot be altered by the outcome or other external factors. Therefore, Mendelian randomisation studies are not as susceptible to inherent biases that exist in observational research such as reverse causality and confounding.

If we hypothesise that it is either the exogenous oestrogen component of CHC or the anti-androgenic effects of CHC that are associated with IBD, then Mendelian randomisation studies could be designed to explore the associations between genetically predicted serum estradiol (variants in/near *CYP19A1, FAM9B, Xq27.3, TRIM4, CYP11B1/B2*) or genetically predicted testosterone (variants in the *JMJD1C & SHBG* gene region) with the development of IBD. Although variants in these gene regions have not previously been highlighted as at-risk loci for IBD, they may have been missed by genome wide association studies (GWAS). Importantly, in GWAS studies, a very high threshold for significance must be used when

studying >100,000s of genetic variants. As Mendelian randomisation studies are hypothesis driven and look at a small number of gene variants, such adjustments for multiple comparisons do not need to be made. Additionally, some of the relevant genetic variants may not have been included on the DNA microarrays in previous GWAS literature.

5.6.3.2 How contraception affects IBD disease outcomes

I have demonstrated that oestrogen containing contraception is associated with development of IBD. However, it is not known whether oestrogen containing contraception can modify disease course in established IBD. The results of a study addressing this research question would be of great importance to women living with IBD who are seeking contraception. An observational study of this nature had been planned using The Lothian IBD Registry (72). However, the work had to be abandoned due to unforeseen circumstances arising from the COVID-19 pandemic (1.13).

Another approach would be a head-to-head RCT of POP vs CHC in women living with IBD. However, this study might be difficult to design and obtain ethical approval given the length of follow up that would be required and the number of women that are likely to switch or stop contraception during the follow up period.

5.6.3.3 Safety of combined hormonal contraception in established IBD

Another potential avenue of research would be exploring the safety of CHC in the context of IBD. It is established that both taking CHC and having IBD represent independent risk factors for venous thromboembolic disease (VTE) (134, 281). Additionally, drugs used to treat IBD such as steroids and the small molecule agent tofacitinib which has shown to infer increased

risk of VTE in patients with rheumatoid arthritis may put patients at further risk of thrombosis (282). Despite these factors, having IBD is not listed as a contraindication to the prescription of CHC in the UK (82). To explore whether CHC should be recommended in IBD it would be important to find out if CHC increases VTE risk to a greater extent than is expected in people living with IBD (i.e. does a synergistic relationship exist between IBD and CHC exposure on VTE risk?). This study might involve looking at interactions between CHC and IBD and could be done in IMRD. VTE often presents in primary care, and if diagnosed in elsewhere, the GP is likely to be informed for ongoing prescription of anticoagulation. Therefore, I anticipate that a diagnosis of VTE would be well recorded in the database.

5.7 Conclusion

Work from this thesis has contributed substantially to the understanding of the epidemiology of IBD in the UK, changes in contraceptive prescribing patterns and the hormonal contribution to IBD pathogenesis. Important concerns for public health and service delivery include: a projected ongoing rise in IBD prevalence in an ageing population, a dramatic increase in adolescent IBD incidence and a finding that withdrawal of a pay-per-performance incentive may have adversely affected adolescent LARC uptake. These challenges will need to be addressed in the context of increasing financial pressure on the health service.

My descriptive studies showed that female IBD incidence was disproportionately falling in the context of nationwide reductions in the prescription of CHC. This finding went on to inform the first study to show that development of IBD (particularly CD) is associated with exposure to oestrogen-containing and not progestogen-only contraception. Future work to

better define this association and explore the effect of contraception on IBD disease course is required.

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Chapter 6: Appendices

6.1 Appendix A: Publications arising from the work described in this thesis

Open access Original research

BMJ Open

Incidence and prevalence of inflammatory bowel disease in UK primary care: a population-based cohort study

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ABSTRACT

Objectives We describe temporal trends in the recorded incidence of inflammatory bowel disease (IBD) in UK primary care patients between 2000 and 2018.

Design A cohort study.

Setting The IQVIA Medical Research data (IMRD) primary care database.

Participants All individuals registered with general practices contributing to IMRD during the period 01 January 2000–31 December 2018.

Main outcome measures The primary outcome was the recorded diagnosis of IBD.

Results 11 325 025 individuals were included and 65 700 IBD cases were identified, of which 22 560 were incident diagnoses made during the study period. Overall, there were 8077 incident cases of Crohn's disease (CD) and 12 369 incident cases of ulcerative colitis (UC). Crude incidence estimates of 'IBD overall', CD and UC were 28.6 (28.2 to 28.9), 10.2 (10.0 to 10.5) and 15.7 (15.4 to 15.9)/100 000 person years, respectively. No change in IBD incidence was observed for adults aged 17–40 years and children aged 0–9 years. However, for adults aged over 40 years, incidence fell from 37.8 (34.5 to 41.4) to 23.6 (21.3 to 26.0)/100 000 person years (average decrease 2.3% (1.9 to 2.7)/year (p<0.0001)). In adolescents aged 10–16 years, incidence rose from 13.1 (8.4 to 19.5) to 25.4 (19.5 to 32.4)/100 000 person years (average increase 3.0% (1.7 to 4.3)/year (p<0.0001)). Point prevalence estimates on 31 December 2018 for IBD overall, CD and UC were 725, 276 and 397 per 100 000 people, respectively.

Conclusions This is one of the largest studies ever undertaken to investigate trends in IBD epidemiology. Although we observed stable or falling incidence of IBD in adults, our results are consistent with some of the highest reported global incidence and prevalence rates for IBD, with a 94% rise in incidence in adolescents. Further investigation is required to understand the aetiological drivers.

Strengths and limitations of this study

- We used a large sample size.
- The data source was prospectively collected healthcare records representative of 'real-life' clinical practice.
- Unlike many previous inflammatory bowel disease incidence/prevalence studies that have relied on external data sources to estimate denominator population characteristics, we were able to extract demographics and person-time follow-up for all individuals in our cohort.
- Data in IQVIA Medical Research Data are recorded for patient management purposes rather than medical research.
- As our records were not linked to secondary care, we were not able to confirm our cases by evidence of radiological, endoscopic or histological findings.

INTRODUCTION

The inflammatory bowel diseases (IBD; Crohn's disease (CD), ulcerative colitis (UC) and IBD unclassified (IBDU)) are chronic inflammatory conditions of unknown aetiology that affect the gastrointestinal tract.[1 2] In North America, over 1.5 million individuals are living with IBD and in Europe it is estimated that 2.5–3 million individuals are affected, with an estimated direct healthcare cost of 4.6–5.6 billion Euros/year.[3 4] Historically, IBD was regarded as a disease of high-income western countries with a substantial rise in incidence observed during the latter half of the 20th century.[5] However, there is evidence that the rate has plateaued in western countries while rising rapidly in newly industrialised countries.[4] Accurate and up-to-date estimates of trends in incidence and prevalence of IBD are an essential step in preparing services for the delivery of future IBD care.

Studies using local hospital records and secondary care databases have been conducted to describe the epidemiology of IBD in the UK.[6–9] However, patient follow-up is challenging and loss to follow-up may introduce bias, notably where patients do

not require hospitalisation and/or move geographical location. More recently, estimates of incidence and prevalence of IBD were reported in a rigorously validated IBD cohort of 10 926 cases in Lothian, Scotland.[10] However, it remains unknown if these findings are generalisable across the UK.

In the UK, over 60 000 000 people are registered with a general practice (GP; about 91% of the population).[11] Electronic GP health records databases can enable large-scale investigation of relatively rare diagnoses such as IBD.[12] The largest such UK study performed to date was undertaken in Northern England and included 179 incident cases of IBD diagnosed in a population of 135 723 during the period 1984–1995.[13]

In the present study, we investigated temporal trends in the incidence of IBD diagnoses from 2000 to the end of 2018 using electronic GP data from the IQVIA Medical Research Data (IMRD) primary care database (formally The Health Improvement Network database).

MATERIALS AND METHODS

Data source

IMRD is a large longitudinal database currently containing the anonymised electronic medical records of 18.3 million patients collected from 797 GPs throughout the UK; 3 million of these patients are presently registered with a practice contributing to IMRD and are currently providing data. It is one of the most comprehensive data sources of its kind and is used worldwide for research by academic institutions, government departments and the pharmaceutical industry. Data are based on patient consultation records and include demographics (eg, gender, age and socioeconomic level of deprivation), presenting symptoms and diagnoses, referrals to secondary care, medications, results of investigations, vaccinations and additional health data such as height, blood pressure, weight and smoking status. Data are recorded in IMRD using the Read code hierarchical coding system.[14] No other coding system was used in IMRD for the duration of the observation period. The GPs in IMRD are broadly representative of all primary care practices in the UK in terms of age and sex of patients, practice size, geographical distribution and the prevalence of numerous chronic conditions such as hypertension, diabetes, asthma and epilepsy.[15] A previous validation study using electronic GP records showed that for individuals with a code for IBD, the diagnosis was highly probable or probable for 92% (95% CI 86% to 96%) of patients.[12] Although IMRD data are not linked to secondary care records, diagnoses made in secondary care are captured in IMRD; either through letters and communications to the GP or during patient consultations.

Study population

All data included in this study were from time periods after the GPs had met acceptable computer usage (ACU) and acceptable mortality reporting (AMR) standards.[16 17] The date of meeting ACU was the date after which the practice was confirmed to have electronically logged an average of at least one medical record, one additional health record and two prescriptions per person year. The date of meeting AMR standards was the date after which the practice was confirmed to record mortality at a similar rate to that expected for a population with comparable demographics as per the Office for National Statistics.

All individuals of any age contributing data between the 1 January 2000 and the 31 December 2018 were included. The study was a dynamic cohort with individuals entering and exiting at different times. Cohort entry was defined as the latest date of the following: 1 January 2000; the date of registration with the GP plus 9 months to account for prevalent disease being recorded as incident disease when patients register with the practice (this time period was selected using previously published methodology)[18]; or the date the practice met predefined quality indicators for electronic data (AMR and ACU). Cohort exit was defined as the earliest date of the following: first diagnosis of IBD; deregistration with the GP contributing data; death; or 31 December 2018.

Main outcome definitions

The main outcomes of interest were newly diagnosed CD, UC or any IBD. The any IBD category included specific and general terms for IBD (comprising CD, UC, IBDU and unspecified IBD). Read code lists, adapted from those used in previous literature,[12 13 19] were generated for all three main outcomes using published methodology,[20] then subsequently discussed with a panel of experts including gastroenterologists, epidemiologists, a GP and a statistician (online supplementary appendix Read code lists).

As a quality filter, individuals were only included in the study as cases if they had at least two IBD Read codes recorded on separate dates or at least one IBD Read code plus at least one prescription for a drug commonly used to treat IBD (any aminosalicylate or rectal steroid enema listed in chapter 1.5 of the British National Formulary,[21] azathioprine, mercaptopurine, methotrexate, ciclosporin, infliximab or adalimumab) (online supplementary appendix Read code lists). As 'incident IBD cases' (who have not been prescribed 'IBD drugs') were required to have their diagnosis verified on a subsequent GP visit, we anticipated that this would result in under ascertainment of those diagnosed in the final months of the study period. Thus, temporal trends in incidence are graphically presented for the period 2000–2017 as opposed to 2000–2018. The date at which the first recording of any IBD code or IBD drug prescription was made was classified as the incident date. For individuals who had been given a code for both UC and CD in their lifetime, the most recent code recorded was used as their final diagnosis.

A separate algorithm was developed to explore the validity of the diagnosis of IBD in IMRD. This involved checking whether individuals who had ever been given a

medical Read code for IBD had a record of (1) presentation with symptoms suggestive of IBD (abdominal pain, diarrhoea, bloody stools, weight loss); (2) a prescription for a drug commonly used to treat IBD. 'Incident cases' were not required to meet these criteria to be included in the analysis.

Covariates

The following covariates were included in the analyses: (1) birth gender, (2) age by Montreal/Paris classification[22 23] (A classification system for IBD whereby the 'A' variable describes 'age at diagnosis', the levels of which are: A1a (0–9 years); A1b (10–17 years); A2 (17–40 years) and A3 (40+ years)), (3) calendar time, (4) Townsend Deprivation Index (a quintile measurement of social deprivation based on post code linked census data)[24] and (5) geographical location of GP. This was included at the level of former Strategic Health Authority (a defined region responsible for the management of health services for that particular area) for England and at the level of country for Scotland, Wales and Northern Ireland.

Statistical analyses

Crude incidence estimates per 100 000 person years at risk were calculated by dividing the total number of cases by the total number of person years of follow-up then multiplying by 100 000. This was done separately for CD, UC and any IBD with 95% CIs estimated assuming a Poisson distribution. Stratified incidence rates were calculated by sex, age, Townsend Deprivation Index and geographical location. Time period was fitted as both a continuous variable and a categorical variable by calendar year. Mixed multivariable Poisson regression was used to estimate incidence rate ratios (IRRs). Individuals with missing data on Townsend score were included in the analysis using 'missing' as a level to the Townsend variable. GP was included as a random effect to account for any data clustering by practice; the other covariates were included as fixed effects. The Wald test was used to test for significance of categorical variables in the regression model and to test for multiplicative interactions.

Point prevalence was calculated by dividing all cases of IBD (both incident and prevalent) by the total number of individuals contributing data to the cohort on the last day of the study period.

StataCorp. 2017. *Stata Statistical Software: Release 15*. College Station, Texas: StataCorp LLC was used for all analyses.

Sensitivity analysis

In the sensitivity analysis, we broadened our case definition to include any individual who had a single IBD medical Read code (as opposed to two medical Read codes or one medical Read code plus one relevant prescription).

Patient and public involvement

We involved representatives from the University College Hospitals NHS Foundation Trust patient with IBD panel in the early stages of protocol design. However, we did not involve patient and public involvement (PPI) representatives in other aspects of study design or analysis due to IMRD licence agreements and the technical computer programming methods that were involved. We intend to involve PPI representatives in writing a plain language summary for dissemination to peers and patient groups.

RESULTS

11 325 025 individuals (78 985 977 person years of follow-up) were included in the cohort. 5 541 508 (48.9%) were male. 7 944 975 (70.0%) were registered with a GP in England, 1 690 503 (14.9%) Scotland, 1 285 722 (11.4%) Wales and 403 825 (3.6%) Northern Ireland. Mean (SD) age at cohort entry was 34 (22.8) years and median (IQR) follow-up was 5.4 (2.0–11.6) years. We identified 65 700 cases of IBD, including 24 991 cases of CD and 36 705 cases of UC. Among these, 22 560 (8077 for CD and 12 369 for UC) were incident diagnoses made during study follow-up. Overall, crude incidence estimates were 28.6 (95% CI 28.2 to 28.9), 10.2 (95% CI 10.0 to 10.5) and 15.7 (95% CI 15.4 to 15.9)/100 000 person years for 'any IBD', CD and UC, respectively. Point prevalence estimates on 31 December 2018 were 725, 276 and 397 per 100 000 people for 'any IBD', CD and UC, respectively.

Of 28 879, 24 173 (83.7%) individuals given a new code for IBD since entering the study had a record of a prescription for a drug commonly used to treat IBD, comparing to 1.8% for the whole cohort. Additionally, 23 337/28 879 (80.8%) with a code for IBD had a record of presentation to their GP with either diarrhoea, bloody stools, abdominal pain or weight loss, comparing to 33.6% for the whole cohort.

For the period 2000–2017, incidence of 'any IBD' remained relatively stable for those aged 17–40 years (A2 disease) and those aged 0–9 years (A1a disease). However, for those aged over 40 years (A3 disease), crude incidence fell from 37.8 (95% CI 34.5 to 41.4) to 23.6 (21.3–26.0) at an average rate of 2.3% (95% CI 1.9% to 2.7%) per calendar year (p<0.0001) and for those aged 10–16 years (A1b disease), incidence rose from 13.1 (95% CI 8.3 to 19.5) to 25.4 (95% CI 19.5 to 32.4) at an average rate of 3.0% (95% CI 1.7% to 4.3%) per calendar year (p<0.0001; figure 1). When adding an age–time interaction term to the model, we found an interaction for all three main outcomes (p<0.00001, p=0.0046, p<0.00001 for 'any IBD', CD and UC, respectively). Ageband-specific age–time interaction coefficients confirmed increasing incidence in adolescents ages 10–16, decreasing incidence in those aged 40+ years and stable incidence in age groups 0–9 and 17–40 years (online supplementary appendix table 1).

CD incidence

During the study period, CD incidence fell slightly from 10.7 (95% CI 9.5 to 12.1) to 9.0 (95% CI 8.0 to 10.1)/100 000 person years at an average rate of 1.0% (95% CI 0.6% to 1.5%) per calendar year (p<0.0001; figure 2).

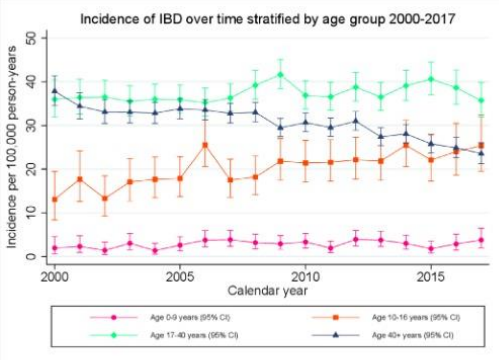

Figure 1 Crude incidence estimates for any inflammatory bowel diseases (IBD), stratified by Montreal/Paris age classification and calendar year, over the period 2000–2017.

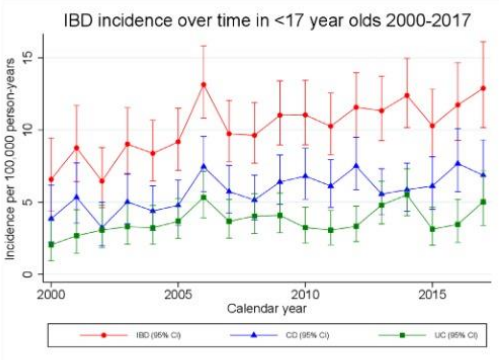

Figure 3 Crude incidence estimates of inflammatory bowel diseases (IBD) in children <17 years, stratified by calendar year, over the period 2000–2017. CD, Crohn's disease; UC, ulcerative colitis.

However, in children <17 years, incidence rose from 3.9 (95% CI 2.2 to 6.2) to 6.9 (95% CI 4.9 to 9.3)/100 000 person years at an average rate of 2.9% (95% CI 1.3% to 4.4%) per calendar year (p<0.0001; figure 3). Although overall crude incidence was higher for boys than for girls (7.4 (95% CI 6.8 to 8.0) vs 4.1 (95% CI 3.6 to 4.6)), a significant rise in incidence was observed for both sexes (average 2.7% (95% CI 0.8% to 4.6%) and 3.3% (95% CI −0.6% to 6.0%) rise per calendar year for boys and girls respectively). No change in incidence was observed for children aged 0–9 years. However, for adolescents aged 10–16 years, incidence rose from 7.6 (95% CI 4.2 to 12.8) to 13.1 (95% CI 9.0 to 18.4)/100 000 person years at an average rate of 2.8% (1.2–4.5) per calendar year (p=0.001).

Incidence of CD was highest in Northern Ireland, Scotland and the North West (13.1 (95% CI 12.0 to 14.4), 12.3 (95% CI 11.7 to 12.9) and 11.9 (95% CI 11.1 to 12.7)/100 000 person years, respectively) and lowest in Wales, London and the West Midlands (8.9 (95% CI 8.4 to 9.6), 8.9 (95% CI 8.3 to 9.6) and 8.4 (95% CI 7.7 to 9.1)/100 000 person years, respectively, figure 4). We observed no association between social deprivation and incidence of CD after adjusting for sex, calendar year, age and geographical location (table 1).

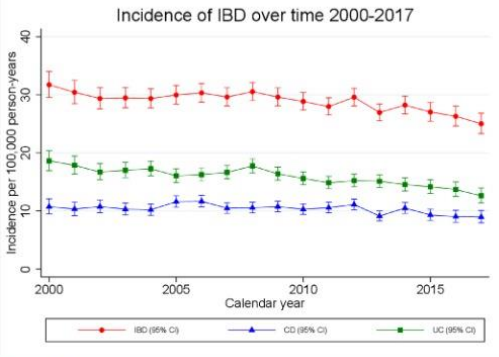

Figure 2 Crude incidence estimates of inflammatory bowel diseases (IBD), stratified by calendar year, over the period 2000–2017. CD, Crohn's disease; UC, ulcerative colitis.

UC incidence

Incidence of UC dropped to a greater extent than for CD over the study period; from 18.6 (95% CI 17.0 to 20.4) to 12.6 (95% CI 11.4 to 13.9)/100 000 person years at an average rate of 1.6% (95% CI 1.3% to 2.0%) per calendar year (p<0.0001; figure 2). The fall in incidence was most pronounced for those aged over 40 years, in whom a 45% drop in incidence was observed, falling from 24.1 (95% CI 21.5 to 26.9) to 13.3 (95% CI 11.6 to 15.2)/100 000 person years (average 3.1% (95% CI 2.6% to 3.6%) decrease per calendar year (p<0.0001)).

In children aged <17, incidence rose from 2.0 (95% CI 0.9 to 3.9) to 5.0 (95% CI 3.4 to 7.2)/100 000 person years (average 2.5% (95% CI 0.5% to 4.4%) rise per calendar year (p=0.01); figure 3). The rise in incidence was largely driven by adolescent boys aged 10–16 in whom incidence rose by 3.4% (95% CI 0.8% to 6.2%) per calendar year (p=0.01). No significant change in incidence was observed in girls aged 10–16 years or children of either sex aged 0–9 years.

Incidence of UC was highest in the North East, the East of England and the East Midlands (18.1 (95% CI 16.0 to 20.5), 17.4 (95% CI 16.2 to 18.6) and 17.5 (95% CI 15.6 to 19.6)/100 000 person years, respectively) and lowest in Wales, the South West and London (14.1 (95% CI 13.4 to 14.9), 15.2 (95% CI 14.2 to 16.2) and 15.3 (95% CI 14.5 to 16.2)/100 000 person years, respectively; figure 4). We observed higher incidence of UC in individuals from the least deprived quintile compared with most deprived (16.8 (95% CI 16.2 to 17.5) vs 13.3 (95% CI 12.6 to

Table 1 Incidence rates and adjusted incidence rate ratios (IRRs) of Crohn's disease (CD) and ulcerative colitis (UC) by sex, age, calendar year, geographical location and social deprivation

	Incidence of CD		Incidence of UC	
	Rate per 100 000		Rate per 100 000	
	Person years (95% CI)	Adjusted IRR (95% CI)*	Person years (95% CI)	Adjusted IRR (95% CI)*
Overall	10.2 (10.0 to 10.5)		15.7 (15.4 to 15.9)	
Sex				
Male	9.3 (0.00 to 9.6)	1	16.7 (16.3 to 17.1)	1
Female	11.1 (10.8 to 11.5)	1.20 (1.15 to 1.25)	14.7 (14.3 to 15.0)	0.87 (0.84 to 0.90)
Age, years				
0–9	1.6 (1.3 to 1.9)	0.11 (0.09 to 0.13)	1.0 (0.8 to 1.3)	0.05 (0.04 to 0.07)
10–16	11.5 (10.7 to 12.4)	0.77 (0.71 to 0.84)	7.4 (6.8 to 8.1)	0.38 (0.35 to 0.42)
17–40	14.9 (14.4 to 15.4)	1	19.2 (18.7 to 19.8)	1
40+	9.2 (8.9 to 9.5)	0.62 (0.59 to 0.64)	17.9 (17.5 to 18.3)	0.92 (0.89 to 0.96)
Year (linear change)		0.99 (0.98 to 0.99)		0.98 (0.98 to 0.99)
Year (categorical variable)				
2000	10.7 (9.5 to 12.1)	1	18.6 (17.0 to 20.4)	1
2001	10.3 (9.2 to 11.6)	0.97 (0.82 to 1.14)	17.9 (16.4 to 19.5)	0.96 (0.85 to 1.09)
2002	10.8 (9.7 to 11.9)	1.00 (0.85 to 1.17)	16.7 (15.4 to 18.1)	0.89 (0.79 to 1.01)
2003	10.3 (9.3 to 11.4)	0.95 (0.82 to 1.11)	17.0 (15.8 to 18.4)	0.91 (0.81 to 1.03)
2004	10.2 (9.3 to 11.2)	0.94 (0.80 to 1.09)	17.3 (16.1 to 18.6)	0.93 (0.82 to 1.04)
2005	11.6 (10.6 to 12.6)	1.07 (0.92 to 1.24)	16.1 (14.9 to 17.3)	0.86 (0.77 to 0.97)
2006	11.7 (10.7 to 12.7)	1.07 (0.93 to 1.24)	16.3 (15.1 to 17.5)	0.87 (0.78 to 0.98)
2007	10.5 (9.6 to 11.4)	0.96 (0.83 to 1.12)	16.7 (15.5 to 17.9)	0.89 (0.80 to 1.00)
2008	10.6 (9.7 to 11.5)	0.97 (0.84 to 1.13)	17.8 (16.6 to 19.0)	0.95 (0.85 to 1.07)
2009	10.8 (9.9 to 11.7)	0.99 (0.86 to 1.15)	16.4 (15.3 to 17.6)	0.88 (0.79 to 0.99)
2010	10.3 (9.4 to 11.2)	0.95 (0.82 to 1.10)	15.6 (14.5 to 16.8)	0.84 (0.75 to 0.94)
2011	10.6 (9.7 to 11.5)	0.97 (0.84 to 1.13)	14.9 (13.8 to 16.0)	0.80 (0.71 to 0.90)
2012	11.1 (10.2 to 12.1)	1.02 (0.88 to 1.18)	15.2 (14.2 to 16.3)	0.82 (0.73 to 0.92)
2013	9.1 (8.3 to 10.0)	0.84 (0.72 to 0.97)	15.1 (14.0 to 16.2)	0.82 (0.73 to 0.92)
2014	10.5 (9.6 to 11.5)	0.96 (0.82 to 1.11)	14.5 (13.5 to 15.7)	0.79 (0.70 to 0.89)
2015	9.3 (8.4 to 10.3)	0.84 (0.72 to 0.98)	14.2 (13.0 to 15.4)	0.77 (0.68 to 0.87)
2016	9.0 (8.1 to 10.1)	0.80 (0.68 to 0.95)	13.7 (12.5 to 15.0)	0.74 (0.65 to 0.84)
2017	9.0 (8.0 to 10.1)	0.79 (0.67 to 0.94)	12.6 (11.4 to 13.9)	0.68 (0.60 to 0.78)
2018	5.9 (5.1 to 6.9)	0.52 (0.43 to 0.63)	10.0 (8.9 to 11.2)	0.54 (0.47 to 0.63)
Region				
East Midlands	9.6 (8.2 to 11.2)	1	17.5 (15.6 to 19.6)	1
East of England	10.9 (10.0 to 11.9)	1.18 (0.96 to 1.44)	17.4 (16.2 to 18.6)	1.01 (0.86 to 1.19)
London	8.9 (8.3 to 9.6)	0.94 (0.77 to 1.14)	15.3 (14.5 to 16.2)	0.94 (0.81 to 1.09)
North East	9.8 (8.2 to 11.6)	1.03 (0.80 to 1.34)	18.1 (16.0 to 20.5)	1.08 (0.88 to 1.32)
North West	11.9 (11.1 to 12.7)	1.27 (1.05 to 1.54)	15.8 (14.9 to 16.7)	0.93 (0.80 to 1.08)
Northern Ireland	13.1 (12.0 to 14.4)	1.43 (1.16 to 1.75)	16.2 (14.9 to 17.5)	1.02 (0.87 to 1.21)
Scotland	12.3 (11.7 to 12.9)	1.36 (1.13 to 1.64)	15.3 (14.7 to 16.0)	0.97 (0.84 to 1.13)
South Central	9.5 (8.9 to 10.2)	1.01 (0.83 to 1.23)	16.1 (15.2 to 17.0)	0.92 (0.79 to 1.07)
South East Coast	9.4 (8.7 to 10.1)	1.04 (0.85 to 1.26)	15.7 (14.9 to 16.6)	0.95 (0.81 to 1.10)
South West	10.1 (9.3 to 11.0)	1.08 (0.89 to 1.32)	15.2 (14.2 to 16.2)	0.88 (0.75 to 1.03)

Continued

Table 1 Continued

	Incidence of CD		Incidence of UC	
	Rate per 100 000		Rate per 100 000	
	Person years (95% CI)	Adjusted IRR (95% CI)*	Person years (95% CI)	Adjusted IRR (95% CI)*
Wales	8.9 (8.4 to 9.6)	0.98 (0.81 to 1.19)	14.1 (13.4 to 14.9)	0.87 (0.75 to 1.01)
West Midlands	8.4 (7.7 to 9.1)	0.89 (0.73 to 1.09)	16.2 (15.3 to 17.2)	0.96 (0.82 to 1.12)
Yorkshire and Humber	9.6 (8.2 to 11.2)	1.00 (0.78 to 1.28)	15.8 (14.0 to 17.8)	0.91 (0.74 to 1.10)
Townsend, quintile				
Missing	10.1 (9.6 to 10.7)	1.08 (0.99 to 1.17)	15.1 (14.4 to 15.7)	0.95 (0.89 to 1.02)
1	9.6 (9.1 to 10.1)	1	16.8 (16.2 to 17.5)	1
2	10.0 (9.5 to 10.5)	1.02 (0.95 to 1.10)	16.5 (15.9 to 17.2)	0.97 (0.92 to 1.03)
3	10.7 (10.1 to 11.2)	1.07 (1.00 to 1.15)	16.2 (15.5 to 16.8)	0.96 (0.91 to 1.01)
4	10.4 (9.8 to 11.0)	1.03 (0.96 to 1.12)	14.8 (14.1 to 15.5)	0.88 (0.83 to 0.94)
5	11.2 (10.5 to 11.9)	1.08 (0.99 to 1.17)	13.3 (12.6 to 14.1)	0.80 (0.74 to 0.86)

*Adjusted for other variables considered: sex, ageband, year, region, Townsend quintile, respectively; IRRs compared with the reference group for each categorical variable.

14.1)/100 000 person years, adjusted IRR 0.80 (95% CI 0.74 to 0.86), table 1).

Sensitivity analysis

When broadening the case definition to include any individual who had a single IBD medical Read code, we observed overall incidence rates of 36.6 (95% CI 36.2 to 37.0), 12.9 (95% CI 12.7 to 13.2) and 19.3 (95% CI 19.0 to 19.6)/100 000 person years for 'any IBD', CD and UC, respectively. We observed a similar fall in incidence of UC, decreasing from 21.8 (95% CI 20.0 to 23.8) to 17.9 (95% 16.4 to 19.4)/100 000 person years (average decrease 1.3% (95% CI 0.9% to 1.6%) per calendar year). However, no fall in CD incidence was observed (online supplementary appendix figure 1). When stratifying IBD incidence by 5 year age bands, the peak in incidence later in life was higher and occurred later than in the primary analysis (online supplementary appendix figures 2 and 3).

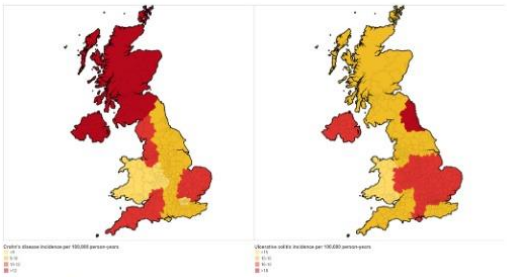

Figure 4 Map showing overall crude incidence of Crohn's disease and ulcerative colitis stratified by geographical region.

DISCUSSION

This is one of the largest observational studies undertaken to investigate trends in IBD epidemiology. Although incidence of IBD remained relatively stable for those aged 17–40 years and those aged 0–9 years, we observed a 38% fall in incidence for those aged over 40 years and a 94% rise in incidence in the adolescent population. The most recent incidence estimates are in line with some of the highest reported rates of paediatric IBD internationally.[25–27]

Study strengths include the large sample size and the prospective collection of healthcare records representative of 'real-life' clinical practice. Unlike previous incidence/prevalence studies that have relied on external data sources to estimate denominator population characteristics, we were able to extract demographics and person-time follow-up for all individuals in our cohort, including those who did not develop IBD. Additionally, IMRD has been shown to be broadly representative of the UK in terms of age, sex, mortality rates and prevalence of numerous comorbidities,[15] allowing us to draw inferences from our data and relate this to the UK population as a whole. Not only has the diagnosis of IBD been validated in a similar GP database,[12] but we have demonstrated that the majority of individuals coded for IBD in IMRD have been prescribed drugs commonly used to treat IBD and presented with symptoms in keeping with IBD. This would support the argument that IMRD represents an important and useful resource for further epidemiological studies of IBD.

Limitations arise when conducting GP database research, particularly as the primary use of the software that contributes to IMRD is for patient management purposes rather than medical research. Thus, data can be incomplete and will often only reflect those events

that are deemed to be relevant to the patient's care. Given that we were also reasonably strict with our case definition, this may have resulted in underascertainment of cases. Although we find reason to be confident in the validity of the data, we were not able to confirm our cases by evidence of radiological, endoscopic or histological findings. Therefore, it is possible that some individuals were misclassified. There was a small risk of duplication of medical records. This could occur if a patient deregistered with one practice contributing to IMRD then subsequently registered with another IMRD practice during the observation period. This is likely to be the case for a very small number of individuals as IMRD only covered 5%–6% of UK GP during the study period. Although the total number of individuals contributing may be a slight overestimate, this would have no effect on incidence or prevalence rates. This is for two reasons: (1) duplicated records would cover different time periods during the study without overlap; (2) we took steps to ensure that prevalent cases of IBD newly transferring to practices were not counted as incident cases[18] Therefore, incident cases were not counted twice.

Data from a multicentre European study (including two UK sites in North West London and East Yorkshire) reported site incidence rates of 2.6 and 8.4/100 000 person years for CD and 15.9 and 8.2/100 000 years for UC.[28] However, only a small number of UK cases were included (n=167). Incidence rates of 8.3 (3.4 to 13.2) and 13.9 (95% CI 7.5 to 20.3)/100 000 person years for CD and UC, respectively, have been reported in North-East England for the period 1990–1994.[13] We report overall incidence rates of 10.2 (95% CI 10.0 to 10.5) and 15.6 (95% CI 15.3 to 15.9)/100 000 person years for CD and UC, respectively, in a far larger cohort and at a national level. We report considerable geographical variation in IBD incidence across the UK with notably high CD incidence in Scotland and Northern Ireland and high UC incidence in the East of England. This may reflect variation in lifestyle factors such as dietary habits and importantly smoking (it is estimated that 14.4% adults in England smoke compared with 15.9% in Scotland and 16.3% in Northern Ireland).[29]

A Danish study based on nationwide registry data (1995–2012) observed comparable incidence rates: 8.9 (95% CI 8.3 to 9.5) and 10.3 (95% CI 9.7 to 11.0)/100 000 person years for CD and 23.4 (95% CI 22.4 to 24.5) and 23.2 (95% CI 22.2 to 24.3)/100 000 person years for UC in males and females, respectively.[30] In contrast to our results, they observed overall rising incidence rates of IBD, but their study was conducted in a different country over an earlier time period including the 1990s when a rise in IBD incidence was described in many high-income countries. Although they adjusted for age in their analysis, temporal trends in incidence stratified by age group were not reported.

In the sensitivity analysis, we observed higher than expected overall incidence rates. Additionally, for UC, the observed peak in incidence for older individuals was higher than the peak in incidence for younger individuals (online supplementary appendix figure 2); this would be unusual in clinical practice. An explanation for this could be that a number of these patients, who perhaps had colitis of a different aetiology, had been misclassified as IBD. On the basis of these findings, one Read code alone was deemed not specific enough for the diagnosis of IBD.

In keeping with published literature, we observed a rising incidence of paediatric IBD during the early 21st century[31] and we provide further evidence of male preponderance in paediatric IBD when compared with adult onset disease.[32 33] Uniquely, in our study, we have demonstrated rising incidence of adolescent IBD in the context of stable incidence in those aged 17–40 years and falling incidence in the over 40s. This may represent a general shift towards earlier diagnosis of IBD for all age groups except the very young (age 0–9 years). Given that IBD most commonly presents in the second to fourth decade of life,[1 2] rising incidence in adolescents might be explained by a number of factors, including improvements in referral pathways and the introduction of new diagnostic tools (eg, faecal calprotectin testing or capsule endoscopy) resulting in cases being picked up earlier. However, one would expect stepwise increases in incidence when new diagnostic tools are rolled out, which we did not observe. Moreover, if rising incidence of adolescent IBD is due to improved referral pathways, a corresponding rise in incidence might be expected in very young children as well as adolescents. It could be argued that changes in GP coding practice may be contributing. But again, one would expect comparable changes in younger age groups if this were the case. On the other hand, if the epidemiological patterns we observed reflect real increases in the incidence of pathology, this is of great concern and could represent earlier manifestation of disease related to environmental exposures in childhood and adolescence.

Our prevalence estimates were very similar to those reported in a well-validated IBD cohort in Lothian, Scotland[10]; our estimate of IBD prevalence for Scotland on 31 August 2018 was 810 per 100 000 compared with 832 per 100 000 reported by their group. Although our study lacked linkage to secondary care records, the similar prevalence estimates would support the argument that few cases were missed. In 2018, 67 150 000 people were estimated to be living in the UK from which we might extrapolate from our data that there were approximately 487 000 people living with IBD in the UK at that time.

Compounding prevalence of IBD has been demonstrated in Canada and in Scotland.[10 34] This relates to the principle that although IBD incidence may be static or falling, while IBD mortality remains very low, overall prevalence will increase (more people are being diagnosed than are dying). In Scotland, IBD prevalence is estimated to reach 1.0% by 2028. We report rising incidence rates of IBD in younger populations and falling incidence in older age groups. Thus, not only will services need to be attuned to rising IBD prevalence and an ageing

demographic, but also to increasing numbers of new diagnoses in young people who will require lifelong care. This is in the context of significant financial challenges to health services.

CONCLUSION

Although we observed a stable or falling incidence of IBD in adults over an 18-year period, our results are consistent with some of the highest reported global incidence and prevalence rates for IBD, with a 94% rise in incidence in adolescents. These findings are concerning and suggest that detailed prospective studies are required to understand the aetiological drivers.

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Patient consent for publication Not required.

Ethics approval IMRD data collection was approved by the NHS South-East Multicentre Research Ethics Committee in 2003. This study was approved by the Scientific Research Committee (SRC) on 29/09/2018 (SRC reference 18THIN082).

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Data availability statement Due to licence agreements with IQVIA, we are unable to share patient level data from the IQVIA Medical Research Database. However, we are happy to share our data extractions upon reasonable request. Data requesters should email the corresponding author to request the relevant data.

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Original research

OPEN ACCESS

Time trends in contraceptive prescribing in UK primary care 2000–2018: a repeated cross-sectional study

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ABSTRACT

Background Over the last 20 years, new contraceptive methods became available and incentives to increase contraceptive uptake were introduced. We aimed to describe temporal trends in non-barrier contraceptive prescribing in UK primary care for the period 2000–2018.

Methods A repeated cross-sectional study using patient data from the IQVIA Medical Research Data (IMRD) database. The proportion (95% CI) of women prescribed non-barrier contraception per year was captured.

Results A total of 2 705 638 women aged 15–49 years were included. Between 2000 and 2018, the proportion of women prescribed combined hormonal contraception (CHC) fell from 26.2% (26.0%–26.3%) to 14.3% (14.2%–14.3%). Prescriptions for progestogen-only pills (POPs) and long-acting reversible contraception (LARC) rose from 4.3% (4.3%–4.4%) to 10.8% (10.7%–10.9%) and 4.2% (4.1%–4.2%) to 6.5% (6.5%–6.6%), respectively. Comparing 2018 data for most deprived versus least deprived areas, women from the most deprived areas were more likely to be prescribed LARC (7.7% (7.5%–7.9%) vs 5.6% (5.4%–5.8%)) while women from the least deprived areas were more likely to be prescribed contraceptive pills (20.8% (21.1%–21.5%) vs 26.2% (26.5%–26.9%)). In 2009, LARC prescriptions increased irrespective of age and social deprivation in line with a pay-for-performance incentive. However, following the incentive's withdrawal in 2014, LARC prescriptions for adolescents aged 15–19 years fell from 6.8% (6.6%–7.0%) in 2013 to 5.6% (5.4%–5.8%) in 2018.

Conclusions CHC prescribing fell by 46% while POP prescribing more than doubled. The type of contraception prescribed was influenced by social deprivation. Withdrawal of a pay-for-performance incentive may have adversely affected adolescent LARC uptake, highlighting the need for further intervention to target this at-risk group.

Key messages

- Over a 19-year period, prescription of combined hormonal contraception almost halved while progestogen-only prescriptions more than doubled.
- Long-acting reversible contraception (LARC) prescriptions were higher in women from most deprived areas while oral contraception prescriptions were higher in women from least deprived areas.
- Pay-for-performance incentives to increase LARC prescription were effective, but their withdrawal may have adversely affected adolescent LARC uptake.

INTRODUCTION

In the UK, approximately 26% of women aged 16–49 years use hormonal contraception.[1] Several new hormonal methods have become available during the last 20 years, including the desogestrel progestogen-only pill (POP), combined oral contraceptive pills (COCPs) containing drospirenone, combined hormonal patches and vaginal rings. Additionally, the UK has seen a number of policy-related initiatives aimed at reducing unwanted pregnancy.[2 3]

In 2005, the National Institute for Health and Care Excellence (NICE) published its first long-acting reversible contraception (LARC) guideline advising that all women requiring contraception should be given information about LARC.[4] In 2009, a pay-for-performance Quality and Outcomes (QOF) incentive for LARC counselling was introduced. This incentive aimed to increase LARC uptake by paying general practitioners (GPs) a premium for providing information relating to LARC to women attending for contraception.[3]

Despite its success, the incentive was retired in 2014, and at the same time funding to sexual and reproductive health (SRH) services was reduced.[5]

Detailed data on trends in contraceptive provision from SRH services is published annually by NHS Digital.[6] However, the majority of women seek contraception from primary care,[7] with only 5% of females aged 13 to 54 years using SRH service for contraception between 1 April 2019 and 31 March 2020.[6] Data on contraceptive prescriptions issued in primary care in England are reported in absolute numbers but they are not linked to individual patients nor is data available for the devolved nations of the UK.[6]

Describing trends in contraceptive prescribing and how they relate to demographic factors such as age and deprivation is an essential step in planning future service delivery as the model of contraceptive care undergoes change. We aimed to investigate sociodemographic and temporal trends in the prescribing of non-barrier contraception in primary care from 2000 to 2018.

METHODS

Study design

A repeated cross-sectional study using electronic UK general practice (GP) records from the IQVIA Medical Research Data (IMRD) database

Data source

In the UK National Health Service (NHS), GPs look after patients in the community and are often the first point of contact for anyone with a health problem. IMRD is a longitudinal database containing the anonymised medical records of 18.3 million patients across 797 UK GP practices. IMRD represents approximately 6% of the UK population and goes back to 1994. Data are recorded using the Read code hierarchical coding system.[8] The GP practices included in IMRD are broadly representative of the UK in terms of practice size, age, gender, mortality and the prevalence of a number of chronic conditions such as diabetes, epilepsy and asthma.[9] IMRD incorporates data from THIN, a Cegadim Database. Reference made to THIN is intended to be descriptive of the data asset licensed by IQVIA.

Study population

Source cohort

First, a source cohort of women was extracted from IMRD. All women aged 15–49 years who contributed data to IMRD for the period 1 January 2000 to 31 December 2018 were eligible for inclusion. This was a dynamic cohort, with women entering and exiting throughout the study period. The age range 15–49 years was selected as this is the World Health Organization (WHO) definition of 'women of reproductive age'.[10] All data included were from time periods after the GP practices had met electronic data quality standards.[11 12]

Women were censored from the cohort at the first recording of any medical event which would usually preclude future use of contraception (hysterectomy, bilateral salpingo-oophorectomy or sterilisation), the first recording of a prescription for hormone replacement therapy (online supplemental code lists), the date they de-registered from the practice or the date of death.

Repeated-cross sectional data

Separate cross-sections were then identified for each calendar year (2000–2018). To be included, each woman was required to contribute data to the source cohort for the entire year from 1 January to 31 December. A woman could contribute data to multiple cross-sections. In each cross-section, a woman's age was defined as the age she would be on 1 July of that year (ie, the midpoint of the year).

Outcomes

The main outcome of interest was the prescription of non-barrier contraceptives. Prescription code lists for the following contraceptives were developed and reviewed by a GP: combined hormonal contraception (CHC) (COCPs, ethinylestradiol and cyproterone acetate (co-cyprindiol), transdermal patches and intravaginal rings), POPs and LARC (intramuscular injections, subdermal implants, intrauterine systems (IUSs) and intrauterine devices (IUDs)).For LARC, Read codes were also used to search the medical records for documented evidence of administration/insertion (online supplemental code lists). Due to a number of non-specific Read codes for IUD/IUS such as 'reinsertion of coil', these two contraceptives were grouped together.

COCPs were stratified by pill generation. Pill generation is the four-level UK classification system used for COCPs as they were rolled out chronologically. The majority of pills contain ethinylestradiol and the difference between the generations is the formulation of the progestogen. First-generation pills were not included in the study as they had all been discontinued in the UK by the early 1990s. Co-cyprindiol, a treatment for acne and also a contraceptive, was included separately. Desogestrel 75 μg was separated from other POPs as it works in a similar way to COCPs by inhibiting ovulation.

Independent variables

The following data were captured for each patient: age (in 5-year bands), country of GP practice, Townsend score (a postcode-linked quintile measurement of deprivation which was taken from the patient's home address at GP registration. 'Townsend 1' is the least deprived and 'Townsend 5' is the most deprived).[13]

Analysis

Stata Statistical Software: Release 15 (2017; StataCorp LLC, College Station, TX, USA) was used for all analyses.

Descriptive characteristics were summarised using numbers and percentages for categorical variables and medians and interquartile ranges (IQRs) for non-normally distributed continuous variables.

The number of women who received each type of contraceptive was reported as a proportion (95% confidence interval (95% CI)) of the total number of women in the cross-section for each year. Multiple prescriptions of the same method within a year were treated the same as a single prescription. Women could be prescribed multiple different types of contraception within 1 year. Proportions were stratified by age group, country and deprivation.

Patient and public involvement

Patients and the public were not involved in this study.

Ethics

IMRD data collection was approved by the NHS South-East Multicentre Research Ethics Committee in 2003. This study was approved by the Scientific Research Committee (SRC) on 11 May 2021 (SRC reference 18'THIN082-A1).

RESULTS

Demographics

A total of 3 577 421 women were included in the source cohort. Nineteen cross-sections were identified, one for each calendar year. 2 705 638 women (15 251 805 person-years) contributed cross-sectional data (table 1). There was minimal difference in median age between cross-sections (range 32.5–33.5 years). Median size of each yearly cross-section was 869 844 (range 4 58 446–9 95 579) patients. Townsend data were missing in 561 233 (20.7%) patients. There was minimal difference in demographics after exclusion of those with missing data (table 1).

Table 1 Descriptive characteristics of women contributing cross-sectional data with and without the inclusion of those with missing Townsend score

Characteristic	Primary analysis	Exclusion of women with missing data
Overall (n)	2 705 638	2 144 405
Country (n (%))		
England	1 885 015 (69.7)	1 555 734 (72.6)
Scotland	405 013 (15.0)	310 706 (14.5)
Wales	314 468 (11.6)	201 680 (9.4)
Northern Ireland	101 142 (3.7)	76 285 (3.6)
Townsend, quintile (n (%))		
Missing	561 233 (20.7)	N/A
1 (least deprived)	482 529 (17.8)	482 529 (22.5)
2	427 003 (15.8)	427 003 (19.9)
3	470 492 (17.4)	470 492 (21.9)
4	446 378 (16.5)	446 378 (20.8)
5 (most deprived)	318 003 (11.8)	318 003 (14.8)
Age at cohort entry (years) (median (IQR))	28.0 (20.5–35.8)	28.0 (20.5–36.1)
Cohort follow-up (years) (median (IQR))	4.9 (2.7–9.1)	5.2 (2.9–9.4)

IQR, interquartile range; N/A, not applicable.

Overall trends

Between 2000 and 2018, the proportion of women receiving a prescription for any contraceptive fell from 32.9% (32.7%–33.0%) to 29.2% (29.1%–29.3%). However, this was in the context of a rise in prescription of LARC from 4.2% (4.1%–4.2%) to 6.5% (6.5%–6.6%) and POPs from 4.3% (4.3%–4.4%) to 10.8 (10.7%–10.9%) and a fall in prescription of CHCs from 26.2% (26.0%–26.3%) to 14.3% (14.2%–14.3%) (figure 1).

Combined hormonal contraception

Second-generation COCP, third-generation COCP and co-cyprindiol prescriptions fell from 20.9% (20.8%–21.0%) to 11.0% (11.0%–11.1%), 4.1% (4.0%–4.1%) to 1.7% (1.7%–1.7%) and 2.2% (2.2%–2.3%) to 0.5% (0.5%–0.5%), respectively. Fourth-generation COCP prescriptions increased from 0.0% to 2.7% (2.7%–2.8%) in 2010 and then declined to 1.4% (1.4%–1.5%) in 2018. Less than 0.1% were prescribed intravaginal rings and contraceptive patches throughout (figure 2).

Prescribing of CHCs fell in all countries. The largest fall was seen in England, falling from 26.5% (26.3%–26.6%) to 13.8% (13.6%–13.9%) and the smallest fall in Northern Ireland; 24.8% (24.1%–25.6%) to 16.8% (16.4%–17.1%) of women (online supplemental figure 1). CHCs were more commonly prescribed in less deprived areas; 26.5% (26.2%–26.9%) and 21.2% (20.9%–21.5%) in least deprived versus most deprived in 2018, respectively (online supplemental figure 2). Women in their twenties saw the most dramatic reduction in CHC prescribing over the study period, falling from 47.0% (46.6%–47.5%) to 25.2% (24.9%–25.5%) in those aged 20–24 years and 42.8% (42.4%–43.2%) to 20.0% (19.7%–20.3%) in those aged 25–29 years (online supplemental figure 3).

Progestogen-only pills

Desogestrel prescriptions increased from 0.0% in 2000 to 10.0% (95% CI 9.9 to 10.1) in 2018 (desogestrel 75 μg was introduced in 2002), whereas prescription of other POPs fell from 4.3% (4.3%–4.4%) to 1.0% (0.9%–1.0%). Prescribing of POPs rose in all countries, the most dramatically in Northern Ireland from 3.2% (2.9%–3.5%) to 11.6% (11.3%–11.9%) (online supplemental figure 4). A similar increase in POP prescribing was observed across all age and

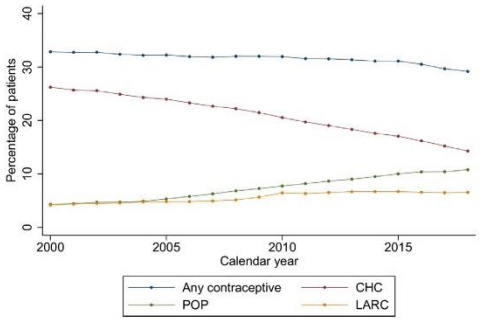

Figure 1 Temporal trends in all non-barrier contraceptive prescribing over the period 2000–2018. CHC, combined hormonal contraception; LARC, long-acting reversiblel contraception; POP, progestogen-only pill.

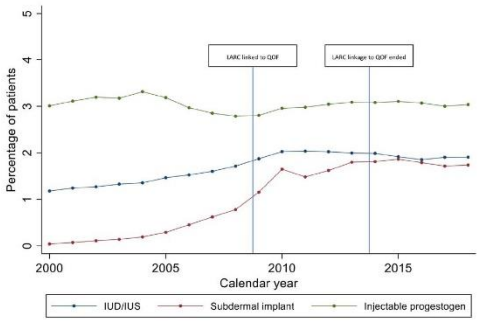

Figure 3 Temporal trends in long-acting reversible contraceptive prescribing over the period 2000–2018. IUD, intrauterine device; IUS, intrauterine system.

socioeconomic groups (online supplemental figure 5 and 6).

Long-acting reversible contraception

IUD/IUS prescribing increased from 1.2% (1.1%–1.2%) in 2000 to 1.9% (1.9%–1.9%) in 2018. Implant prescribing increased from 0.0% to 1.7% (1.7%–1.8%); the older levonorgestrel implants were discontinued and replaced by etonogestrel implants in 1999. IUD/IUS and implant uptake increased more rapidly in line with LARC linkage to QOF in 2009 and plateaued after this date (figure 3). Injectable contraception prescribing was fairly constant throughout the study period fluctuating from 2.8% (2.8%–2.8%) to 3.3% (3.3%–3.4%). However, injectable prescribing fell during the period 2005–2009, then rose marginally when LARC was linked to QOF in 2009 (figure 3). After the pay-for-performance QOF ended in 2014, LARC prescribing fell from 6.7% (6.6%–6.7%) in 2013 to 6.5% (6.5%–6.6%) in 2018 (figure 1).

All countries saw a rise in uptake of LARC over the study period; the largest in Scotland from 4.6% (4.4%–4.8%) to 8.0% (7.9%–8.2%) and the smallest in Northern Ireland from 3.6% (3.3%–3.9%) to 4.8% (4.6%–5.0%) (online supplemental figure 7). LARC was more commonly prescribed in areas of greater deprivation 5.6% (5.4%–5.8%) and 7.7% (7.5%–7.9%) for least deprived versus most deprived, respectively, in 2018 (online supplemental figure 8).

Adolescents aged 15–19 years and women aged 20–24 years saw the biggest increase in LARC prescribing between 2000 and 2013; from 3.9% (3.7%–4.1%) to 6.8% (6.6%–7.0%) and 6.1% (5.9%–6.3%) to 8.9% (8.7%–9.0%), respectively. The only age group to see a reduction in LARC prescription after linkage to QOF ended was adolescents, falling from 6.8% (6.6%–7.0%) in 2013 to 5.6% (5.4%–5.8%) in 2018 (online supplemental figure 9).

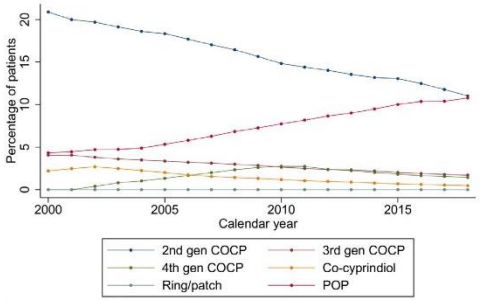

Figure 2 Temporal trends in combined hormonal contraception and progestogen-only pill prescribing over the period 2000–2018. COCP, combined oral contraceptive pill; POP, progestogen-only pill.

DISCUSSION

Over a 19-year period, prescription of CHCs almost halved, but a 2.5-fold increase in POP prescription was found. LARC prescription increased in line with the introduction of the NICE guidance in 2005, with a further increase following the pay-for-performance QOF indicator in 2009. Adolescents were the only age group to see a fall in LARC uptake after the QOF indicator was withdrawn in 2014.

Strengths of this study include the large sample size and the use of a database generalisable to the UK population. Unlike survey studies which rely on self-reporting of contraceptive use, our data are based on prospectively collected electronic prescribing records, thus avoiding recall bias.

There are a number of limitations to this study. First, contraceptive prescriptions from SRH services were not included. Additionally, some GPs do not offer implant or IUD/IUS insertion and women will have to obtain these elsewhere. Therefore, results are an underestimate of actual contraceptive uptake, but still an accurate representation of prescribing in primary care. Second, it is acknowledged that a proportion of women will have been prescribed methods for non-contraceptive reasons (eg, IUS for menorrhagia).

Third, although we captured LARC insertions, some of these devices can remain in situ for up to 10 years. Therefore, we are not able to provide reliable estimates of prevalent use for these methods. Finally, although IMRD has been shown to be generalisable to the UK population, when stratifying by country, contributing practices are not necessarily generalisable to the region.

Similarly to the USA, Ireland, Australia and Canada, oral contraception was the most commonly prescribed method.[14–17] We observed comparable estimates of prescribing to a population-based Northern Irish study for the period 2010–2016 (20.2% vs 16.6% for COCPs and 9.4% vs 8.0% for POPs).[18] The small difference could be explained by the fact that these researchers were unable to link 11% of dispensed contraceptives to individuals and these were not included. In comparison to a Clinical Practice Research Datalink study focusing on the impact of QOF on LARC uptake for the period 2004–2014, our estimates of LARC prescribing were higher (5.7% vs 3.0% for 2009 and 6.7% vs 3.9% for 2014).[19] This could be because this research group classified LARC uptake as 'a branded or generic prescription for LARC' whereas we additionally included documentation of insertion in the medical records. We observed similar trends in LARC prescribing before and during the period that LARC was linked to QOF. However, our study provides new evidence that LARC prescribing has fallen in adolescents since the QOF indicator was withdrawn in 2014. An explanation could be the fact that young people are more likely to be new users of contraception; new users may be more likely to take up LARC when offered it than women already established on contraception that works for them. Young women are the most at risk of unplanned pregnancy,[20] and if LARC uptake in adolescents has fallen then this is a concern. A study assessing rates of unplanned pregnancies in relation to withdrawal of the QOF indicator would a useful piece of work. This could guide decision-making regarding re-implementation of the incentive or the introduction of new interventions.

In keeping with data from Canada and Ireland,[14 16] we found LARC to be more commonly prescribed in deprived areas and oral contraception to be more commonly prescribed in less deprived areas. These trends are likely to be influenced by social inequalities. Contraceptive failure rates have been shown to be higher across all methods in low-income groups.[21] Additionally, in England and Wales, the rate of abortion in the most deprived decile is more than double the rate in the least deprived.[22] These factors could generate prejudice among GPs when selecting appropriate contraception. Practitioners must be trained to provide informed contraceptive choices, including appropriate information and education to avoid prescribing inequalities.

An increase in prescribing of POPs was expected since the introduction of desogestrel 75 μg in 2002.[23] POP prescribing may have also increased due to a shift towards administration of medications via patient group direction; non-medical prescribers may be more likely to supply medications with fewer risks and contraindications.[24] This would account for the reduction in COCP prescribing mirroring the increase in POP prescription. Recently, desogestrel 75 μg became available over-the-counter.[25] While this broadens contraceptive availability, desogestrel 75 μg is not as effective as LARC. We hope that pharmacists will use the opportunity to signpost women, particularly adolescents, to information on LARC and reverse the falling trend in this population.

Our study highlights temporal and sociodemographic trends in contraceptive prescribing across the UK. How contraceptive care is delivered is currently in a period of transition. Prescribers will need to be attuned to changes in demand for contraception, so that any evolving model responds to women's choices and needs.

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Contributors TJP: overall guarantor of the study, study concept and design; generation and manual review of code lists; analysis and interpretation of data; statistical analysis; drafting of the manuscript; obtained funding. EAM: study concept and design; interpretation of data; critical revision of the manuscript for important intellectual content. GR: study concept and design; manual review of code lists; statistical analysis and interpretation of data; critical revision of the manuscript for important intellectual content. LH: study concept and design; statistical analysis and interpretation of data; critical revision of the manuscript for important intellectual content; study supervision.

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Use of contraceptives and risk of inflammatory bowel disease: A nested case–control study

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Summary

Background: How contraceptive formulation, dose, duration of therapy and mode of delivery affects the risk of inflammatory bowel disease (IBD) is poorly described.

Aim: To examine associations between types of hormonal contraception and development of IBD.

Methods: This was a nested case–control study using IQVIA Medical Research Data. Women aged 15-49 years with a new diagnosis of IBD were matched with up to six controls by age, practice and year. Odds ratios (OR) and 95% confidence intervals (95% CI) for incident IBD and use of contraception were calculated.

Results: 4932 incident cases of IBD were matched to 29 340 controls. Use of combined oral contraceptive pills (COCPs) was associated with the development of Crohn's disease and ulcerative colitis (OR 1.60 [1.41-1.82] and 1.30 [1.15-1.45], respectively). Each additional month of COCP exposure per year of follow-up increased risk of Crohn's disease by 6.4% (5.1%-7.7%) and ulcerative colitis by 3.3% (2.1%-4.4%). Progestogen-only pills had no effect on Crohn's disease risk (OR 1.09 [0.84-1.40]) but there was a modest association with ulcerative colitis (OR 1.35 [1.12-1.64]). Parenteral contraception was not associated with the development of Crohn's disease or ulcerative colitis (OR 1.15 [0.99-1.47] and 1.17 [0.98-1.39], respectively).

Conclusions: We observed an increase in the risk of IBD with increasing duration of exposure to COCPs. Progestogen-only pills were not associated with Crohn's disease but there was a modest association with ulcerative colitis. There was no association between parenteral progestogen-only contraception and IBD. These findings are broadly consistent with a hypothesis that the oestrogen component of contraception may drive IBD pathogenesis.

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1 | INTRODUCTION

Changes in the epidemiology of inflammatory bowel disease (IBD) across geographical location and time suggest that environmental risk factors play a major role in disease development.[1]

In the UK, approximately 26% of women of reproductive age use hormonal contraception[2] and combined oral contraceptive pills (COCPs) which work by releasing an oestrogen and a progestogen are the most popular method. An increased risk of development of IBD in association with oral contraceptive pill exposure has been shown in numerous studies.[3-5] However, the precise biological mechanism remains unknown. A number of proposed theories exist, largely relating to the effect of exogenous oestrogen on immunomodulation, intestinal wall function, gut microbiome and hypercoagulability.

Oestrogen has been linked to inhibition of TH1 mediated cytokines and stimulation of TH2 mediated cytokines.[6] Additionally, oestrogen has been implicated in the pathogenesis and disease progression in a number of TH2 mediated inflammatory conditions.[7,8] This would support a relationship between exogenous oestrogens and development of UC but not CD.

It is established that exogenous oestrogen affects oral and vaginal microbiota.[9,10] However, more recent research has implicated the oestrogen-gut microbiome axis as playing a crucial role in the pathogenesis of several oestrogen-mediated diseases.[11] If a complex relationship exists between oestrogen levels and the gut microbiome then one could hypothesise that changing circulating levels of oestrogen may, in turn, disrupt gut flora and precipitate gastrointestinal disease.

Oestrogen has been shown to modulate intestinal wall barrier function[12,13] and individuals who have an episode of bacterial gastroenteritis have been shown to be fourfold more likely to develop IBD in the following year.[14] Therefore, if the barrier function of the intestinal wall is compromised by exogenous oestrogen then this may potentially increase the risk of triggering IBD in a genetically susceptible individual. Additionally, some enteric infections can be sexually acquired and one could hypothesise that women taking contraception may be at greater risk of exposure.[15]

Some have theorised that IBD development may be related to micro-ischaemia within the vasculature of the gut[16] and it is established that COCPs are associated with thromboembolic disease.[17]

How hormone formulation, dose and duration of contraceptive pill exposure relate to IBD risk is poorly characterised. Additionally, there is a paucity of literature on how progestogen-only and parenteral preparations of contraception affect IBD risk.

We hypothesise that oestrogen-containing contraceptives are associated with an increased risk of IBD and progestogen-only methods are not. We aimed to examine the association between various types of contraception and development of IBD. We were particularly interested in the impact of hormone formulation, dose and duration of therapy on subsequent IBD.

2 | MATERIALS AND METHODS

2.1 | Data source

IQVIA Medical Research Data (IMRD) (incorporating data supplied by The Health Improvement Network, a Cegedim SA Database. Reference made to The Health Improvement Network is intended to be descriptive of the data asset licensed by IQVIA) is a large longitudinal database containing the anonymised electronic medical records of 18.3 million patients from 797 general practices throughout the UK. Data in IMRD are based on patient consultation records and are recorded using the Read code hierarchical coding system.[18] The GP practices in IMRD are broadly representative of the UK in terms of age and gender of patients, practice size, geographical distribution, smoking prevalence[19,20] and the prevalence of numerous chronic conditions such as hypertension, asthma and diabetes.[21]

Not only has the diagnosis of IBD been validated in a similar GP database,[22] but we have demonstrated that 98.2% of individuals coded for incident IBD in IMRD have a record of at least one additional clinical event supportive of the diagnosis with 87.7% having at least two supporting events.[23] Clinical events included a prescription for IBD drugs (any aminosalicylate or rectal steroid enema listed in chapter 1.5 of the British National Formulary,[24] azathioprine, mercaptopurine, methotrexate, ciclosporin, infliximab, adalimumab, ustekinumab or vedolizumab [supplementary code lists]), a presentation with symptoms in keeping with IBD (abdominal pain, diarrhoea, bloody stools, weight loss), a referral to a gastroenterologist or an endoscopy.

2.2 | Study population

A cohort of women aged 15-49 years who were registered with study practices contributing to IMRD for the period 1 January 2000-31 December 2018 was identified. Women were required to be registered with the practice for at least 9 months prior to cohort entry to avoid misclassifying prevalent IBD as incident disease.[27] GP practices were required to meet acceptable standards of electronic data quality prior to cohort entry.[25,26] Women were censored from the cohort at the first recording of a condition which would usually preclude future contraceptive use (bilateral salpingo-oophorectomy, hysterectomy, sterilisation) or the first prescription of hormone replacement therapy (supplementary code lists).

Within the cohort, we designed two nested case–control studies, one for CD and one for UC. Cases were those diagnosed with incident CD or UC during study follow-up. Case definition was taken from our previously published incidence study of IBD; In order to qualify as a case, an individual had to have either (a) two codes for IBD at different time points, (b) one code for IBD plus one prescription for a drug commonly used to treat IBD[23] (supplementary code lists). Eligible cases were required to have at least one year of prescribing history prior to the date of diagnosis. One year was selected

because prescriptions for contraceptive pills are typically not longer than one year in length.

Each case was matched with up to six controls by year of birth and GP practice using incidence density sampling. Each control was allocated an index date which was the date of diagnosis for their matched case. Each control was required to have the same (or greater) prescribing history prior to the index date as their matched case. Any additional prescribing history that a control may have had did not contribute towards the analysis (ie all controls contributed the same amount of prescribing history as their matched cases over the same calendar period). The lookback period was defined as the period between the start of the prescribing history and the IBD diagnosis date (or matched index date for controls).

2.3 | Exposures

Exposure to contraceptives was based on the total lookback period. COCPs were subdivided by pill generation. Pill generation is the standard four-level classification system used for COCPs as they were rolled out chronologically, first-generation pills being the oldest and fourth generation the newest. Most pills contain ethinylestradiol and the difference between the generations of pill is the type of progestogen that is included. First-generation pills were not included as they had all been discontinued by the early 1990s. Co-cyprindiol, a pill containing ethinylestradiol and cyproterone acetate which is used as a treatment for acne and as a contraceptive was also included.

For the primary analysis, women were categorised as either non-contraceptive users (no prescribed contraceptive use during the lookback period), second-generation COCP users, newer generation COCP users (including third-generation and fourth-generation COCPs in addition to co-cyprindiol), POP users, long-acting reversible contraception users (these are parenteral progestogen-only methods including intrauterine systems, contraceptive implants and contraceptive intramuscular injections) or mixed contraceptive users (any combination of contraceptives during the lookback period) (supplementary code lists).

Specifically for contraceptive pills, women were classed as current users if their most recent prescription would finish ≤28 days before (or after) the index date. Twenty-eight days was selected because contraceptive pills come in boxes which last 28 days. COCPs were subdivided by oestrogen content; low strength (<30 μg ethinylestradiol) and standard strength (≥30 μg ethinylestradiol). For those pills containing mestranol, we treated 50 μg mestranol as bioequivalent to 35 μg ethinylestradiol.[28] For those pills-containing estradiol, we treated 200 μg estradiol as bioequivalent to 1 μg ethinylestradiol.[29,30]

"Average months of contraceptive pill exposure per year of follow-up" was calculated and treated as both a continuous variable and separately as categorical variable in quantiles of three months per year to check for evidence of non-linearity with the development of IBD. This was done separately for COCPs and POPs. We also calculated "Average daily dose of oral oestrogen over follow-up" and similarly analysed as both a continuous variable and a categorical variable in quantiles of 5 μg ethinylestradiol per day (or equivalent).

2.4 | Covariates and confounding factors

History of endometriosis, acne and polycystic ovarian syndrome were included as covariates because they are all commonly treated with COCPs and are also potentially linked to the development of IBD (supplementary code lists); increased risk of IBD has been shown in women with endometriosis in a nationwide Danish cohort study,[31] severe acne can be a feature of IBD[32,33] and polycystic ovarian syndrome has been shown to be associated with reduced biodiversity in the gut microbiome.[34]

We adjusted for smoking status treating smoking as a categorical variable with the levels "never smoker," "ex-smoker" and "current smoker" (supplementary code lists). Smoking was included as it is an established risk factor for CD and may decrease the risk of developing UC.[35] Additionally, smoking is a relative contraindication to the prescription of COCPs.[36,37]

We adjusted for body mass index (BMI) as a categorical variable using the levels "underweight" (BMI <18), "normal weight" (BMI 18-25), "overweight" (BMI 25-30) and "obese" (over 30) for the primary analysis and as a continuous variable in a sensitivity analysis. BMI was included as CD often presents with weight loss and BMI is an important factor to consider when choosing appropriate contraception.[37]

Social deprivation as measured by Townsend score[38] was included as we found there to be an association between Townsend score and risk of UC in a previous study.[23] Additionally, contraceptive uptake is lower in more deprived socio-economic groups.[39] Evidence of pregnancy during follow-up was included as a yes/no binary variable; pregnancy would usually preclude the use of contraception and women may be less likely to conceive if they are unwell and developing a chronic inflammatory illness (supplementary code lists).

Data on BMI and smoking were captured using the earliest value recorded during the lookback period. If data were missing during this period then the latest value recorded prior to the start of the lookback period was substituted.

2.5 | Statistical analysis

Crude incidence estimates per 100 000 person-years at risk were calculated for the source cohort. Ninety-five per cent confidence intervals (95% CI) were then calculated assuming a Poisson distribution.

Conditional logistic regression was used to analyse the nested-case control studies and obtain odds ratios (OR) for each exposure with 95% CI. The Wald test was used to test for the significance of exposures and categorical variables in the regression model and to test for multiplicative interactions. We were particularly interested

in an interaction between contraceptive pill exposure and smoking as it was reported in a large cohort study that the increased risk of UC with contraceptive pills was exclusive to smokers.[40] To check for secular trends we stratified ORs for OCP exposure by calendar period of IBD diagnosis date/index date using five-yearly quantiles.

Missing data were dealt with using complete case analysis for continuous variables and including "missing" as a level to categorical variables.

StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC was used for all analyses.

2.6 | Ethics

IMRD data collection was approved by the NHS South-East Multicentre Research Ethics Committee in 2003. This study was approved by the Scientific Research Committee (SRC) on 29 September 2018 (SRC reference 18THIN082).

2.7 | Patient and public involvement

We involved representatives from the University College Hospitals NHS Foundation Trust IBD patient panel in refining the research question and designing the study protocol.

3 | RESULTS

A source cohort of 3 202 575 women contributing 16 300 866 person-years of follow-up was identified. Median (IQR) age at cohort entry was 28.2 (21.1-36.1) years. Overall incidence was 14.7 (95% CI 14.1-15.3) and 17.8 (95% CI 17.2-18.5) per 100 000 person-years for CD and UC, respectively.

2231 incident cases of CD were matched to 13 279 controls and 2701 incident cases of UC were matched to 16 061 controls (Table 1). Median (IQR) lookback period was 5.4 (3.0-8.7) years in the CD study and 5.2 (2.9-8.8) years in the UC study.

Amongst the 4932 IBD cases, 4917 (99.7%) had at least one additional event supportive of the diagnosis recorded in the GP notes (a prescription for IBD drugs, gastrointestinal symptoms in keeping with IBD, a referral to a gastroenterologist, an endoscopy) with 4642 (94.1%) having at least two supporting events.

3.1 | Crohn's disease

Use of COCPs was associated with an increased risk of CD (OR 1.60 [95% CI 1.41-1.82]). The increased risk was higher for second-generation COCPs than newer COCPs when compared to non-use (OR 1.69 [95% CI 1.48-1.93] vs 1.25 [95% CI 1.01-1.57], respectively) (Figure 1, Table S1). The risk of CD was increased further amongst current users of COCPs (OR 2.12 [95% CI 1.83-2.44] and 1.64 [95% CI 1.33-2.01] for second-generation and newer COCPs, respectively). However, amongst current COCP users, there was no difference in CD risk for those using low strength oestrogen pills compared to standard strength oestrogen pills (OR 1.16 [95% CI 0.74-1.80]). Use of POPs and parenteral contraceptive methods was not associated with an increased risk of CD compared to non-use (OR 1.09 [95% CI 0.84-1.40] and 1.15 [95% CI 0.99-1.47], respectively; Figure 1, Table S1).

The risk of CD went up with increasing duration of exposure to COCPs (Figure 2). When treating "average months of COCP exposure per year" as a continuous linear variable, each additional month per year of COCP exposure, increased risk of CD by 6.4% (95% CI 5.1-7.7) compared to non-users. When treating average daily dose of oral oestrogen over follow-up as a continuous linear variable, CD risk increased by 3.1% (95% CI 2.5-3.7) per µg/day of ethinylestradiol (or equivalent) compared to non-users. Longer durations of exposure to POPs had no effect on CD risk (OR 0.99 [95% CI 0.97-1.02]). We found no evidence of an interaction between smoking and contraceptive pill exposure on risk of CD (Tables S2-S4). We found no evidence of temporal changes in the relationship between OCP exposure and CD (Table S5).

3.2 | Ulcerative colitis

We found use of all types of contraceptive pills to be associated an increase in risk of UC; OR 1.27 (95% CI 1.12-1.44) for second-generation COCPs, 1.38 (95% CI 1.14-1.67) for newer generation COCPs and 1.25 (95% CI 1.03-1.53) for POPs, with risk increasing slightly amongst current users; OR 1.48 (95% CI 1.29-1.69) for second-generation COCPs, 1.62 (95% CI 1.34-1.95) for newer generation COCPs and 1.35 (95% CI 1.12-1.64) for POPs. Amongst current COCP users, there was no difference in UC risk for those using low strength oestrogen pills compared to standard strength oestrogen pills (OR 1.33 [95% CI 0.81-2.18]). Parenteral methods had no effect on UC risk (OR 1.17 [95% CI 0.98-1.39]) (Figure 1, Table S1).

When treating "average months of COCP exposure per year" as a continuous linear variable, each additional month per year of COCP exposure, increased risk of UC by 3.3% (95% CI 2.1-4.4) compared to non-users (Figure 2), equating to an additonal 1.7% (95% CI 1.1-2.2) increase in risk per µg/day of ethinylestradiol (or equivalent). However, a similar dose-response relationship was not observed with POPs (OR 1.02 [95% CI 1.00-1.04]). No interaction was found between POP exposure and smoking (Table S2). However, we found that the development of UC was slightly more associated with non-smokers taking COCPs than smokers taking COCPs ($P = 0.03$) (Table S3). We found no evidence of temporal changes in the relationship between OCP exposure and UC (Table S5).

TABLE 1 Patient demographics for cases and controls

	Crohn's disease		Ulcerative colitis	
	Cases (n = 2231) (%)	Controls (n = 13 279) (%)	Cases (n = 2701) (%)	Controls (n = 16 061) (%)
Median age (IQR) (diagnosis/index date)	29.8 (22.9-38.3)	29.8 (22.9-38.3)	33.2 (26.4-40.1)	33.2 (26.4-40.1)
Townsend				
1	412 (18.5)	2670 (20.1)	567 (21.0)	3385 (21.1)
2	382 (17.1)	2353 (17.7)	526 (19.5)	2934 (18.3)
3	401 (17.8)	2387 (18.0)	481 (17.8)	2981 (18.6)
4	354 (15.9)	2096 (15.8)	394 (14.6)	2496 (15.5)
5	268 (12.0)	1522 (11.5)	251 (9.3)	1704 (10.6)
Missing	414 (18.6)	2251 (17.0)	482 (17.9)	2561 (16.0)
Weight				
Median BMI (IQR)	23.6 (21.0-27.6)	23.8 (21.2-27.9)	23.1 (20.8-26.4)	23.9 (21.3-28.0)
Normal weight (BMI 18-25)	1042 (46.7)	5532 (41.7)	1436 (53.2)	7119 (44.3)
Overweight (BMI 25-30)	428 (19.2)	2252 (17.0)	476 (17.6)	3050 (19.0)
Obese (BMI >30)	310 (13.9)	1874 (14.1)	294 (10.9)	2313 (14.4)
Underweight (BMI <17)	81 (3.6)	358 (2.7)	91 (3.4)	380 (2.4)
Missing	370 (16.6)	3263 (24.6)	404 (15.0)	3199 (19.9)
Smoking				
Non-smoker	968 (43.4)	6480 (48.8)	1384 (51.2)	8078 (50.3)
Ex-smoker	238 (10.7)	1112 (8.4)	395 (14.6)	1505 (9.4)
Smoker	690 (30.9)	2980 (22.4)	563 (20.8)	3552 (22.1)
Missing	335 (15.0)	2707 (20.4)	359 (13.3)	2926 (18.2)
Polycystic ovarian syndrome	56 (2.5)	328 (2.5)	58 (2.2)	464 (2.9)
Endometriosis	37 (1.7)	148 (1.1)	35 (1.3)	215 (1.3)
Pregnancy	630 (28.2)	3553 (26.8)	867 (32.1)	4606 (28.7)
Acne	341 (15.3)	2333 (17.6)	491 (18.2)	2710 (16.9)

Abbreviation: BMI, body mass index.

3.3 | Sensitivity analysis

When treating BMI as a continuous variable and excluding those with missing BMI, results were similar to the primary analysis across all methods of contraception for both CD and UC. However, confidence intervals were wider and crossed the null value for CD and newer generation COCPs (Table S6).

4 | DISCUSSION

This is the first study to describe IBD diagnosis in relation to a range of different contraceptives including progestogen-only methods. We observed an increase in the risk of CD with increasing durations of exposure to COCPs but not to POPs. We observed a more modest increase in the risk of UC with exposure to COCPs and POPs. There was no association between the use of parenteral progestogen-only contraception and IBD. Although there were inconsistencies, these findings are broadly in accordance with the hypothesis that exogenous oral oestrogen is the component of contraception associated with development of IBD.

Study strengths include the large number of included cases and controls and the use of a database which has been shown to be generalisable to the UK population. Unlike other studies which have relied on self-reporting of historic contraceptive use which is a potential source of recall bias, our data is based on prospectively collected electronic prescribing records which include detailed information on treatment duration, formulation and dosage. In comparison to other case–control studies, where controls have been peer-nominated or recruited from clinic, all women aged 15-49 years from IMRD were eligible for inclusion, thus minimising selection bias.

Our study has a number of limitations. Firstly, the potential misclassification of exposure. Although the vast majority of women in the UK obtain contraception from primary care, our study does not capture those contraceptives obtained from sexual and reproductive health services. In the UK, 5% of females aged 13-54 years used a sexual and reproductive health service for reasons of contraception between 1 April 2019 and 31 March 2020.[41] Additionally,

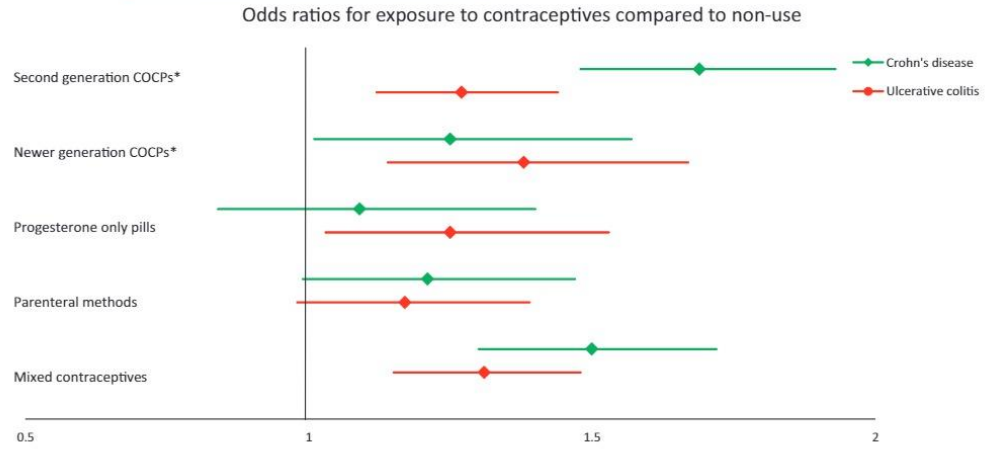

FIGURE 1 Adjusted odds ratios for Crohn's disease and ulcerative colitis exposed to contraceptives compared with non-use. Odds ratios with 95% confidence intervals are adjusted for Townsend score, body mass index, smoking status and history of polycystic ovarian syndrome, endometriosis, acne and pregnancy. *Abbreviation: COCP, combined oral contraceptive pill

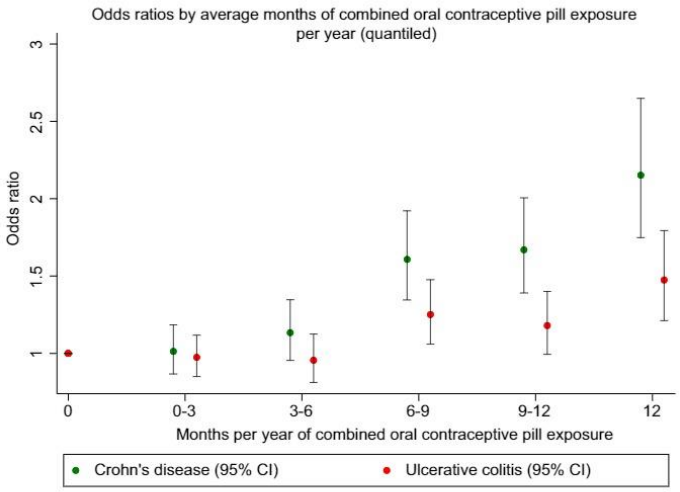

FIGURE 2 Adjusted odds ratios for Crohn's disease and ulcerative colitis exposed to COCPs compared to non-use. Average months per year of exposure to COCPs are stratified in 3-monthly quantiles. Odds ratios and 95% confidence intervals are adjusted for Townsend score, body mass index, smoking status and history of polycystic ovarian syndrome, endometriosis, acne and pregnancy

although IMRD includes detailed prescribing data, we were unable to capture information on patient adherence. It has been reported that up to 52% of women miss their contraceptive pill once or more per month with 14% missing twice or more per month.[42] These factors could potentially result in a shift in the ORs towards unity and an underestimate in the effect of contraceptives on IBD risk. Secondly, BMI and smoking data was unavailable for a slightly larger proportion of controls than cases (Table 1). Thirdly, although our sample size was large, we lacked statistical power to analyse newer classes of COCPs separately; third generation, fourth generation and co-cyprindiol were grouped together. Fourthly, we were not able to confirm our cases with radiological, endoscopic or histological findings. Therefore, it is possible that a small number were misclassified. Finally, although a validation paper has shown that median time between IBD diagnosis and the electronic recording in the primary care records is only eight days,[22] there are bound to be delays in IBD diagnosis for a number of other reasons such as misdiagnosis or extended wait times for colonoscopy. This could introduce bias if

we have included contraceptive exposure after a woman has already developed IBD; being diagnosed with a chronic illness may influence contraceptive uptake.

In keeping with published literature, we found an association between contraceptive pill use and risk of IBD.[3-5] Our overall ORs for contraceptive pill exposure in relation to IBD were similar to a meta-analysis including 20 studies published in 2017[4]; 1.51 (95% CI 1.34-1.71) vs 1.32 (95% CI 1.17-1.49) for CD and 1.29 (95% CI 1.15-1.44) vs 1.30 (95% CI 1.13-1.49) for UC. In comparison to a smaller nested-case control study from the Asia-Pacific region,[43] we observed similar ORs for newer generations of OCPs (1.25 [95% CI 1.01-1.57] vs 1.31 [95% CI 0.55-1.99] for CD and 1.38 [95% CI 1.14-1.67] vs 1.20 [95% CI 0.70-1.70] for UC). However, they concluded that these associations were non-significant which could be explained by insufficient study power. In keeping with the small number of previous studies looking at the duration of exposure, we found that the risk of IBD increased with longer periods of exposure. We observed a more than doubling in risk of CD in those taking COCPs continuously throughout follow-up. Contrary to a large US cohort study, we found that the development of UC was slightly more associated with non-smokers taking COCPs.[40] However, we did not observe this effect for POPs or contraceptive pills overall (Tables S3-S5). As the effect was small, this may represent a chance finding.

No previous studies have looked at IBD risk specifically in relation to progestogen-only contraceptive methods and our finding that increased CD risk was isolated to oestrogen-containing contraception is novel. Of note, a study exploring associations between contraceptive pills and disease outcomes in CD found that there was an increased risk of surgery in those taking COCPs but not progestogen-only methods.[44] Although we found no difference in IBD risk between users of low strength and standard strength oestrogen-containing COCPs, it should be noted that differences in oestrogen content amongst most COCPs are small (usually containing 20-35 μg ethinyloestradiol or equivalent).

Although a number of studies have associated oestrogens with IBD pathogenesis, genome-wide association studies have not implicated a number of genetic determinants of circulating oestrogen levels (variants in/near CYP19A1, FAM9B, Xq27.3, TRIM4 and CYP11B1/B2)[45] as at risk loci for IBD[46] and a mendelian randomisation analysis has found that genetically predicted 17β-estradiol reduced low-grade systemic inflammatory markers in women.[47] However, it is important to note that COCPs do not work by slightly increasing background levels of endogenous oestrogen, they provide exogenous hormones which have a number of inhibitory effects on the pituitary and hypothalamus to prevent ovulation and anti-androgenic properties.

The benefits of contraceptives greatly outweigh the risk of developing IBD in the vast majority of individuals. However, our results may be useful to those women seeking contraception who have a strong family history of IBD. Importantly, our research does begin to shed some light on the potential biological mechanisms involved in the pathogenesis of these two diseases, highlighting the importance of future studies focusing on specific exogenous sex hormones.

ACKNOWLEDGEMENTS

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Declaration of personal interests: TJP and AWS have received research funding from The Charles Wolfson Charitable Trust and The Harbour Foundation. LH has received research funding from The Welcome Trust.

AUTHORSHIP

Guarantor of the article: Thomas Joshua Pasvol

Author contributions: The lead author (Thomas Joshua Pasvol) confirms the independence of researchers from funders and that all authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. The lead author affirms that this manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained.

TJP, SB, AWS, GR and LH designed the study. TJP extracted the data. TJP and LH performed the statistical analysis. TJP, SB, AWS, GR and LH interpreted the results. TJP wrote the manuscript. SB, AWS, GR and LH revised the manuscript for important intellectual content. TJP confirms that all authors approved the final version of the article, including the authorship list.

DATA AVAILABILITY STATEMENT

Data may be obtained from a third party and are not publicly available. Data were obtained from IQVIA Medical Research Data. The authors' licence for using these data does not allow sharing of raw data with third parties. However, the authors are happy to share the code used in this study upon reasonable request. Requesters should email the corresponding author to request the relevant code.

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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6.2 Appendix B: Ethical approvals

6.2.1 Scientific Research Committee ethical approval

SRC Feedback

Researcher Name: Thomas Pasvol
Organisation: University College London
SRC Reference Number: 18THIN082
Date: 25th October 2018
Study title: Inflammatory bowel disease in UK primary care: Time trends in incidence and associations with contraception

Committee opinion: Approved

The following feedback has been supplied by the SRC.

Notes from the Chair:

Approved

Approved documents:

Approved document	Version	Date
SRC_Protocol_18THIN082_v1_29-09-2018	1	29/09/2018

We are pleased to inform that you can proceed with the study as this is now approved. IQVIA will let the relevant Ethics committee know this study has been approved by the SRC.

Once the study has been completed and published, it is important for you to inform IQVIA in order for us to advise the SRC and your reference number to be closed.

References to all published studies are added to our website enabling other researchers to become aware of your work. In order to identify your study as using the THIN database, we recommend that you include the words "The Health Improvement Network (THIN)" within your title. Copies of publication(s), where available, will be appreciated.

I wish you and your team all the best with the study progression.

Mustafa Dungarwalla
Consultant

6.2.2 Scientific Research Committee ethical approval: amendment

SRC Feedback

Researcher Name: Thomas Pasvol
Organisation: University College London
SRC Reference Number: 18THIN082-A1
Date: 11th May 2021
Study title: Inflammatory bowel disease in UK primary care: Time trends in incidence and associations with contraception

Committee opinion: Amendment Approved

The following feedback has been supplied by the SRC.

Notes from the Chair:

Approved

Approved documents:

Approved document	Version	Date
SRC_Protocol_18THIN082_A1_v1.1_04-05-2021	1.1	04/05/2021
18THIN082_Researcher responses		

We are pleased to inform that your protocol has been approved and you can proceed with the study.

As part of our ongoing commitment to improve transparency and public awareness in the use of patient data in research, all manuscripts, abstracts and posters using IQVIA Medical Research Data (IMRD) are to be reviewed and approved prior to publication.

This is to ensure that:

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IQVIA will let the Health Research Authority (HRA REC) that this study protocol has been approved by the SRC.

I wish you and your team all the best with the study progression.

Mustafa Dungarwalla
Senior consultant

6.3 Read code lists

6.3.1 Any Inflammatory bowel Disease

Read code	Description
14C4.11	H/O: ulcerative colitis
8Cc5.00	Management of inflammatory bowel disease
8Cc5.11	Management of IBD (inflammatory bowel disease)
J08z900	Orofacial Crohn's disease
J4...12	Inflammatory bowel 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
J400500	Exacerbation of Crohn's disease of small intestine
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
J401200	Exacerbation of Crohn's disease of large intestine
J401z00	Crohn's disease of the large bowel NOS
J401z11	Crohn's colitis
J402.00	Regional ileocolitis
J40z.00	Regional enteritis NOS
J40z.11	Crohn's disease NOS
J41..12	Ulcerative colitis and/or proctitis
J410.00	Ulcerative proctocolitis
J410100	Ulcerative colitis
J410200	Ulcerative rectosigmoiditis
J410300	Ulcerative proctitis
J410400	Exacerbation of ulcerative colitis
J410z00	Ulcerative proctocolitis NOS
J413.00	Ulcerative pancolitis
J41y.00	Other idiopathic proctocolitis
J41yz00	Other idiopathic proctocolitis NOS
J41z.00	Idiopathic proctocolitis NOS
J4z6.00	Indeterminate colitis
Jyu4000	[X]Other Crohn's disease
Jyu4100	[X]Other ulcerative colitis

6.3.2 Crohn's disease

Read code	Description
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
J400500	Exacerbation of Crohn's disease of small intestine
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
J401200	Exacerbation of Crohn's disease of large intestine
J401z00	Crohn's disease of the large bowel NOS
J401z11	Crohn's colitis
J402.00	Regional ileocolitis
J40z.00	Regional enteritis NOS
J40z.11	Crohn's disease NOS
Jyu4000	[X]Other Crohn's disease

6.3.3 Ulcerative colitis

Read code	Description
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
J410400	Exacerbation of ulcerative colitis
J410z00	Ulcerative proctocolitis NOS
J413.00	Ulcerative pancolitis
J41y.00	Other idiopathic proctocolitis
J41yz00	Other idiopathic proctocolitis NOS
J41z.00	Idiopathic proctocolitis NOS
Jyu4100	[X]Other ulcerative colitis

6.3.4 Acne

Read code	Description
2FG5.00	Acne scar
679g000	Acne management education
M153.00	Rosacea
M153000	Acne rosacea
M153200	Rosacea hypertrophica
M153400	Ocular rosacea
M153z00	Rosacea NOS
M25y600	Acne keloid
M261.00	Other acne
M261000	Acne vulgaris
M261100	Acne conglobata
M261600	Cystic acne
M261A00	Pustular acne
M261B00	Steroid acne
M261C00	Tropical acne
M261F00	Acne fulminans
M261H00	Acne keloid
M261K00	Acne keloidalis
M261L00	Excoriated acne
M261X00	Acne, unspecified
M261z00	Other acne NOS
Myu6800	[X]Other acne
Myu6900	[X]Other rosacea
Myu6F00	[X]Acne, unspecified

6.3.5 Polycystic ovarian syndrome

Read code	Description
C164.00	Polycystic ovaries
C164.12	Stein - Leventhal syndrome
C164.13	Multicystic ovaries
C165.00	Polycystic ovarian syndrome

6.3.6 Endometriosis

Read code	Description
7E0D800	Laparoscopic laser destruction of endometriosis
BBL1.11	[M]Stromal endometriosis
K50..00	Endometriosis
K500.00	Endometriosis of uterus
K500000	Internal endometriosis

K500100	Endometriosis of myometrium
K500200	Endometriosis of cervix
K500z00	Endometriosis of uterus NOS
K501.00	Endometriosis of ovary
K502.00	Endometriosis of the fallopian tube
K503.00	Endometriosis of the pelvic peritoneum
K503000	Endometriosis of the broad ligament
K503100	Endometriosis of the pouch of Douglas
K503200	Endometriosis of the parametrium
K503300	Endometriosis of the round ligament
K503z00	Endometriosis of the pelvic peritoneum NOS
K504.00	Endometriosis of the rectovaginal septum and vagina
K504000	Endometriosis of the rectovaginal septum
K504100	Endometriosis of the vagina
K504z00	Endometriosis of the rectovaginal septum and vagina NOS
K505.00	Endometriosis of the intestine
K505000	Endometriosis of the appendix
K505100	Endometriosis of the colon
K505200	Endometriosis of the rectum
K505z00	Endometriosis of the intestine NOS
K506.00	Endometriosis in scar of skin
K50y.00	Other endometriosis
K50y000	Endometriosis of the bladder
K50y100	Endometriosis of the lung
K50y200	Endometriosis of the umbilicus
K50y300	Endometriosis of the vulva
K50yz00	Other endometriosis NOS
K50z.00	Endometriosis NOS

6.3.7 Pregnancy

Due to the length of this codelist (3,085 codes), it has been omitted from the electronic and hard copies of this thesis. It can be found in the supporting information of my open access publication in Alimentary Pharmacology and Therapeutics. Available at:

https://onlinelibrary.wiley.com/doi/10.1111/apt.16647?af=R

6.3.8 Smoking

Read code	Description	Smoking status
13p0.00	Negotiated date for cessation of smoking	smoker
ZRh4.11	RFS - Reasons for smoking scale	smoker
137N.00	Ex pipe smoker	ex-smoker

9kn..00	Non-smoker annual review - enhanced services administration	never-smoker
137Q.11	Smoking restarted	smoker
137A.00	Ex-heavy smoker (20-39/day)	ex-smoker
6791.00	Health ed. - smoking	smoker
137j.00	Ex-cigarette smoker	ex-smoker
ZRao.00	Occasions for smoking scale	smoker
67A3.00	Pregnancy smoking advice	smoker
8CAL.00	Smoking cessation advice	smoker
E251z00	Tobacco dependence NOS	smoker
137V.00	Smoking reduced	smoker
ZG23300	Advice on smoking	smoker
137l.00	Ex roll-up cigarette smoker	ex-smoker
9ko..00	Current smoker annual review - enhanced services admin	smoker
8IEK.00	Smoking cessation programme declined	smoker
137P.11	Smoker	smoker
ZRao.11	OFS - Occasions for smoking scale	smoker
137H.00	Pipe smoker	smoker
1373.00	Light smoker - 1-9 cigs/day	smoker
9kf2.11	COPD structured smoking assessment declined	smoker
8IEo.00	Referral to smoking cessation service declined	smoker
1372.00	Trivial smoker - < 1 cig/day	smoker
137f.00	Reason for restarting smoking	smoker
9ko..11	Current smoker annual review	smoker
137..11	Smoker - amount smoked	smoker
137h.00	Minutes from waking to first tobacco consumption	smoker
8T08.00	Referral to smoking cessation service	smoker
E251200	Tobacco dependence, episodic	smoker
137d.00	Not interested in stopping smoking	smoker
8IEM.00	Smoking cessation drug therapy declined	smoker
137m.00	Failed attempt to stop smoking	smoker
8H7i.00	Referral to smoking cessation advisor	smoker
137e.00	Smoking restarted	smoker
137Q.00	Smoking started	smoker
8HkQ.00	Referral to NHS stop smoking service	smoker
ZRh4.00	Reasons for smoking scale	smoker
1376.00	Very heavy smoker - 40+cigs/d	smoker
E251000	Tobacco dependence, unspecified	smoker
ZRaM.00	Motives for smoking scale	smoker
137K000	Recently stopped smoking	ex-smoker
1377.00	Ex-trivial smoker (<1/day)	ex-smoker
137b.00	Ready to stop smoking	smoker

8IAj.00	Smoking cessation advice declined	smoker
9kf1.11	Referred for COPD structured smoking assessment	smoker
1378.00	Ex-light smoker (1-9/day)	ex-smoker
8IEM000	Varenicline smoking cessation therapy declined	smoker
1379.00	Ex-moderate smoker (10-19/day)	ex-smoker
9NS0200	Referral for smoking cessation service offered	smoker
67H1.00	Lifestyle advice regarding smoking	smoker
9kf1.00	Refer COPD structured smoking assessment - enhanc serv admin	smoker
1371.11	Non-smoker	never-smoker
137C.00	Keeps trying to stop smoking	smoker
1372.11	Occasional smoker	smoker
137J.00	Cigar smoker	smoker
1V08.00	Smokes drugs in cigarette form	smoker
E251300	Tobacco dependence in remission	ex-smoker
137P.00	Cigarette smoker	smoker
137B.00	Ex-very heavy smoker (40+/day)	ex-smoker
137R.00	Current smoker	smoker
ZV4K000	[V]Tobacco use	smoker
137G.00	Trying to give up smoking	smoker
8HTK.00	Referral to stop-smoking clinic	smoker
9kf2.00	COPD structured smoking assessment declined - enh serv admin	smoker
67H6.00	Brief intervention for smoking cessation	smoker
137c.00	Thinking about stopping smoking	smoker
1374.00	Moderate smoker - 10-19 cigs/d	smoker
SMC..00	Toxic effect of tobacco and nicotine	smoker
1375.00	Heavy smoker - 20-39 cigs/day	smoker
ZRaM.11	MFS - Motives for smoking scale	smoker
137O.00	Ex cigar smoker	ex-smoker
E251100	Tobacco dependence, continuous	smoker
137T.00	Date ceased smoking	ex-smoker
9km..11	Ex-smoker annual review	ex-smoker
9kn..11	Non-smoker annual review	never-smoker
9km..00	Ex-smoker annual review - enhanced services administration	ex-smoker
137M.00	Rolls own cigarettes	smoker
1371.00	Never smoked tobacco	never-smoker
137F.00	Ex-smoker - amount unknown	ex-smoker
E251.00	Tobacco dependence	smoker
8CAg.00	Smoking cessation advice provided by community pharmacist	smoker
137S.00	Ex smoker	ex-smoker

137K.00	Stopped smoking	ex-smoker

6.3.9 Conditions precluding the use of contraception

Read code	Description
1599.00	H/O: hysterectomy
159A.11	H/O: sterilisation - female
159B.00	H/O: bilateral oophorectomy
15A9.11	H/O: hysterotomy
61H..00	Contraception: female sterilis
685H.00	No smear - benign hysterectomy
685H.11	No smear - hysterectomy
7E04.00	Abdominal excision of uterus
7E04.11	Abdominal hysterectomy
7E04.12	Wertheim hysterectomy
7E04000	Abdominal hysterocolpectomy and excision periuterine tissue
7E04100	Abdominal hysterectomy & excision of periuterine tissue NEC
7E04200	Abdominal hysterocolpectomy NEC
7E04300	Total abdominal hysterectomy NEC
7E04311	Bonney abdominal hysterectomy
7E04312	Hysterectomy NEC
7E04400	Subtotal abdominal hysterectomy
7E04500	Abdominal hysterectomy and bilateral salpingoophorectomy
7E04511	Abdominal hysterectomy & bilateral salpingoophorectomy (BSO)
7E04512	TAH - total abdom hysterectomy & bilateral salpingoophorect
7E04600	Radical hysterectomy
7E04700	Abdominal hysterectomy and right salpingoopherectomy
7E04711	Abdominal hysterectomy and left salpingoopherectomy
7E04800	Abdominal hysterectomy and left salpingoophorectomy
7E04900	TAH - Tot abdom hysterectomy and BSO - bilat salpingophorect
7E04A00	Abdominal hysterectomy with conservation of ovaries
7E04B00	Lapar total abdominal hysterect bilat salpingo-oophorectomy
7E04C00	Laparoscopic hysterectomy
7E04E00	Laparoscopic subtotal hysterectomy
7E04F00	Subtotal abdominal hysterectomy with conservation of ovaries
7E04G00	Total abdominal hysterectomy with conservation of ovaries
7E04H00	Subtotl abdominal hysterectomy & bilat salpingo-oophorectomy
7E04J00	Subtotl abdominal hysterectomy & right salpingo-oophorectomy
7E04K00	Subtotal abdominal hysterectomy & left salpingo-oophorectomy

7E04N00	Radical hysterectomy with conservation of ovaries
7E04P00	Radical hysterectomy with bilateral salpingo-oophorectomy
7E04y00	Other specified abdominal excision of uterus
7E04z00	Abdominal excision of uterus NOS
7E05.00	Vaginal excision of uterus
7E05.11	Schauta radical vaginal hysterectomy
7E05.12	Vaginal hysterectomy
7E05000	Vaginal hysterocolpectomy and excision of periuterine tissue
7E05100	Vaginal hysterectomy and excision of periuterine tissue NEC
7E05200	Vaginal hysterocolpectomy NEC
7E05300	Vaginal hysterectomy NEC
7E05311	Heaney vaginal hysterectomy
7E05400	Laparoscopic vaginal hysterectomy
7E05500	Vaginal hysterectomy with conservation of ovaries
7E05600	Lap assist vag hysterectomy with bilat salpingo-oophorectomy
7E05700	Vaginal hysterectomy and right salpingo-oophorectomy
7E05800	Vaginal hysterectomy and left salpingo-oophorectomy
7E05y00	Other specified vaginal excision of uterus
7E05y11	Ward vaginal hysterectomy
7E05z00	Vaginal excision of uterus NOS
7E10000	Bilateral salpingoophorectomy
7E10100	Bilateral salpingectomy NEC
7E10200	Bilateral oophorectomy NEC
7E11100	Salpingoophorectomy remaining solitary fallop tube and ovary
7E11300	Salpingectomy of remaining solitary fallopian tube NEC
7E11500	Oophorectomy of remaining solitary ovary NEC
7E15.00	Open bilateral occlusion of fallopian tubes
7E15.11	Open bilateral female sterilisation
7E15000	Open bilateral ligation of fallopian tubes
7E15011	Pomeroy open bilateral ligation of fallopian tubes
7E15100	Open bilateral clipping of fallopian tubes
7E15111	Open bilateral ringing of fallopian tubes
7E15y00	Other specified open bilateral occlusion of fallopian tubes
7E15z00	Open bilateral occlusion of fallopian tubes NOS
7E16.11	Other open female sterilisation
7E16000	Open ligation of remaining solitary fallopian tube
7E16200	Open clipping of remaining solitary fallopian tube
7E16211	Open clipping of residual solitary fallopian tube
7E16212	Open ringing of remaining solitary fallopian tube
7E1C.00	Endoscopic bilateral occlusion of fallopian tubes
7E1C.11	Endoscopic bilateral female sterilisation
7E1C.12	Laparoscopic bilateral female sterilisation
7E1C000	Endoscopic bilateral cauterisation of fallopian tubes
7E1C100	Endoscopic bilateral clipping of fallopian tubes

7E1C200	Endoscopic bilateral ringing of fallopian tubes
7E1C300	Endoscopic bilateral placement of intrafallopian implants
7E1Cy00	Endoscopic bilateral occlusion of fallopian tubes OS
7E1Cz00	Endoscopic bilateral occlusion of fallopian tubes NOS
7E1D.12	Other endoscopic female sterilisation
7E1D.13	Other laparoscopic female sterilisation
7E1D000	Endoscopic occlusion of remaining solitary fallopian tube
7E1D300	Endo place intrafallop implant remain solitary fallop tube
7F1A000	Caesarean hysterectomy
9O8W.00	Cervical smear to continue post hysterectomy
K515.00	Post hysterectomy vaginal vault prolapse
L398500	Delivery by caesarean hysterectomy
ZV25200	[V]Sterilisation

6.3.10 LARC insertion/administration

Read code	Description
6151.00	IUD fitted
6153.00	IUD re-fitted
61A2.00	"Morning after" IUD fitted
61A2.11	Post-coital IUD fitted
7E09.12	Intrauterine device procedure
7E09000	Introduction of intrauterine contraceptive device
7E09011	Fitting of intrauterine contraceptive device
7E09100	Replacement of intrauterine contraceptive device
7E09111	Change of intrauterine contraceptive device
7E09400	Introduction of Mirena coil
7E09600	Replacement of intrauterine system
7E09700	Insertion of intrauterine system
ZV25100	[V]Intrauterine contraceptive device insertion
ZV25112	[V]Intrauterine contraceptive device insertion
ZV25113	[V]Intrauterine contraceptive device insertion
ZV25412	[V]Reinsertion of coil
ZV25415	[V]Reinsertion of intrauterine contraceptive device
ZV2541A	[V]Reinsertion of intrauterine contraceptive device
ZV25D00	[V]Reinsertion of intrauterine contraceptive device
ZV25D11	[V]Reinsertion of coil
7G2AG00	Insertion of Implanon
7G2AJ00	Insertion of etonogestrel radiopaque contraceptive implant
61KA.00	Insertion of subcutaneous contraceptive
61KC.00	Insert subcutaneous contraceptive implnt othr healthcre prov
7G2AB00	Insertion of subcutaneous contraceptive
7G2AH00	Reinsertion of subcutaneous contraceptive
61B..00	Depot contraceptive
61B..11	Depot contraception

61B1.00	Depot contraceptive given
61B1.11	Depo-provera injection given
61B2.00	Depot contraceptive repeated
61B3.00	Depot contraceptive-no problem
61BZ.00	Depot contraceptive NOS

6.3.11 LARC removal

Read code	Description
6152.00	IUD removed
615B.00	IUD expelled
615B.11	IUD fallen out
7D1E400	Removal intrauterine contracept device from pouch of Douglas
7D1E411	Removal of contraceptive coil from pouch of Douglas
7E09200	Removal of intrauterine contraceptive device NEC
7E09300	Removal of displaced intrauterine contraceptive device
7E09500	Removal of Mirena coil
7E09800	Removal of intrauterine system
ZV25413	[V]Removal of coil
ZV25416	[V]Removal of intrauterine contraceptive device
ZV2541B	[V]Removal of intrauterine contraceptive device
ZV25E00	[V]Removal of intrauterine contraceptive device
ZV25E11	[V]Removal of coil
61KF.00	Remov subcutaneous contraceptive implant othr healthcre prov
7G2HA00	Removal of Implanon
7G2HB00	Removal of etonogestrel radiopaque contraceptive implant
7G2H700	Removal of subcutaneous contraceptive

6.3.12 IBD symptoms

Read code	Description
1625.00	Abnormal weight loss
1625.11	Abnormal weight loss - symptom
1627.00	Unintentional weight loss
196..11	Abdominal pain type
1962.00	Colicky abdominal pain
1963.00	Non-colicky abdominal pain
1969.00	Abdominal pain
196B.00	Painful rectal bleeding
196C.00	Painless rectal bleeding
197..13	Site of abdominal pain
1971.00	Central abdominal pain
197A.00	Generalised abdominal pain

197A.11	General abdominal pain-symptom
197B.00	Upper abdominal pain
197C.00	Lower abdominal pain
19E6.00	Blood in faeces
19E6.11	Blood in faeces symptom
19EH.00	Mucus in faeces
19F..00	Diarrhoea symptoms
19F..11	Diarrhoea
19F..12	Loose stools
19F2.00	Diarrhoea
19F3.00	Spurious (overflow) diarrhoea
19F4.00	Toddlers diarrhoea
19FZ.00	Diarrhoea symptom NOS
19FZ.11	Diarrhoea & vomiting, symptom
19G..00	Diarrhoea and vomiting
1D1A.00	Complaining of weight loss
22A8.00	Weight loss from baseline weight
4737.11	Melaena - O/E of faeces
4762.00	Faeces: fresh blood present
4762.11	Blood in faeces
4763.00	Faeces: mucous present
4764.11	Pus in faeces
A076.11	Viral diarrhoea
A082.00	Infectious diarrhoea
A082.11	Travellers' diarrhoea
A082000	Dysenteric diarrhoea
A082100	Epidemic diarrhoea
A082z00	Infectious diarrhoea NOS
A083.00	Diarrhoea of presumed infectious origin
A083.11	Diarrhoea & vomiting -? infect
Ayu0H00	[X]Diarrhoea+gastroenteritis of presumed infectious origin
E264300	Psychogenic diarrhoea
E264311	Spurious diarrhoea
Eu45317	[X]Psychogenic diarrhoea
J4...13	Noninfective diarrhoea
J432.11	Allergic diarrhoea
J433.11	Dietetic diarrhoea
J43z.11	Chronic diarrhoea
J4z..11	Presumed noninfectious diarrhoea
J4zz.11	Diarrhoea - presumed non-infectious
J521000	Irritable bowel syndrome with diarrhoea
J524000	Diarrhoea after gastrointestinal tract surgery
J525.00	Functional diarrhoea
J573011	Rectal bleeding
J573012	PRB - Rectal bleeding
J681.11	Blood in stool
J681.12	Altered blood in stools
J681.13	Blood in stools altered
L16y500	Abdominal pain in pregnancy
Q46y100	Neonatal diarrhoea
R077100	[D] Stools loose
R090.00	[D]Abdominal pain

R090400	[D]Abdominal cramps
R090E00	[D]Recurrent acute abdominal pain
R090H00	[D]Upper abdominal pain
R090N00	[D]Nonspecific abdominal pain
R090P00	[D]Functional abdominal pain syndrome
R090y00	[D]Other specified abdominal pain
R090z00	[D]Abdominal pain NOS
R121200	[D]Mucus in stool
R121300	[D]Pus in stool
Ryu1100	[X]Other and unspecified abdominal pain
1623.00	Weight decreasing
197..11	Flank pain
197..12	Iliac fossa pain
197..14	Subcostal pain
1972.00	Epigastric pain
1973.00	Left subcostal pain
1974.00	Right subcostal pain
1975.00	Left flank pain
1976.00	Right flank pain
1977.00	Right iliac fossa pain
1978.00	Left iliac fossa pain
1979.00	Suprapubic pain
197D.00	Right upper quadrant pain
19E4.12	C/O - melaena
R090000	[D]Abdominal tenderness
R090500	[D]Epigastric pain
R090600	[D]Umbilical pain
R090700	[D]Hypochondrial pain
R090800	[D]Suprapubic pain
R090900	[D]Pain in right iliac fossa
R090A00	[D]Pain in left iliac fossa
R090J00	[D]Right upper quadrant pain
R090K00	[D]Left upper quadrant pain
R090L00	[D]Left lower quadrant pain
R090M00	[D]Right lower quadrant pain

6.3.13 Endoscopy

Read code	description
316C.00	Wireless capsule endoscopy
36...00	Endoscopy / administration
361..00	Endoscopy: general admin
3611.00	Endoscopy arranged
3612.00	Endoscopy carried out
3614.00	Endoscopy normal
3614000	Gastroscopy normal
3615.00	Endoscopy abnormal
3615000	Gastroscopy abnormal
3616.00	Check endoscopy - condition resolved

3617.00	Colonoscopy normal
3618.00	Colonoscopy abnormal
3619.00	Colonoscopy equivocal
361Z.00	Endoscopy - general admin NOS
36Z..00	Endoscopy admin NOS
760E.00	Diagnostic fibreoptic endoscopic examination of oesophagus
760E000	Diagnostic fibreoptic endoscopic exam & biopsy lesion oesoph
760E100	Diagnost fibreoptic endoscopic exam of oesophagus via stoma
760Ey00	Diagnost fibreoptic endoscopic examination of oesophagus OS
760Ez00	Diagnost fibreoptic endoscopic examination of oesophagus NOS
761F.00	Diagnostic fibreoptic endoscopic exam of upper GI tract
761F.11	Diagnostic fibreoptic gastroscopy
761F000	Diagnostic fibreoptic endoscopy & biopsy of upper GI tract
761F100	Diagnostic gastroscopy NEC
761F200	Diagnostic gastroscopy via stoma
761Fy00	Diagnostic fibreoptic endoscopic exam upper GI tract OS
761Fz00	Diagnostic fibreoptic endoscopic exam upper GI tract NOS
761Fz11	Gastroscopy NEC
761Fz12	Upper Gastrointestinal endoscopy
7625.00	Diagnostic endoscopic examination of duodenum
7625000	Diagnostic endoscopic examination and biopsy duodenum lesion
7625y00	Diagnostic endoscopic examination of duodenum OS
7625z00	Diagnostic endoscopic examination of duodenum NOS
7637.00	Diagnostic endoscopic examination of jejunum
7637000	Diagnostic endoscopic examination and biopsy lesion jejunum
7637y00	Other specified diagnostic endoscopic examination of jejunum
7637z00	Diagnostic endoscopic examination of jejunum NOS
764A.00	Diagnostic endoscopic examination of ileum
764A000	Diagnostic endoscopic examination and biopsy of ileum lesion
764A100	Diagnostic endoscopic examination of ileum via stoma
764A400	Wireless capsule endoscopy
764Ay00	Other specified diagnostic endoscopic examination of ileum
764Az00	Diagnostic endoscopic examination of ileum NOS
771J.00	Diagnostic endoscopic examination on colon
771J.11	Diagnostic colonoscopy
771J000	Diagnostic fibreoptic endoscopic exam & biopsy colon lesion
771J100	Check colonoscopy
771J200	Limited colonoscopy
771Jy00	Other specified diagnostic endoscopic examination of colon
771Jz00	Diagnostic endoscopic examination of colon NOS
771Q.12	Diagnostic rigid endoscopic examination of sigmoid colon
772A.11	Diagnostic endoscopic examination of rectum
772B.11	Therapeutic endoscopic examination of rectum
773F.00	Diag endoscopic examination enteric pouch using colonoscope

773F100	Diag endoscopic exam colonic pouch using colonoscope NEC
773F300	Diag endoscopic exam ileoanal pouch using colonoscope NEC
773Fy00	OS diagnos endos examination enteric pouch using colonoscope
773Fz00	Diag endosc examination enteric pouch using colonoscope NOS
773G100	Diag endoscopic exam colonic pouch using fibre sigmoid NEC
773Gy00	OS diag endoscopic exam enteric pouch using fibre sigmoid
773H.00	Diagnostic endoscopic exam enteric pouch using rigid sigmoid
773H100	Diag endoscopic exam colonic pouch using rigid sigmoid NEC
773H300	Diag endoscop exam ileoanal pouch using rigid sigmoid NEC
773Hy00	OS diagnostic endoscopic exam enteric pouch us rigid sigmoid
8HS..00	Referral for endoscopy
8HS..11	Referral for gastroscopy
8HU1.00	Referral for colonoscopy
8LJ..00	Colonoscopy planned
9EV4.00	Endoscopy report received
9EV5.00	Colonoscopy report received
9N1Y.00	Seen in gastroscopy clinic
ZV58700	[V]Other endoscopy normal
773F000	Diag endos exam col pouch biopsy colonic pouch using colono
773F200	Diag endos exam ileoan pou biopsy ileoanal pouch using colon
773G.00	Diag endos exam enteric pouch using fibreoptic sigmoidoscope
773G000	Diag endos exam col pouch biop of col pouch us fibre sigmoid
773G200	Diag endo exam ileo pou biop of ileo pouch us fibre sigmoid
773G300	Diag endos exam ileoanal pouch using fibreoptic sigmoid NEC
773Gz00	Diagnostic endos exam enteric pouch using fibre sigmoid NOS
773H000	Diag endos exam colon pouch biop col pouch us rigid sigmoid
773H200	Diag end exam ileoanal pouc biop ileo pouch us rigid sigmoid
773Hz00	Diagnostic endos exam enteric pouch using rigid sigmoid NOS

6.4 Prescription code lists

6.4.1 Post-menopausal hormone-replacement therapy

Drug code	Generic name
54611979	Estradiol 500micrograms / Dydrogesterone 2.5mg tablets
60462979	Estradiol 50micrograms/24hours / Levonorgestrel 7micrograms/24hours transdermal patches
60489979	Estradiol 25micrograms/24hours transdermal patches
60490979	Estradiol 25micrograms/24hours transdermal patches
78588978	Estradiol 50micrograms/24hours transdermal patches
82739998	Estradiol 1mg gel sachets
82740998	Estradiol 1mg gel sachets
82741998	Estradiol 500microgram gel sachets
82742998	Estradiol 500microgram gel sachets
83058998	Generic hormonin tablets
83429998	Estradiol 100micrograms/24hours transdermal patches
83430998	Estradiol 75micrograms/24hours transdermal patches
83431998	Estradiol 25micrograms/24hours transdermal patches
83432998	Estradiol 50micrograms/24hours transdermal patches
84780998	Conjugated oestrogens 300microgram tablets
84781998	Conjugated oestrogens 300microgram tablets
84862998	Estradiol 0.06% gel (750microgram per actuation)
85771979	Ethinylestradiol 33.9micrograms/24hours / Norelgestromin 203micrograms/24hours transdermal patches
85772979	Ethinylestradiol 33.9micrograms/24hours / Norelgestromin 203micrograms/24hours transdermal patches
85962998	Estradiol 100micrograms/24hours transdermal patches
85963998	Estradiol 100micrograms/24hours transdermal patches
85964998	Estradiol 75micrograms/24hours transdermal patches
85965998	Estradiol 50micrograms/24hours transdermal patches
85966998	Estradiol 50micrograms/24hours transdermal patches
85967998	Estradiol 25micrograms/24hours transdermal patches
85973998	Estradiol 100micrograms/24hours transdermal patches
85974998	Estradiol 75micrograms/24hours transdermal patches
85975998	Estradiol 50micrograms/24hours transdermal patches
85976998	Estradiol 25micrograms/24hours transdermal patches
86050998	Generic Clinorette tablets
86058998	Estradiol 2mg tablets
86546979	Estradiol 1mg gel sachets
86831998	Estradiol 1mg / Drospirenone 2mg tablets
86832998	Estradiol 1mg / Drospirenone 2mg tablets
87042998	Estradiol 100micrograms/24hours transdermal patches
87043998	Estradiol 75micrograms/24hours transdermal patches
87044998	Estradiol 50micrograms/24hours transdermal patches

87045998	Estradiol 37.5micrograms/24hours transdermal patches
87046998	Estradiol 25micrograms/24hours transdermal patches
87047998	Estradiol 100micrograms/24hours transdermal patches
87048998	Estradiol 75micrograms/24hours transdermal patches
87049998	Estradiol 50micrograms/24hours transdermal patches
87050998	Estradiol 37.5micrograms/24hours transdermal patches
87051998	Estradiol 25micrograms/24hours transdermal patches
87076979	Generic Femoston 2/10mg tablets
87082979	Generic Evorel Sequi transdermal patches
87549998	Conjugated oestrogens 300microgram / Medroxyprogesterone 1.5mg modified-release tablets
87550998	Conjugated oestrogens 300microgram / Medroxyprogesterone 1.5mg modified-release tablets
87759998	Ethinylestradiol 2microgram tablets
87898979	Generic climagest 1mg tablets
87901979	Generic climagest 1mg tablets
87953998	Conjugated oestrogens equine with medroxyprogesterone acetate 625micrograms with 10mg tablets
88207998	Estradiol 1mg / Dydrogesterone 5mg tablets
88320998	Estradiol 2mg / Norethisterone acetate 1mg tablets
88327998	Estradiol 100micrograms/24hours transdermal patches
88329998	Estradiol 75micrograms/24hours transdermal patches
88331997	Estradiol 100micrograms/24hours transdermal patches
88331998	Estradiol 75micrograms/24hours transdermal patches
88561998	Phyto progesterone cream
88634979	Estradiol 1mg / Dydrogesterone 5mg tablets
88635979	Estradiol 1mg / Dydrogesterone 5mg tablets
88638979	Estradiol 1mg / Dydrogesterone 5mg tablets
88826998	Estradiol 80micrograms/24hours transdermal patches
88828998	Estradiol 40micrograms/24hours transdermal patches
88835998	Estradiol 50micrograms/24hours transdermal patches
88887997	Generic Evorel Sequi transdermal patches
88887998	Generic Evorel Sequi transdermal patches
88889998	Estradiol 50micrograms/24hours / Norethisterone 170micrograms/24hours transdermal patches
88912998	Estradiol valerate 2mg / norethisterone 700microgram tablets
88915998	Estradiol 1mg gel sachets
88935998	Estradiol hemihydrate 150mcg nasal spray
88937998	Estradiol 150micrograms/dose nasal spray
89082996	Estradiol 100micrograms/24hours transdermal patches
89082997	Estradiol 50micrograms/24hours transdermal patches
89082998	Estradiol 25micrograms/24hours transdermal patches
89171979	Conjugated estrogens & medroxyprogesterone 0.625mg+5mg tablets
89173979	Conjugated estrogens & medroxyprogesterone 0.625mg+5mg tablets
89176979	Conjugated estrogens & medroxyprogesterone 0.625mg+5mg tablets
89209996	Estradiol 75micrograms/24hours transdermal patches

89209997	Estradiol 50micrograms/24hours transdermal patches
89209998	Estradiol 25mcg transdermal patches
89212998	Estradiol and (estradiol with levonorgestrel) 80mcg/24hrs with (50mcg+20mcg/24hr) twice weekly patch
89216998	Generic nuvelle ts transdermal patches
89253998	Phyto progesterone cream
89295998	Ethinylestradiol 33.9micrograms/24hours / Norelgestromin 203micrograms/24hours transdermal patches
89321998	Generic FemSeven Sequi transdermal patches
89359998	Estradiol with dydrogesterone 1mg +10mg tablets
89399998	Estradiol 1mg / Norethisterone acetate 500microgram tablets
89469998	Generic Novofem tablets
89500998	Estradiol 50mcg/24hours vaginal ring
89627998	Estradiol 75micrograms/24hours transdermal patches
89629998	Estradiol 75micrograms/24hours transdermal patches
89684979	Conjugated oestrogens 625microgram tablets and norgestrel 150microgram tablets
89685979	Conjugated oestrogens 625microgram tablets and norgestrel 150microgram tablets
89722979	Estradiol 50micrograms/24hours / Norethisterone 170micrograms/24hours transdermal patches
89723979	Estradiol 50micrograms/24hours / Norethisterone 170micrograms/24hours transdermal patches
89725979	Estradiol 50micrograms/24hours / Norethisterone 170micrograms/24hours transdermal patches
89803998	Estradiol 1mg / dydrogesterone 5mg tablets
89869998	Phyto progesterone 1.5% cream
89901998	Progesterone 3% cream
89907998	Phyto progesterone 3% cream
89953998	Estradiol 2mg tablets
90083998	Generic Evorel Sequi transdermal patches
90241996	Estradiol 100micrograms/24hours transdermal patches
90241997	Estradiol 50micrograms/24hours transdermal patches
90241998	Estradiol 25micrograms/24hours transdermal patches
90247996	Estradiol 100micrograms/24hours transdermal patches
90247997	Estradiol 50micrograms/24hours transdermal patches
90247998	Estradiol 25micrograms/24hours transdermal patches
90523998	Estradiol valerate & norethisterone 2mg+0.7mg tablets
90617998	Estradiol valerate 2mg / Medroxyprogesterone 5mg tablets
90618996	Estradiol valerate 2mg / Medroxyprogesterone 5mg tablets
90618997	Estradiol valerate 1mg / Medroxyprogesterone 2.5mg tablets
90618998	Estradiol valerate 1mg / Medroxyprogesterone 5mg tablets
90620998	Estradiol 40micrograms/24hours transdermal patches and dydrogesterone 10mg tablets
90645998	Estradiol 50micrograms/24hours / Levonorgestrel 7micrograms/24hours transdermal patches

90646998	Estradiol 50micrograms/24hours / levonorgestrel 7micrograms/24hours transdermal patches
90770998	Piperazine oestrone sulphate 1.5mg with medroxyprogesterone 10mg tablet
90771998	Piperazine oestrone sulphate 1.5mg with medroxyprogesterone 10mg tablet
90813998	Estradiol acetate 1.25mg vaginal ring
90819997	Estradiol 100micrograms/24hours transdermal patches
90819998	Estradiol 50micrograms/24hours transdermal patches
90834996	Estradiol 25micrograms/24hours transdermal patches
90834997	Estradiol 100micrograms/24hours transdermal patches
90834998	Estradiol 75micrograms/24hours transdermal patches
90835996	Estradiol 100micrograms/24hours transdermal patches
90835997	Estradiol 50micrograms/24hours transdermal patches
90835998	Estradiol 50micrograms/24hours transdermal patches
90873997	Generic Elleste Duet 1mg tablets
90873998	Generic Elleste Duet 2mg tablets
90875997	Estradiol 2mg tablets
90875998	Estradiol 1mg tablets
90894998	Estradiol 50micrograms/24hours transdermal patches
91052998	Estradiol 80micrograms/24hours transdermal patches and dydrogesterone 10mg tablets
91054998	Estradiol 40micrograms/24hours transdermal patches
91086998	Estradiol valerate 2mg / Norethisterone 1mg tablets
91090996	Estradiol 75micrograms/24hours transdermal patches
91090997	Estradiol 50micrograms/24hours transdermal patches
91090998	Estradiol 37.5micrograms/24hours transdermal patches
91096998	Conjugat oestrogen equi and (conjugat oestrogen equi with medroxyprogesterone acetate 625 micrograms with (625 microgram
91097998	Generic premique cycle tablets
91113998	Conjugated oestrogens 625microgram / medroxyprogesterone 5mg tablets
91114998	Conjugated estrogens & medroxyprogesterone 0.625mg+5mg tablets
91307997	Estradiol 40micrograms/24hours transdermal patches and dydrogesterone 10mg tablets
91307998	Estradiol 80micrograms/24hours transdermal patches and dydrogesterone 10mg tablets
91328998	Generic adgyn combi tablets
91350996	Estradiol valerate 1mg / Medroxyprogesterone 2.5mg tablets
91350997	Estradiol valerate 1mg / Medroxyprogesterone 5mg tablets
91350998	Estradiol valerate 1mg / Medroxyprogesterone 2.5mg tablets
91351998	Generic Tridestra tablets
91388996	Estradiol and (estradiol with dydrogesterone) 2mg with (2mg with 20mg) tablets
91388997	Estradiol and (estradiol with dydrogesterone) 2mg with (2mg with 10 mg) tablets

91388998	Estradiol and (estradiol with dydrogesterone) 1mg with (1mg with 10mg) tablets
91389996	Generic femoston 2/20mg tablets
91389997	Generic Femoston 2/10mg tablets
91389998	Generic Femoston 1/10mg tablets
91399997	Estradiol 1mg gel sachets
91399998	Estradiol 0.06% gel (750microgram per actuation)
91400998	Estradiol 1.25g/dose gel
91412996	Estradiol 1mg / Norethisterone acetate 500microgram tablets
91412997	Estradiol with norethisterone acetate (continuous combined) 2mg with 0.7mg tablets
91412998	Estradiol valerate 2mg / Norethisterone 1mg tablets
91423998	Estradiol 2mg / Norethisterone acetate 1mg tablets
91457998	Estradiol 80micrograms/24hours transdermal patches
91469998	Estradiol and (estradiol with levonorgestrel) 50mcg/24hrs with (50mcg+10mcg/24hrs) once weekly patch
91479998	Generic Tridestra tablets
91546998	Estradiol valerate 2mg / Norethisterone 1mg tablets
91560998	Progesterone 1.5% cream
91620996	Estradiol 75micrograms/24hours transdermal patches
91620997	Estradiol 50micrograms/24hours transdermal patches
91620998	Estradiol 37.5micrograms/24hours transdermal patches
91680998	Estradiol with norethisterone acetate 50mcg/24hours(4mg/unit) with 1mg patch with tablet
91859998	Estradiol valerate 1mg tablets
91862998	Estradiol 2mg / Norethisterone acetate 1mg tablets
91864998	Generic nuvelle tablets
91865998	Estradiol valerate 2mg tablets
91871998	Estradiol valerate with norgestrel 2mg+500micrograms tablets
91878998	Ethinylestradiol 33.9micrograms/24hours / Norelgestromin 203micrograms/24hours transdermal patches
92065998	Estradiol 100micrograms/24hours transdermal patches
92171998	Estradiol 1mg / Dydrogesterone 5mg tablets
92221998	Estradiol 25micrograms/24hr once weekly patch
92251998	Estradiol with (estradiol with norethisterone acetate) 1mg with (1mg with 1mg) tablets
92366998	Estradiol 100micrograms/24hours transdermal patches
92371998	Estradiol 50micrograms/24hours transdermal patches
92440998	Estradiol 2mg / Norethisterone acetate 1mg tablets
92585998	Estradiol with norethisterone 0mcg/24hours(3.2mg/unit) with 1mg patch with tablet
92586998	Estradiol 50micrograms/24hours transdermal patches and norethisterone 1mg tablets
92962996	Estradiol 40micrograms/24hours transdermal patches
92962997	Estradiol 80micrograms/24hours transdermal patches
92962998	Estradiol 100micrograms/24hours transdermal patches

93073996	Estradiol 75micrograms/24hours transdermal patches
93073997	Estradiol 25micrograms/24hours transdermal patches
93073998	Estradiol 50micrograms/24hours transdermal patches
93164979	Estradiol valerate & norethisterone 2mg+0.7mg tablets
93165979	Estradiol valerate & norethisterone 2mg+0.7mg tablets
93169979	Estradiol 2mg / Norethisterone acetate 1mg tablets
93174979	Estradiol 2mg / Norethisterone acetate 1mg tablets
93189992	Estradiol 50micrograms/24hours transdermal patches
93191979	Estradiol 0.06% gel (750microgram per actuation)
93192979	Estradiol 0.06% gel (750microgram per actuation)
93193979	Estradiol 0.06% gel (750microgram per actuation)
93194979	Estradiol 0.06% gel (750microgram per actuation)
93195979	Estradiol 0.06% gel (750microgram per actuation)
93197979	Tibolone 2.5mg tablets
93201979	Tibolone 2.5mg tablets
93204979	Tibolone 2.5mg tablets
93211979	Conjugated oestrogens 625microgram tablets
93251979	Estradiol 100micrograms/24hours transdermal patches
93254979	Estradiol 100micrograms/24hours transdermal patches
93260979	Estradiol 100micrograms/24hours transdermal patches
93262979	Estradiol 100micrograms/24hours transdermal patches
93267979	Estradiol 50micrograms/24hours transdermal patches
93269979	Estradiol 50micrograms/24hours transdermal patches
93276979	Estradiol 50micrograms/24hours transdermal patches
93278979	Estradiol 50micrograms/24hours transdermal patches
93281979	Estradiol 50micrograms/24hours transdermal patches
93283979	Estradiol 50micrograms/24hours transdermal patches
93284979	Estradiol 50micrograms/24hours transdermal patches
93285979	Estradiol 50micrograms/24hours transdermal patches
93287979	Estradiol 50micrograms/24hours transdermal patches
93288979	Estradiol 50micrograms/24hours transdermal patches
93293979	Estradiol 25micrograms/24hours transdermal patches
93296979	Estradiol 25micrograms/24hours transdermal patches
93303979	Estradiol 25micrograms/24hours transdermal patches
93308979	Estradiol 75micrograms/24hours transdermal patches
93311979	Estradiol 75micrograms/24hours transdermal patches
93315998	Tibolone 2.5mg tablets
93319998	Tibolone 2.5mg tablets
93321979	Estradiol valerate 2mg tablets
93325979	Estradiol valerate 2mg tablets
93336992	Ethinyloestradiol 5 mg tab
93341979	Estradiol valerate 1mg tablets
93352979	Estradiol 37.5micrograms/24hours transdermal patches
93354979	Estradiol 80micrograms/24hours transdermal patches
93387992	Ethinyloestradiol 2 mcg tab
93461992	Oestradiol 17b

93578998	Ethinylestradiol 1mg tablets
93696997	Estradiol valerate 2mg tablets
93696998	Estradiol valerate 1mg tablets
93764992	Conjugated oestrogens / norgestrel 1.25 mg tab
94156992	Ethinyloestradiol 15 mcg tab
94161997	Estradiol and (estradiol with norethisterone) and (estradiol) triphasic forte 4mg with (4mg with 1mg) with (1mg) tablets
94161998	Generic Trisequens tablets
94162998	Generic Cyclo-Progynova 2mg tablets
94252992	Conjugated oestrogens 625/norgestrel 500 mcg tab
94309992	Prempak 1.25mg mg tab
94361992	Tace 12 mg cap
94458992	Ethinyloestradiol 25 mcg tab
94472997	Conjugated oestrogens 1.25mg tablets and norgestrel 150microgram tablets
94472998	Conjugated oestrogens 625microgram tablets and norgestrel 150microgram tablets
94516996	Estradiol 100micrograms/24hours transdermal patches
94516997	Estradiol 50micrograms/24hours transdermal patches
94516998	Estradiol 25micrograms/24hours transdermal patches
94517998	Estradiol 50micrograms/24hours transdermal patches and norethisterone acetate 1mg tablets
94518996	Estradiol 25micrograms/24hours transdermal patches
94518997	Estradiol 100micrograms/24hours transdermal patches
94518998	Estradiol 25micrograms/24hours transdermal patches
94519996	Estradiol 75micrograms/24hours transdermal patches
94519997	Estradiol 25micrograms/24hours transdermal patches
94519998	Estradiol 50micrograms/24hours transdermal patches
94737997	Estradiol valerate 2mg tablets
94737998	Estradiol valerate 1mg tablets
94918998	Ethinylestradiol 33.9micrograms/24hours / Norelgestromin 203micrograms/24hours transdermal patches
94971998	Estropipate 1.5mg tablets
94989992	Ethinyloestradiol 30 mcg tab
94990992	Ethinyloestradiol 100 mcg tab
95339998	Quinestradol 250mcg tablets
95351992	Estradiol 50mg implant
95363992	Estriol 250mcg tablets
95603998	Generic nuvelle tablets
95657997	Estradiol valerate and (estradiol valerate with levonorgestrel) 1mg with (1mg with 250micrograms) tablets
95657998	Estradiol valerate and (estradiol valerate with levonorgestrel) 2mg with (2mg with 75micrograms) tablets
95698997	Norgestrel and conjugated oestrogens (equine) 150micrograms + 1.25mg tablet

95698998	Norgestrel and conjugated oestrogens (equine) 150micrograms + 625micrograms tablet
96371992	Oestradiol .01 mg tab
96392997	Dienestrol 5mg tablets
96392998	Dienestrol 1mg tablets
96609996	Conjugated oestrogens 2.5mg tablets
96609997	Conjugated oestrogens 1.25mg tablets
96609998	Conjugated oestrogens 625microgram tablets
96744997	Estriol 1mg tablets
96744998	Estriol 250micrograms tablets
96745998	Estradiol with estrone and estriol tablets
96746992	Premarin 1.25mg/norgestrel 0.15mg mg tab
96746998	Estradiol with estrone and estriol tablets
96747996	Estradiol 40micrograms/24hours transdermal patches
96747997	Estradiol 1mg tablets
96747998	Estradiol 2mg tablets
96748997	Estradio; 5m/ml injection
96748998	Estradiol 1mg/ml injection
96892992	Estradiol 50micrograms/24hours transdermal patches
97387992	Ethinyloestradiol 20 mcg pes
97397992	Ethinyloestradiol 5 mcg cap
97404992	Ethisterone 5 mg tab
97457997	Estradiol valerate 2mg tablets
97457998	Estradiol valerate 1mg tablets
97458997	Generic Cyclo-Progynova 2mg tablets
97458998	Generic cyclo-progynova 1mg tablets
97482997	Generic trisequens forte tablets
97482998	Generic Trisequens tablets
97625997	Estradiol valerate (2mg) with norethisterone (1 mg) tablets
97625998	Estradiol valerate and (estradiol valerate with norethisterone) 1mg with (1mg with 1mg) tablets
97732998	Generic estracombi tts transdermal patches
97759996	Estradiol 50micrograms/24hours / Norethisterone 170micrograms/24hours transdermal patches
97759998	Estradiol with (estradiol with norethisterone acetate) 50mcg/24 hr with (50mcg+250mcg/24 hr) twice weekly patch
97762997	Estradiol 1mg tablets
97762998	Estradiol 2mg tablets
97765997	Estradiol & norethisterone acetate 2mg+1mg tablets
97765998	Generic climagest 1mg tablets
97826992	Estradiol 1mg tablets
97947992	Premarin 0.625mg/norgestrel 0.15mg mg tab
97993996	Ethinylestradiol 50microgram tablets
97993997	Ethinylestradiol 20micrograms tablet
97993998	Ethinylestradiol 10microgram tablets
98468989	Estradiol 50mg implant

98468990	Estradiol 25mg implant
98728998	Ethinylestradiol with methyltestosterone 4.4micrograms + 3.6mg tablet
98839998	Conjugated oestrogens 1.25mg tablets and norgestrel 150microgram tablets
98840998	Conjugated oestrogens 1.25mg tablets and norgestrel 150microgram tablets
98892998	Conjugated oestrogens 625microgram tablets and norgestrel 150microgram tablets
98897998	Mestranol with norethisterone tablet
98911996	Estradiol 100mg implant
98911997	Estradiol 50mg implant
98911998	Estradiol 25mg implant
99219998	Conjugated oestrogens 625microgram tablets and norgestrel 150microgram tablets
99220996	Conjugated estrogens 2.5mg tablets
99220997	Conjugated oestrogens 1.25mg tablets
99220998	Conjugated oestrogens 625microgram tablets
99295997	Estriol 1mg tablets
99295998	Estriol 250mcg tablets
99571998	Estropipate 1.5mg tablets
99602989	Ethinylestradiol 50microgram tablets
99602990	Ethinylestradiol 10microgram tablets

6.4.2 Drugs used to treat inflammatory bowel disease

Drug code	Generic name
30104978	Adalimumab 40mg/0.4ml solution for injection pre-filled syringes
30105978	Adalimumab 40mg/0.4ml solution for injection pre-filled syringes
30106978	Adalimumab 40mg/0.4ml solution for injection pre-filled disposable devices
53189979	Ciclosporin 50mg capsules
53190979	Ciclosporin 100mg capsules
53191979	Ciclosporin 25mg capsules
53913979	Mesalazine 800mg gastro-resistant tablets
54552979	Mesalazine 400mg gastro-resistant tablets
55164978	Mesalazine 4g modified-release granules sachets sugar free
55165978	Mesalazine 4g modified-release granules sachets sugar free
55193978	Mercaptopurine 75mg tablets
55575979	Ciclosporin 50mg capsules
55576979	Ciclosporin 100mg capsules
55577979	Ciclosporin 25mg capsules
55799978	Mercaptopurine 30mg capsules
56901978	Ciclosporin 100mg capsules
56902978	Ciclosporin 25mg capsules
58121979	Mercaptopurine 25mg tablets

58800979	Mesalazine 1.2g gastro-resistant modified-release tablets
60097979	Prednisolone 20mg/application foam enema
60124979	Ciclosporin 50mg capsules
60584979	Mesalazine 3g gastro-resistant modified-release granules sachets sugar free
60585979	Mesalazine 3g gastro-resistant modified-release granules sachets sugar free
61544979	Adalimumab 40mg/0.8ml solution for injection vials
61545979	Adalimumab 40mg/0.8ml solution for injection vials
62953979	Sulfasalazine 250mg/5ml oral suspension sugar free
64115979	Methotrexate 25mg/3ml solution for injection pre-filled syringes
64868979	Mesalazine 2g modified-release granules sachets sugar free
65098979	Sulfasalazine 500mg/5ml oral suspension
67089979	Mesalazine 1.2g gastro-resistant modified-release tablets
69316979	Azathioprine 125mg/5ml oral suspension
70274978	Azathioprine 50mg tablets
70879979	Adalimumab 40mg prefilled pen
70880979	Adalimumab 40mg/0.8ml solution for injection pre-filled disposable devices
72688978	Ciclosporin 50mg capsules
73065978	Methotrexate 7.5mg/0.15ml solution for injection pre-filled disposable devices
73066978	Methotrexate 7.5mg/0.15ml solution for injection pre-filled disposable devices
73067978	Methotrexate 30mg/0.6ml solution for injection pre-filled disposable devices
73068978	Methotrexate 30mg/0.6ml solution for injection pre-filled disposable devices
73069978	Methotrexate 27.5mg/0.55ml solution for injection pre-filled disposable devices
73071978	Methotrexate 25mg/0.5ml solution for injection pre-filled disposable devices
73072978	Methotrexate 25mg/0.5ml solution for injection pre-filled disposable devices
73073978	Methotrexate 22.5mg/0.45ml solution for injection pre-filled disposable devices
73074978	Methotrexate 22.5mg/0.45ml solution for injection pre-filled disposable devices
73075978	Methotrexate 20mg/0.4ml solution for injection pre-filled disposable devices
73076978	Methotrexate 20mg/0.4ml solution for injection pre-filled disposable devices
73077978	Methotrexate 17.5mg/0.35ml solution for injection pre-filled disposable devices
73078978	Methotrexate 17.5mg/0.35ml solution for injection pre-filled disposable devices

73079978	Methotrexate 15mg/0.3ml solution for injection pre-filled disposable devices
73080978	Methotrexate 15mg/0.3ml solution for injection pre-filled disposable devices
73081978	Methotrexate 12.5mg/0.25ml solution for injection pre-filled disposable devices
73082978	Methotrexate 12.5mg/0.25ml solution for injection pre-filled disposable devices
73083978	Methotrexate 10mg/0.2ml solution for injection pre-filled disposable devices
73084978	Methotrexate 10mg/0.2ml solution for injection pre-filled disposable devices
76424978	Mesalazine 1g modified-release tablets
76878978	Methotrexate 2.5mg tablets
78442979	Methotrexate 50mg/2ml solution for injection vials
78447979	Methotrexate 25mg/1ml solution for injection pre-filled syringes
78449979	Methotrexate 20mg/0.8ml solution for injection pre-filled syringes
78452979	Methotrexate 12.5mg/0.5ml solution for injection pre-filled syringes
79522979	Mercaptopurine 25mg/5ml oral suspension
79524979	Mercaptopurine 20mg/ml oral suspension
79739978	Sulfasalazine 500mg gastro-resistant tablets
79867978	Mesalazine 400mg gastro-resistant tablets
80925979	Azathioprine 25mg/5ml oral suspension
80927979	Azathioprine 25mg/5ml oral solution
80928998	Mesalazine 3g gastro-resistant modified-release granules sachets sugar free
80929979	Azathioprine 20mg/5ml oral suspension
80929998	Mesalazine 3g gastro-resistant modified-release granules sachets sugar free
80961979	Azathioprine 10mg/5ml oral suspension
81193998	Mesalazine 1g modified-release tablets
81194998	Mesalazine 1g modified-release tablets
81282998	Ciclosporin 100mg capsules
81283998	Ciclosporin 50mg capsules
81284998	Ciclosporin 25mg capsules
81490998	Methotrexate 27.5mg/0.55ml prefilled syringes
81491998	Methotrexate 22.5mg/0.45ml prefilled syringes
81492998	Methotrexate 17.5mg/0.35ml prefilled syringes
81493998	Methotrexate 12.5mg/0.25ml prefilled syringes
81494998	Methotrexate 27.5mg/0.55ml solution for injection pre-filled syringes
81495998	Methotrexate 22.5mg/0.45ml solution for injection pre-filled syringes
81496998	Methotrexate 17.5mg/0.35ml solution for injection pre-filled syringes
81498998	Methotrexate 12.5mg/0.25ml solution for injection pre-filled syringes
81638998	Methotrexate 30mg/1.5ml solution for injection pre-filled syringes
81640998	Methotrexate 25mg/1.25ml solution for injection pre-filled syringes
81642998	Methotrexate 20mg/1ml solution for injection pre-filled syringes

81643998	Methotrexate 7.5mg/0.75ml prefilled syringes
81683998	Mesalazine 1g suppositories
81689998	Mesalazine 500mg gastro-resistant tablets
81690998	Mesalazine 500mg gastro-resistant tablets
81771998	Ciclosporin 25mg capsules
81772998	Mesalazine 800mg gastro-resistant tablets
81773998	Ciclosporin 100mg capsules
81774998	Ciclosporin 50mg capsules
81815998	Methotrexate 30mg/0.6ml prefilled syringes
81816998	Methotrexate 30mg/0.6ml solution for injection pre-filled syringes
81868998	Mesalazine 400mg gastro-resistant tablets
82203998	Azathioprine 50mg tablets
82204998	Azathioprine 25mg tablets
82480998	Ciclosporin 100mg capsules
82481998	Ciclosporin 50mg capsules
82482998	Ciclosporin 25mg capsules
82840998	Methotrexate 25mg/0.5ml prefilled syringes
82841998	Methotrexate 20mg/0.4ml prefilled syringes
82842998	Methotrexate 15mg/0.3ml prefilled syringes
82843998	Methotrexate 10mg/0.2ml prefilled syringes
82844998	Methotrexate 7.5mg/0.15ml prefilled syringes
82845998	Methotrexate 25mg/0.5ml solution for injection pre-filled syringes
82846998	Methotrexate 20mg/0.4ml solution for injection pre-filled syringes
82847998	Methotrexate 15mg/0.3ml solution for injection pre-filled syringes
82848998	Methotrexate 10mg/0.2ml solution for injection pre-filled syringes
82849998	Methotrexate 7.5mg/0.15ml solution for injection pre-filled syringes
83228978	Ciclosporin 50mg capsules
83229978	Ciclosporin 100mg capsules
83485998	Azathioprine 10mg capsules
83503998	Mesalazine 1.5g gastro-resistant modified-release granules sachets sugar free
83504998	Mesalazine 1.5g gastro-resistant modified-release granules sachets sugar free
83559978	Mercaptopurine 50mg tablets
83743998	Mesalazine 2g modified-release granules sachets sugar free
83769998	Sulfasalazine 250mg/5ml oral suspension sugar free
83987998	Mesalazine 2g modified-release granules sachets sugar free
84059998	Mesalazine 1g modified-release granules sachets sugar free
84209998	Mesalazine 800mg gastro-resistant tablets
84290998	Mesalazine 1.2g gastro-resistant modified-release tablets
84291998	Mesalazine 1.2g gastro-resistant modified-release tablets
84438998	Methotrexate 2mg/ml oral solution sugar free
84439998	Methotrexate 10mg/5ml oral suspension
84636998	Budesonide 2mg foam enema
84637998	Budesonide 2mg foam enema
84741998	Prednisolone 40mg/100ml enema

84920998	Ciclosporin 250mg/5ml solution for infusion ampoules
84921998	Ciclosporin 50mg/1ml solution for infusion ampoules
84927998	Ciclosporin 250mg/5ml solution for infusion ampoules
84928998	Ciclosporin 50mg/1ml solution for infusion ampoules
85097998	Methotrexate 1g/40ml solution for injection vials
85100998	Methotrexate 7.5mg/5ml oral suspension
85188978	Methotrexate 2.5mg tablets
85252998	Azathioprine 50mg/5ml oral suspension
85556998	Mercaptopurine oral solution
85560998	Mesalazine 800mg gastro-resistant tablets
85639998	Methotrexate 7.5mg/0.75ml prefilled syringes
85640998	Methotrexate 10mg/ml prefilled syringes
85641998	Methotrexate 15mg/1.5ml prefilled syringes
85642998	Methotrexate 20mg/2ml prefilled syringes
85643998	Methotrexate 25mg/2.5ml prefilled syringes
85644998	Methotrexate 7.5mg/0.75ml solution for injection pre-filled syringes
85645998	Methotrexate 10mg/1ml solution for injection pre-filled syringes
85646998	Methotrexate 15mg/1.5ml solution for injection pre-filled syringes
85648998	Methotrexate 20mg/2ml solution for injection pre-filled syringes
85650998	Methotrexate 25mg/2.5ml solution for injection pre-filled syringes
85737998	Methotrexate 5g/50ml solution for infusion vials
85738998	Methotrexate 1g/10ml solution for injection vials
85776998	Methotrexate oral solution
85777998	Methotrexate 12.5mg/5ml oral suspension
86327998	Methotrexate 2.5mg/5ml oral suspension
86339998	Methotrexate 5mg/0.2ml solution for injection pre-filled syringes
86342998	Methotrexate 22.5mg/0.9ml solution for injection pre-filled syringes
86343998	Methotrexate 15mg/0.6ml solution for injection pre-filled syringes
86344998	Methotrexate 12.5mg/0.5ml solution for injection pre-filled syringes
86345998	Methotrexate 10mg/0.4ml solution for injection pre-filled syringes
86427998	Methotrexate 17.5mg/0.7ml solution for injection pre-filled syringes
86434998	Methotrexate 20mg/0.8ml solution for injection pre-filled syringes
86435998	Methotrexate 25mg/1ml solution for injection pre-filled syringes
86436998	Methotrexate 500mg/20ml solution for injection vials
86437998	Methotrexate 50mg/2ml solution for injection vials
86438998	Methotrexate 7.5mg/0.3ml solution for injection pre-filled syringes
86439998	Methotrexate 30mg/1.2ml solution for injection pre-filled syringes
86440998	Methotrexate 27.5mg/1.1ml solution for injection pre-filled syringes
86470998	Azathioprine 250mg/5ml oral solution
86519998	Azathioprine 50mg/5ml oral solution
87675998	Mercaptopurine 10mg capsules
87757998	Mercaptopurine 10mg tablets
87761998	Mesalazine 400mg gastro-resistant tablets
87859998	Adalimumab 40mg prefilled syringes
87862998	Adalimumab 40mg injection

87909998	Mesalazine 1g gastro-resistant modified-release granules sachets sugar free
87910998	Mesalazine 500mg gastro-resistant modified-release granules sachets sugar free
87911998	Mesalazine 500mg gastro-resistant modified-release granules sachets sugar free
88489998	Balsalazide 750mg capsules
88492998	Balsalazide 750mg capsules
88517998	Mesalazine 400mg gastro-resistant tablets
88519998	Sulfasalazine 500mg gastro-resistant tablets
89238998	Budesonide 2mg/100ml enema
89239998	Budesonide 2mg/100ml enema
89244979	Adalimumab 40mg prefilled syringes
89245979	Adalimumab 40mg/0.8ml solution for injection pre-filled syringes
89460998	Hydrocortisone 1% / Pramocaine 1% foam enema
89598997	Sulfasalazine 3g/100ml retention enema
89598998	Sulfasalazine 500mg suppositories
89604997	Sulfasalazine 3g/100ml retention enema
89604998	Sulfasalazine 500mg suppositories
89610997	Sulfasalazine 250mg/5ml oral suspension
89610998	Sulfasalazine 500mg tablets
89616997	Sulfasalazine 250mg/5ml oral suspension sugar free
89616998	Sulfasalazine 500mg gastro-resistant tablets
89651998	Infliximab 100mg powder for solution for infusion vials
89992997	Mesalazine 2g/59ml enema
89992998	Mesalazine 500mg suppositories
90310979	Prednisolone 20mg/application foam enema
91215998	Azathioprine 50mg tablets
91309998	Azathioprine capsules
91373997	Ciclosporin 10mg capsules
91373998	Ciclosporin 100mg/ml oral solution sugar free
91601979	Sulfasalazine 500mg gastro-resistant tablets
92244990	Ciclosporin 100mg capsules
92245990	Ciclosporin 50mg capsules
92246990	Ciclosporin 25mg capsules
92346998	Mesalazine 1g/application foam enema
92347998	Mesalazine 400mg gastro-resistant tablets
92400998	Olsalazine 500mg tablets
92401998	Olsalazine 250mg capsules
92488997	Methotrexate 2.5mg tablets
92488998	Methotrexate 5g/200ml solution for infusion vials
92511998	Infliximab 100mg powder for solution for infusion vials
92544979	Ciclosporin 50mg capsules
92552979	Ciclosporin 100mg capsules
92555979	Ciclosporin 100mg capsules
92558979	Ciclosporin 25mg capsules

92559979	Ciclosporin 25mg capsules
92566979	Azathioprine 25mg tablets
92570979	Azathioprine 25mg tablets
92571979	Azathioprine 25mg tablets
92579979	Azathioprine 50mg tablets
92639979	Methotrexate 5g/200ml solution for infusion vials
92650979	Methotrexate 200mg/8ml solution for injection vials
92655979	Methotrexate 50mg/2ml solution for injection vials
92764997	Mesalazine 1g modified-release granules sachets sugar free
92764998	Mesalazine 500mg modified-release tablets
92930998	Azathioprine 50mg tablets
92989996	Ciclosporin 100mg capsules
92989997	Ciclosporin 50mg capsules
92989998	Ciclosporin 25mg capsules
93074990	Methotrexate 2.5mg tablets
93623996	Mesalazine 250mg suppositories
93623997	Mesalazine 1g/application foam enema
93623998	Mesalazine 1g/100ml enema
93624996	Mesalazine 1g suppositories
93624997	Mesalazine 250mg modified release tablets
93624998	Mesalazine 1g/100ml enema
93728992	Mesalazine 500mg modified-release tablets
94042990	Sulfasalazine 500mg gastro-resistant tablets
94078992	Azathioprine 100 mg tab
94153998	Hydrocortisone 10% foam aerosol enema
94155997	Hydrocortisone retention enema
94155998	Hydrocortisone 10% foam aerosol enema
94308990	Azathioprine 50mg tablets
94417992	Azathioprine 50 mg sus
94437997	Olsalazine 500mg tablets
94437998	Olsalazine 250mg capsules
94438997	Olsalazine 500mg tablets
94438998	Olsalazine 250mg capsules
94451998	Prednisolone 20mg/application foam enema
94452998	Prednisolone 20mg/application foam enema
94564992	Mesalazine 500mg modified-release tablets
94593997	Ciclosporin 10mg capsules
94593998	Ciclosporin 50mg capsules
94600990	Methotrexate 20mg/0.8ml solution for injection pre-filled syringes
94690992	Azathioprine 125 mg tab
94691992	Azathioprine 10 mg tab
94697998	Azathioprine 50mg tablets
94818998	Sulfasalazine 250mg/5ml oral suspension
95041990	Mesalazine 400mg gastro-resistant tablets
95153992	Azathioprine 10mg tablets
95252990	Azathioprine 50mg tablets

95255998	Sulfasalazine 500mg gastro-resistant tablets
95256996	Sulfasalazine 3g/100ml enema
95256997	Sulfasalazine 500mg suppositories
95256998	Sulfasalazine 500mg gastro-resistant tablets
95589998	Sulfasalazine 250mg/5ml oral suspension
95725990	Azathioprine 50mg tablets
95866998	Methotrexate 25mg/ml injection
95867996	Methotrexate 5mg/2ml solution for injection vials
95867997	Methotrexate 10mg tablets
95867998	Methotrexate 2.5mg tablets
95868996	Methotrexate 50mg/3ml Injection
95868997	Methotrexate 5g/50ml solution for infusion vials
95868998	Methotrexate 200mg/8ml solution for injection vials
95869997	Methotrexate 10mg tablets
95869998	Methotrexate 2.5mg tablets
95888997	Mesalazine 250mg gastro-resistant tablets
95888998	Mesalazine 400mg gastro-resistant tablets
95890998	Mercaptopurine 50mg tablets
95891998	Mercaptopurine 50mg tablets
96177998	Hydrocortisone 1% / pramocaine 1% foam enema
96199990	Azathioprine 50mg tablets
96279990	Methotrexate 2.5mg tablets
96580998	Ciclosporin 50mg/1ml solution for infusion ampoules
96581996	Ciclosporin 100mg capsules
96581997	Ciclosporin 25mg capsules
96581998	Ciclosporin 100mg/ml oral solution sugar free
96608996	Mesalazine 2g/59ml enema
96608997	Mesalazine 1g suppositories
96608998	Mesalazine 500mg suppositories
96659996	Mesalazine 1g/application foam enema
96659997	Mesalazine 500mg suppositories
96659998	Mesalazine 250mg suppositories
96752989	Methotrexate 10mg tablets
96752990	Methotrexate 2.5mg tablets
96803990	Sulfasalazine 500mg gastro-resistant tablets
96820988	Methotrexate 5mg/2ml solution for injection vials
96883990	Mesalazine 400mg gastro-resistant tablets
96916992	Mesalazine 500mg modified-release tablets
96922989	Azathioprine 50mg tablets
96922990	Azathioprine 25mg tablets
96932998	Azathioprine 50mg powder for solution for injection vials
96933998	Azathioprine 50mg tablets
96934997	Azathioprine 50mg powder for solution for injection vials
96934998	Azathioprine 25mg tablets
97036997	Azathioprine 10mg tablets
97036998	Azathioprine 50mg tablets

97280998	Sulfasalazine 500mg gastro-resistant tablets
97281996	Sulfasalazine 3g/100ml retention enema
97281997	Sulfasalazine 500mg suppositories
97281998	Sulfasalazine 500mg tablets
97287998	Hydrocortisone acetate & pramocaine foam
97362990	Sulfasalazine 500mg gastro-resistant tablets
97363990	Sulfasalazine 500mg gastro-resistant tablets
97381998	Mesalazine 400mg gastro-resistant tablets
97719989	Sulfasalazine 500mg gastro-resistant tablets
97719990	Sulfasalazine 500mg gastro-resistant tablets
97764998	Mesalazine 250mg gastro-resistant tablets
97785990	Azathioprine 50mg tablets
98001992	Mesalazine 250mg gastro-resistant tablets
98013988	Methotrexate 5g/50ml solution for infusion vials
98211990	Azathioprine 50mg tablets
98238996	Ciclosporin 25mg capsules
98238998	Ciclosporin 100mg/ml oral solution sugar free
98365990	Sulfasalazine 500mg gastro-resistant tablets
98639990	Azathioprine 50mg tablets
98640990	Azathioprine 50mg tablets
98950997	Ciclosporin 50mg capsules
98950998	Ciclosporin 100mg capsules
98958988	Methotrexate 2.5mg tablets
98959989	Methotrexate 10mg tablets
98959990	Methotrexate 2.5mg tablets
99374990	Sulfasalazine 500mg gastro-resistant tablets
99394979	Hydrocortisone 10% foam aerosol enema
99472979	Sulfasalazine 500mg gastro-resistant tablets
99486979	Mesalazine 400mg gastro-resistant tablets
99487979	Mesalazine 400mg gastro-resistant tablets
99488979	Mesalazine 400mg gastro-resistant tablets
99490979	Mesalazine 1g modified-release granules sachets sugar free
99492979	Mesalazine 1g suppositories
99494979	Mesalazine 1g suppositories
99495979	Mesalazine 500mg modified-release tablets
99498979	Mesalazine 500mg modified-release tablets
99583996	Mesalazine 1g modified-release granules sachets sugar free
99583997	Mesalazine 500mg modified-release tablets
99583998	Mesalazine 250mg modified-release tablet
99797989	Azathioprine 25mg tablets
99797990	Azathioprine 50mg tablets
99798990	Azathioprine 50mg tablets
99799990	Azathioprine 50mg tablets
99956998	Methotrexate 5mg/2ml solution for injection vials
39760978	Ustekinumab 90mg/1ml solution for injection pre-filled syringes
62544979	Ustekinumab 45mg/0.5ml solution for injection pre-filled syringes

62545979	Ustekinumab 45mg/0.5ml solution for injection pre-filled syringes
64015979	Ustekinumab 45mg/0.5ml solution for injection vials
72853978	Vedolizumab 300mg powder for solution for infusion vials
83106998	Ustekinumab 45mg/0.5ml solution for injection vials
83108998	Ustekinumab 45mg/0.5ml solution for injection vials

6.4.3 Second generation combined oral contraceptive pills

Drug code	Generic name
38631978	Ethinylestradiol 35microgram / Norgestimate 250microgram tablets
42618978	Ethinylestradiol 35microgram / Norgestimate 250microgram tablets
58067979	Ethinylestradiol 30microgram / Levonorgestrel 150microgram tablets
61424979	Ethinylestradiol 35microgram / Norgestimate 250microgram tablets
72983978	Ethinylestradiol 30microgram / Levonorgestrel 150microgram tablets
72984978	Ethinylestradiol 30microgram / Levonorgestrel 150microgram tablets
81388998	Ethinylestradiol 30microgram / Levonorgestrel 150microgram tablets
81713998	Ethinylestradiol 30microgram / Levonorgestrel 150microgram tablets
82039998	Generic Logynon tablets
82040998	Ethinylestradiol 30microgram / Levonorgestrel 150microgram tablets
82343998	Ethinylestradiol 30microgram / Levonorgestrel 150microgram tablets
83562978	Ethinylestradiol 35microgram / Norgestimate 250microgram tablets
89080998	Generic Microgynon 30 ED tablets
89213998	Ethinylestradiol 30microgram / Levonorgestrel 150microgram tablets
90566998	Ethinylestradiol with norethisterone - biphasic 7 x 35mcg+500mcg; 14 x 35mcg+1mg tablet
90641998	Generic Logynon ED tablets
90644998	Generic Logynon tablets
90647998	Levonorgestrel 250microgram / ethinylestradiol 50microgram tablets
90650998	Levonorgestrel 250microgram / ethinylestradiol 30microgram tablets
90654998	Ethinylestradiol 30microgram / Levonorgestrel 150microgram tablets
90658998	Ethinylestradiol & levonorgestrel 50mcg+250mcg tablets
90703997	Ethinylestradiol with norethisterone - triphasic 7 x 35+500mcg; 7 x 35+750mcg; 7 x 35mcg+1mg tablet
90972998	Ethinylestradiol 35microgram / Norgestimate 250microgram tablets
92682998	Mestranol 50microgram / Norethisterone 1mg tablets
92860979	Ethinylestradiol & levonorgestrel 50mcg+250mcg tablets
92862979	Ethinylestradiol 30microgram / Levonorgestrel 150microgram tablets
94158996	Ethinylestradiol 30microgram / Norethisterone acetate 1.5mg tablets
94158997	Ethinylestradiol 20microgram / Norethisterone acetate 1mg tablets
94997992	Ethinylestradiol 30microgram / Levonorgestrel 150microgram tablets
95885998	Mestranol 50microgram / Norethisterone 1mg tablets
97456998	Ethinylestradiol & levonorgestrel 50mcg+250mcg tablets
97462998	Generic Logynon ED tablets
97464998	Ethinylestradiol 30microgram / Levonorgestrel 150microgram tablets
97466998	Ethinylestradiol & levonorgestrel 30mcg+250mcg tablets

97563998	Generic Synphase tablets
98085997	Ethinylestradiol 35microgram / Norethisterone 1mg tablets
98085998	Ethinylestradiol 35microgram / Norethisterone 500microgram tablets
98181997	Ethinylestradiol with norethisterone - triphasic and placebo 7 x 35+500mcg; 7 x 35+750mcg; 7 x 35mcg+1mg tablet
98181998	Generic trinovum tablets
98183998	Ethinylestradiol 35microgram / Norethisterone 500microgram tablets
98185998	Mestranol & norethisterone 50mcg+1mg tablets
98187998	Ethinylestradiol & norethisterone 35mcg+1mg tablets
98189998	Generic binovum tablets
98191998	Mestranol 50microgram / Norethisterone 1mg tablets
98193998	Ethinylestradiol 35microgram / Norethisterone 500microgram tablets
98195998	Ethinylestradiol 35microgram / Norethisterone 1mg tablets
98197998	Generic Logynon tablets
98199998	Ethinylestradiol 30microgram / Levonorgestrel 150microgram tablets
98201998	Ethinylestradiol & levonorgestrel 30mcg+250mcg tablets
98203998	Ethinylestradiol & levonorgestrel 50mcg+250mcg tablets
98205998	Generic Logynon tablets
98207998	Ethinylestradiol 30microgram / Norethisterone acetate 1.5mg tablets
98209998	Ethinylestradiol 20microgram / Norethisterone acetate 1mg tablets
99036998	Ethinylestradiol 35microgram / Norgestimate 250microgram tablets
99047998	Ethinylestradiol 35microgram / Norgestimate 250microgram tablets
89341998	Ethinylestradiol with levonorgestrel 30micrograms + 50micrograms tablet
90703998	Ethinylestradiol with norethisterone - triphasic 7x35+500mcg; 9x35mcg+1mg; 5x35+500mcg tablet
93781998	Ethinylestradiol with levonorgestrel tablet
94995992	Ethinyloestradiol/norethisterone 35 mcg tab
95002992	Ethinylestradiol & levonorgestrel 50mcg+250mcg tablets

6.4.4 Third generation combined oral contraceptive pills

Drug code	Generic name
39702978	Ethinylestradiol 30microgram / Desogestrel 150microgram tablets
47222978	Ethinylestradiol 20microgram / Desogestrel 150microgram tablets
52480979	Ethinylestradiol 30microgram / Desogestrel 150microgram tablets
52481979	Ethinylestradiol 20microgram / Desogestrel 150microgram tablets
53192979	Ethinylestradiol 30microgram / Desogestrel 150microgram tablets
59313978	Ethinylestradiol 30microgram / Desogestrel 150microgram tablets
72985978	Ethinylestradiol 30microgram / Desogestrel 150microgram tablets
72986978	Ethinylestradiol 30microgram / Desogestrel 150microgram tablets
82024998	Ethinylestradiol 20microgram / Gestodene 75microgram tablets
82029998	Ethinylestradiol 30microgram / Gestodene 75microgram tablets
82032998	Ethinylestradiol 20microgram / Desogestrel 150microgram tablets
82041998	Ethinylestradiol 30microgram / Desogestrel 150microgram tablets

84491998	Ethinylestradiol 20microgram / Gestodene 75microgram tablets
84492998	Ethinylestradiol 30microgram / Gestodene 75microgram tablets
90747998	Ethinylestradiol 30microgram / Desogestrel 150microgram tablets
90750998	Ethinylestradiol 20microgram / Desogestrel 150microgram tablets
90760998	Generic Femodene ED tablets
90969997	Ethinylestradiol 20microgram / Gestodene 75microgram tablets
90969998	Ethinylestradiol 30microgram / Gestodene 75microgram tablets
92485998	Ethinylestradiol 20microgram / Gestodene 75microgram tablets
92863979	Ethinylestradiol 30microgram / Desogestrel 150microgram tablets
93263998	Generic Femodene ED tablets
94398997	Ethinylestradiol 20microgram / Gestodene 75microgram tablets
94398998	Ethinylestradiol 30microgram / Gestodene 75microgram tablets
94745998	Ethinylestradiol 20microgram / Desogestrel 150microgram tablets
94773998	Ethinylestradiol 30microgram / Gestodene 75microgram tablets
96439997	Ethinylestradiol 30microgram / Desogestrel 150microgram tablets
96439998	Ethinylestradiol 20microgram / Desogestrel 150microgram tablets
96922998	Ethinylestradiol 30microgram / Gestodene 75microgram tablets
98178998	Ethinylestradiol 30microgram / Desogestrel 150microgram tablets
90757998	Ethinylestradiol with gestodene - triphasic 6 x 30+50mcg; 5 x 40+70mcg; 10 x 30+100mcg tablet
97670998	Generic tri-minulet tablets
97702998	Generic tri-minulet tablets

6.4.5 Fourth generation combined oral contraceptive pills

Drug code	Generic name
45866978	Ethinylestradiol 20microgram / Drospirenone 3mg tablets
46090978	Ethinylestradiol 20microgram / Drospirenone 3mg tablets
47150978	Ethinylestradiol 30microgram / Drospirenone 3mg tablets
53008979	Ethinylestradiol 20microgram / Drospirenone 3mg tablets
53009979	Ethinylestradiol 20microgram / Drospirenone 3mg tablets
72966978	Ethinylestradiol 30microgram / Drospirenone 3mg tablets
74455978	Ethinylestradiol 30microgram / Drospirenone 3mg tablets
78546978	Ethinylestradiol 30microgram / Drospirenone 3mg tablets
83634998	Ethinylestradiol 20microgram / Drospirenone 3mg tablets
83740978	Estradiol 1.5mg / Nomegestrol 2.5mg tablets
83741978	Estradiol 1.5mg / Nomegestrol 2.5mg tablets
84583978	Ethinylestradiol 20microgram / Drospirenone 3mg tablets
59254978	Ethinylestradiol 30microgram / Drospirenone 3mg tablets
59255978	Ethinylestradiol 30microgram / Drospirenone 3mg tablets
82867998	Generic Qlaira tablets
82869998	Generic Qlaira tablets
89914979	Ethinylestradiol 30microgram / Drospirenone 3mg tablets
92571998	Ethinylestradiol 30microgram / Drospirenone 3mg tablets

98852998	Ethinylestradiol 30microgram / Drospirenone 3mg tablets

6.4.6 Co-cyprindiol

Drug code	Generic name
47175978	Co-cyprindiol 2000microgram/35microgram tablets
85864998	Co-cyprindiol 2000microgram/35microgram tablets
86466998	Co-cyprindiol 2000microgram/35microgram tablets
86925998	Co-cyprindiol 2000microgram/35microgram tablets
87351998	Co-cyprindiol 2000microgram/35microgram tablets
90826979	Co-cyprindiol 2000microgram/35microgram tablets
90828979	Co-cyprindiol 2000microgram/35microgram tablets
90833979	Co-cyprindiol 2000microgram/35microgram tablets
91068998	Co-cyprindiol 2000microgram/35microgram tablets
91069998	Co-cyprindiol 2000microgram/35microgram tablets
94832990	Co-cyprindiol 2000microgram/35microgram tablets
94920998	Co-cyprindiol 2000microgram/35microgram tablets
95220990	Co-cyprindiol 2000microgram/35microgram tablets
95396990	Co-cyprindiol 2000microgram/35microgram tablets
96577998	Co-cyprindiol 2000microgram/35microgram tablets
97520998	Co-cyprindiol 2000microgram/35microgram tablets

6.4.7 Progestogen-only pills

Drug code	Generic name
72965978	Desogestrel 75microgram tablets
53167979	Desogestrel 75microgram tablets
90581998	Desogestrel 75microgram tablets
98172998	Norethisterone 350microgram tablets
83545978	Desogestrel 75microgram tablets
61400979	Desogestrel 75microgram tablets
98170998	Levonorgestrel 30microgram tablets
90580998	Desogestrel 75microgram tablets
97451998	Levonorgestrel 75mcg tablets
95699998	Norgestrel 75microgram tablets
53171979	Desogestrel 75microgram tablets
85168978	Desogestrel 75microgram tablets
97599998	Etynodiol diacetate 500mcg tablets
93986998	Levonorgestrel 30microgram tablets
53168979	Desogestrel 75microgram tablets
83189978	Desogestrel 75microgram tablets
97452998	Levonorgestrel 30microgram tablets
82528978	Desogestrel 75microgram tablets

96765998	Etynodiol 500microgram tablets
91333998	Levonorgestrel 750microgram tablets
93893998	Norethisterone 350microgram tablets
53169979	Desogestrel 75microgram tablets
98174998	Norethisterone 350microgram tablets
53166979	Desogestrel 75microgram tablets

6.4.8 Long-acting reversible contraception

Drug code	Generic name
20364978	Levonorgestrel 19.5mg intrauterine device
20365978	Levonorgestrel 19.5mg intrauterine device
50916978	Levonorgestrel 20micrograms/24hours intrauterine device
58042979	Intrauterine contraceptive device
58043979	Intrauterine contraceptive device
58044979	Intrauterine contraceptive device
59356979	Intrauterine contraceptive device
59358979	Intrauterine contraceptive device
59359979	Intrauterine contraceptive device
59360979	Intrauterine contraceptive device
71058994	Intrauterine contraceptive device
75898978	Levonorgestrel 13.5mg intrauterine device
75899978	Levonorgestrel 13.5mg intrauterine device
80741994	Intrauterine contraceptive device
83855994	Intrauterine contraceptive device
83856994	Intrauterine contraceptive device
83858994	Intrauterine contraceptive device
83859994	Intrauterine contraceptive device
84171994	Intrauterine contraceptive device
86053994	Intrauterine contraceptive device
87355979	Intrauterine contraceptive device
87911994	Intrauterine contraceptive device
89797994	Intrauterine contraceptive device
89798994	Intrauterine contraceptive device
90662994	Intrauterine contraceptive device
91073994	Intrauterine contraceptive device
91074994	Intrauterine contraceptive device
91271994	Intrauterine contraceptive device
91324998	Levonorgestrel 20micrograms/24hours intrauterine device
91325998	Levonorgestrel 20micrograms/24hours intrauterine device
92849979	Levonorgestrel 20micrograms/24hours intrauterine device
92851979	Levonorgestrel 20micrograms/24hours intrauterine device
95678994	Intrauterine contraceptive device
97021994	Intrauterine contraceptive device
97339992	Intrauterine contraceptive device

97916994	Intrauterine contraceptive device
97917994	Intrauterine contraceptive device
98212994	Intrauterine contraceptive device
99235994	Intrauterine contraceptive device
99880994	Intrauterine contraceptive device
81886998	Etonogestrel 68mg implant
90908998	Etonogestrel 68mg implant
90909998	Etonogestrel 68mg implant
92888998	Levonorgestrel 38mg implant
98222998	Levonorgestrel 228mg implant
84519978	Medroxyprogesterone 104mg/0.65ml suspension for injection pre-filled disposable devices
84520978	Medroxyprogesterone 104mg/0.65ml suspension for injection pre-filled disposable devices
85241998	Medroxyprogesterone 150mg/1ml suspension for injection pre-filled syringes
85242998	Medroxyprogesterone 150mg/1ml suspension for injection pre-filled syringes
92842979	Medroxyprogesterone 150mg/1ml suspension for injection pre-filled syringes
92843979	Medroxyprogesterone 150mg/1ml suspension for injection pre-filled syringes
92844979	Medroxyprogesterone 150mg/1ml suspension for injection pre-filled syringes
92846979	Medroxyprogesterone 150mg/1ml suspension for injection pre-filled syringes
92847979	Medroxyprogesterone 150mg/1ml suspension for injection pre-filled syringes
95700998	Norethisterone 200mg/1ml solution for injection ampoules
97454998	Norethisterone 200mg/1ml solution for injection ampoules
97920998	Medroxyprogesterone 150mg/1ml suspension for injection pre-filled syringes

6.5 STROBE checklists

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklists were used for all publications arising from this work.

6.5.1 STROBE checklist for cohort studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	
Objectives	3	State specific objectives, including any prespecified hypotheses	
Methods			
Study design	4	Present key elements of study design early in the paper	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	

Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	

6.5.2 STROBE checklist for cross-sectional studies

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	

		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	
Objectives	3	State specific objectives, including any prespecified hypotheses	
Methods			
Study design	4	Present key elements of study design early in the paper	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	

		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	
Outcome data	15*	Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	

Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	

*Give information separately for exposed and unexposed groups.

6.5.3 STROBE checklist for case-control studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	
Objectives	3	State specific objectives, including any prespecified hypotheses	
Methods			
Study design	4	Present key elements of study design early in the paper	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	

Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	
		(*b*) For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how matching of cases and controls was addressed	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	

		(b) Indicate number of participants with missing data for each variable of interest	
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	

*Give information separately for cases and controls.