Clinical and genetic factors associated with disease course in inflammatory bowel disease

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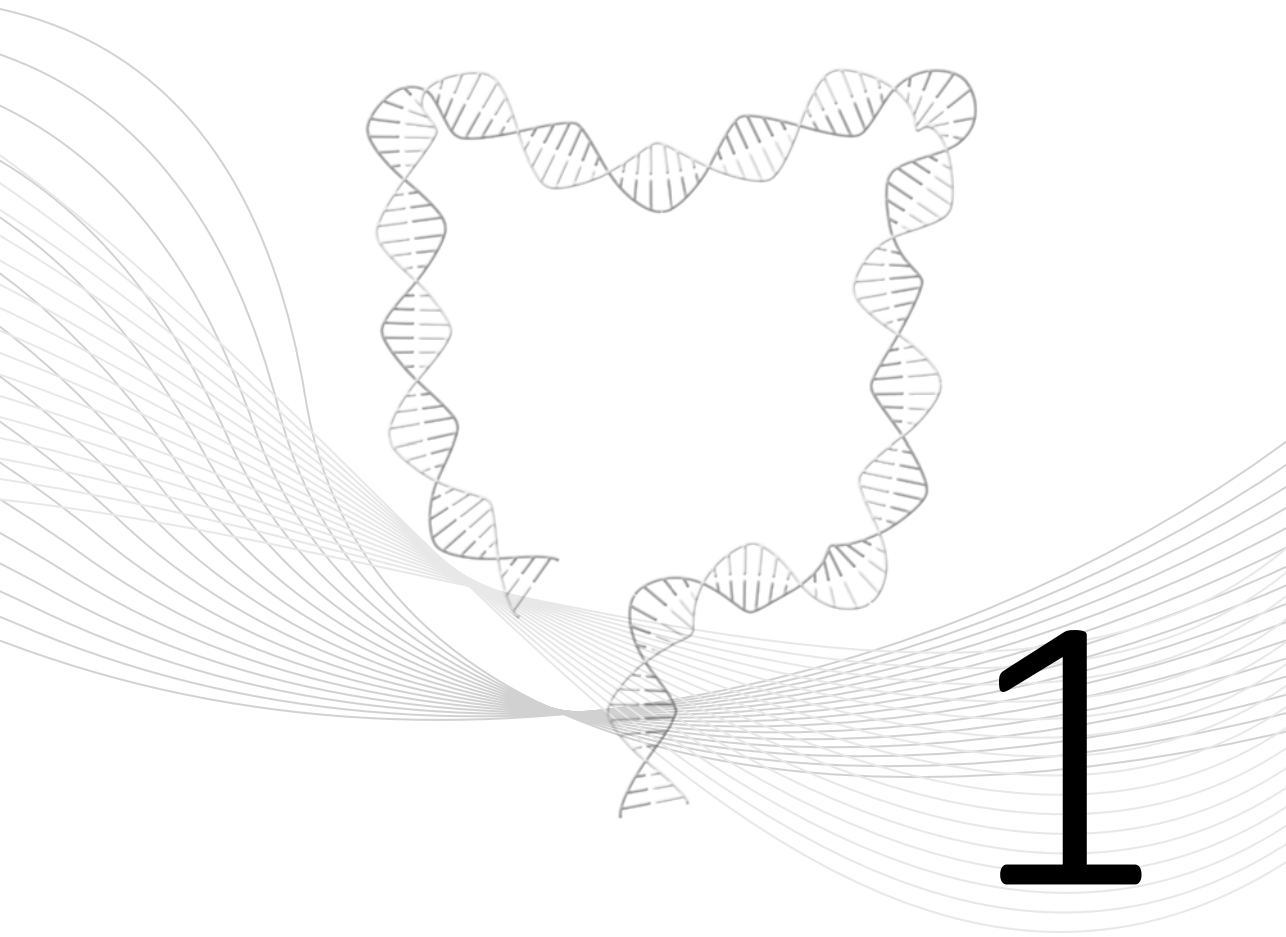

1

Introduction and outline of this thesis

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Inflammatory bowel disease (IBD) is a chronic immune-mediated inflammatory disease of the gastrointestinal tract that is characterized by its heterogeneous presentation and relapsing character. This highly variable presentation makes it very important to identify the clinical and genetic factors that can be used to predict disease course in individual patients. IBD comprises two main types: Crohn's disease (CD) and ulcerative colitis (UC).

Epidemiology

The prevalence of IBD varies greatly per geographic region, but also within these regions. Prevalence is highest in Europe and North America, with a prevalence of ~830 per 100,000 individuals in the Netherlands.[1] The high prevalence in Western nations is believed to be associated with their industrialization, and IBD prevalence is much lower in developing countries and Asia.[2] However, the incidence and prevalence of IBD in the Western world is now stabilizing, while the incidence of IBD in developing countries is increasing. Furthermore, people migrating from low prevalence areas to high prevalence areas become more susceptible to the disease, meaning that the children of adult immigrants acquire the same susceptibility to IBD as the native population, reaching the local prevalence of IBD within 1-2 generations. Together this evidence implies that factors in the Western lifestyle and environment play a role in IBD risk.[2,3]

Disease presentation of CD and UC

IBD patients are usually diagnosed in the second or third decade of life, and an early onset in patients with CD is correlated with a more severe disease phenotype.[4] IBD occurs more frequently in females, with a male:female ratio of 1:1.6 in CD and 1:1.2 in UC.[5] Beyond CD and UC there are several other subtypes of IBD. Patients with chronic colitis without clinical, endoscopic or histological features of either CD or UC are diagnosed with Inflammatory Bowel Disease Unclassified (IBD-U). The diagnosis Inflammatory Bowel Disease Indeterminate (IBD-I) is reserved for colitis patients in whom the pathologist does not find features pathognomonic for either CD or UC in the colectomy specimen.

Depending on disease localization and severity, patients with CD can suffer from symptoms such as abdominal pain, weight loss, fever and bloody diarrhoea. Inflammation in CD mainly affects the terminal ileum, but can occur anywhere in the digestive tract. It can also affect all mucosal layers, which can lead to strictures, abscesses and fistulas from the bowel to skin, bladder, vagina or other bowel segments. Surgical intervention can induce long-term remission[6] but is never a curative option in CD, therefore the principal treatment of inflammatory activity is drug therapy.[7]

Patients with UC typically have symptoms of bloody mucoid diarrhoea and lower abdominal pain. The inflammation in UC is confined to the colon, but in patients with a severe pancolitis a limited part of the terminal ileum can be affected, a condition called “backwash ileitis”. A total proctocolectomy will remove all affected tissue and is therefore curative in patients with UC. Colorectal cancer is a rare complication of IBD, and both CD and UC patients with longstanding inflammation of the colon have a higher risk for colorectal cancer compared to the general population.

Twenty-five percent of patients with IBD have extraintestinal manifestations (EIMs).[8] The most common EIMs are joint complaints (sacroiliitis and ankylosing spondylitis), ocular involvement (uveitis and episcleritis), and skin involvement (pyoderma gangrenosum, erythema nodosum, psoriasis or palmoplantar psoriasiform pustolosis, and metastatic CD). The prevalence of EIMs is higher in CD compared to UC,[9] and active smoking increases risk for EIMs in CD and UC.[10] Primary sclerosing cholangitis (PSC) is a rare liver disease characterized by fibrosis of the bile duct that often co-occurs with IBD. Approximately 68% of patients with PSC have IBD, of which 98% have UC or colonic CD and 6% have isolated ileal CD.[11] Increased risk of thromboembolic events and osteoporosis are considered complications of IBD as opposed to true EIMs. An increased risk of thromboembolic events is associated with disease flares.[12,13] The factors associated with osteoporosis are sustained use of corticosteroids and malabsorption.

Treatment strategies in IBD consist of surgical intervention and medication. Selection of appropriate treatment depends on disease behaviour, location and severity. Choice of medication is further influenced by medication potency, potential side effects and the presence of EIMs or complications.[14,15] Medications used in IBD consist of corticosteroids, mesalazine, immunomodulators (thiopurines or methotrexate) and biologics (anti-TNFα, anti-IL12/IL23 and anti-$\alpha_4\beta_7$ agents). However, 16% of UC patients and up to 47% of CD patients will still require surgery in the ten years following their diagnosis.[16] CD patients with disease activity are often initially treated with corticosteroids, and patients with steroid-refractory disease or steroid dependent disease are often treated with immunomodulators. Anti-TNFα therapy is indicated in patients with severe or refractory disease in whom immunosuppressive drugs are failing. Some patients who use anti-TNFα agents develop anti-TNFα antibodies, which reduces the anti-inflammatory effects of the drug.[17]

UC patients with proctitis can often be treated with local therapy, but when this is insufficient, or the inflammation affects a larger extent of the colon, mesalazine should be started, sometimes in combination with corticosteroids. Immunomodulators can be added later to prevent relapse of inflammation.

Pathogenesis of IBD

Inflammation arises in IBD through an exacerbated immune response to the commensal bacteria in the gut in genetically predisposed individuals. While this process may sound straightforward, environmental factors,[18] the immune response, the gut microbiota and genetics all play a role in disease risk, making the study of the pathogenesis of IBD a complex affair.

Smoking and appendectomy are environmental factors well established to play a role in IBD risk. Being a former smoker is a risk factor for the development of UC, while smoking is protective of an exacerbation once the disease has established. On the other hand, being a current smoker is a risk factor for the development of CD and is associated with a higher risk of disease exacerbations.[19] Prior appendectomy is an environmental factor associated with a reduced risk of acquiring UC.[20]

In recent years, the gut microbiome has become the focus of increased attention for its role in IBD. Many studies report dysbiosis, showing a decreased diversity in the gut microbiome in IBD patients as compared to that of healthy controls. In animal models of gut inflammation it has been shown that some microbial species reduce intestinal inflammation, whereas others (some known to be correlated with IBD) can exacerbate it, implying an important role for the gut microbiome in inflammation in IBD.[21-25]

The genetic background of IBD risk has been studied extensively in the recent and rapid growth of the field of genetic research. Genome-wide association studies (GWAS) initially revealed more than 99 susceptible loci associated with IBD risk.[26] In GWAS, large numbers of patients and healthy individuals are genotyped and compared for thousands of small common genetic variants, called single nucleotide polymorphisms (SNPs). As GWAS for other immune-mediated disease were carried out, it became clear that most genetic risk variants were shared between IBD and other immune-mediated diseases.[27,28] With this in mind, the Immunochip was designed. It is a customized array covering ~200,000 SNPs selected from GWAS results for 12 immune-mediated diseases. Immunochip studies have now been very successful in identifying new genetic risk loci for IBD, increasing the number of known IBD risk loci to 242.[29-31]

Predicting disease course using clinical and genetic risk factors

A major concern in the management and treatment of IBD is the heterogeneity of the disease between patients. The localization, severity and course of the disease can be highly variable between individuals with the same diagnosis, yet we still cannot predict which patients are at risk of a severe disease course and who may require surgical intervention and expensive medication such as biologicals. It is thus important to identify clinical parameters that can predict disease course.

Clinical parameters associated with a severe disease course, such as early age of onset, current smoking, and fistulising disease, should be considered as predictors for severe disease in clinical practice. These factors could, for example, be a reason for starting anti-TNF treatment or performing

surgical intervention earlier in disease course. Smoking, another clinical parameter associated with severe disease course, should be targeted by clinical support for smoking cessation before increasing the intensity of medical treatment. In addition to these clinical parameters known to be associated with severe disease course, there are many factors whose effect on disease phenotype and disease course has not yet been intensively researched, including the influence of ethnicity and sex differences.

Genetic variants should also be considered in efforts to predict disease course. When it comes to disease risk, the role of genetics has been studied extensively. However, studies on genetic risk loci associated with a particular IBD phenotype remain few. A large international collaboration found three risk loci associated with disease location, but little or no genetic association with disease behaviour.[32] Genetic studies on disease course and response to therapy have only just started to evolve and there is much more information to gain in this field of research.

Ultimately, we want to incorporate both clinical and genetic risk factors into an algorithm that can predict whether a given patient will be at risk of a severe disease course. With such a prediction model, we could prevent unfavourable outcomes by starting harsher medical treatment earlier in the disease course in patients at high risk for severe disease outcome. The aim of my thesis is therefore to identify clinical and genetic predictors for specific IBD phenotypes.

Outline of this thesis

This thesis focuses on resolving important questions in two areas of interest in IBD disease course:

- The epidemiology of IBD disease course: Identifying clinical factors that explain phenotypic differences in IBD patients
- The genetics of IBD disease course: Identifying genetic risk loci associated with IBD disease behaviour

Cohorts used in this thesis

To identify clinical and genetic risk factors for specific IBD phenotypes, it is crucial to have detailed data that has been collected in a standardized manner. In the first part of my thesis I use data made available through the Parelsnoer Institute (www.parelsnoer.org). At the time of my study, the IBD Parelsnoer cohort contained 3388 patients with IBD collected via a collaboration of the eight University Medical Centers (UMCs) in the Netherlands. Detailed phenotypic data was collected for 225 IBD-related items. In the second part of my thesis I use the Understanding and Redefining IBD (UR-IBD) cohort collected through the department of Gastroenterology and Hepatology in the University Medical Center Groningen (UMCG). The UR-IBD cohort currently consists of over 1000 patients with IBD, for whom we have extensive phenotype, genotype, and microbiome data as well as serological markers.

Large cohorts are required to assess correlations between clinical factors and IBD phenotypes and to identify genetic risk loci associated with specific IBD phenotypes. Therefore, I collaborated with the University of Utrecht, where a large IBD cohort of 2252 IBD patients, the COIN study (Costs Of Inflammatory bowel disease in the Netherlands), had been collected from both the University and general hospitals.[33] I used this cohort to increase my sample size to gain more power to assess phenotypic differences in patients with IBD. I also collaborated with the Translational Research in Gastrointestinal Disorders (TARGID) research center of the University of Leuven, whose cohort has both genotype data and infliximab antibody data available. Patients in the IBD Parelsnoer cohort, the UR-IBD cohort and the Leuven cohort have all been genotyped using the Immunochip.

Part I. The epidemiology of IBD disease course: Identifying clinical factors that explain phenotypic differences in IBD patients

To identify factors associated with a specific phenotype, it is critical that patient phenotypes are described in a consistent manner. The Montreal classification is a classification system for subphenotypes of both CD and UC. While Montreal classification is used extensively in the clinic, there is virtually no data on its reliability and reproducibility. Therefore, in **chapter 2**, we validated the Montreal classification among 30 observers with different professions (gastroenterologist specialist in IBD, gastroenterologist in training and IBD-nurses) in 20 de-identified medical records. This intra- and inter-observer variability validation is important because **chapter 3** gives an overview of the phenotypic characteristics of patients with IBD present in the IBD Parelsnoer cohort on 17 July 2014. Furthermore, we used the IBD Parelsnoer cohort to further explore the clinical parameters that are associated with phenotypic differences in patients with IBD.

As IBD is most often diagnosed in the second or third decade of life, patients can experience difficulties at work or study early in life. IBD can be a significant burden in daily life, as patients suffer from disease symptoms or flares of the disease. Consequently, patients with IBD are at significant risk for work disability. In **chapter 4** we assess potential risk factors for work disability in IBD, which is of great importance in efforts to improve IBD patient care.

IBD is emerging as a global disease, with a considerable variation within and between geographic regions. The incidence of IBD in developing countries may be increasing because of industrialization and Western lifestyle changes, but these changes cannot explain the phenotypic heterogeneity within and between regions. Population-based studies concerning phenotype differences between ethnicities and different countries of birth remain scarce. In **chapter 5** we explore the role of ethnicity and country of birth on IBD phenotype.

In recent years, diagnostic and treatment strategies for most chronic diseases have increasingly been adjusted to the individual patient, with extra care being taken to address the differential needs of male versus female patients, for example in cardiovascular disease.[34] In IBD care, both

diagnostic and treatment strategies are applied equally to male and female patients. If we want to move further towards personalized treatment, it is important to assess differences in IBD disease course and in disease phenotypes between sexes. **Chapter 6** therefore focuses on differences between male and female IBD patients, comparing phenotype, clinical manifestations, disease course, medical treatment and other healthcare consumption. For this study we used both the IBD Parelsnoer cohort and the COIN study cohort.

Part II. The genetics of IBD disease course: Identifying genetic risk loci that are associated with IBD disease behaviour

Although more than 200 IBD loci are known to be associated with IBD risk there are only a few studies that correlate these loci to IBD disease behaviour. In this second part of my thesis I focus on IBD-associated genetic variants that are associated with a particular disease phenotype.

Chapter 7 is a review of IBD genetics. It describes the clinical presentation of IBD and gives an overview of the progress that has been made in the field of IBD genetics, from linkage and candidate studies to GWAS and Immunochip studies. Chapter 7 also describes the genetic and biological pathways of IBD and its overlap with other immune-mediated disease. The final part of this review focuses on genetic findings and how we can translate them to clinical practice.

Hidradenitis suppurativa (HS) is a chronic inflammation of the apocrine glands often followed by sinus tract formation and scarring. Although HS is not yet a well-recognized EIM in IBD, the prevalence of HS in IBD is much higher than in the general population, which raises the hypothesis of a shared pathogenesis. In **chapter 8**, I aimed to identify genetic and clinical parameters associated with the occurrence of HS in IBD.

The need for surgery for fibrostenotic disease in patients with CD is an indicator of a severe disease course. In **chapter 9**, I aimed to identify disease-modifying genes for recurrent fibrostenotic disease behaviour in CD. I used Immunochip data to perform a within-cases analysis in two independent cohorts by comparing patients with fibrostenotic CD with patients with purely inflammatory CD.

The use of anti-TNFα agents is very important for inducing and maintaining clinical remission in patients with CD. However, some patients develop anti-drug antibodies (ADAs) to anti-TNFα, resulting in loss of response. In **chapter 10**, I aimed to identify genetic variants that play a role in the development of ADAs to anti-TNFα (infliximab and adalimumab), comparing IBD patients who developed anti-TNFα ADAs to IBD patients without these ADAs. This study was carried out in collaboration with University of Leuven, Belgium.

Chapter 11 gives an overview of the studies present in this thesis, discussion and the future perspectives.

References

1. van den Heuvel TRA, Jeuring SFG, Zeegers MP, *et al.* A 20-Year Temporal Change Analysis in Incidence, Presenting Phenotype and Mortality, in the Dutch IBDSL Cohort-Can Diagnostic Factors Explain the Increase in IBD Incidence? *J Crohn's Colitis* 2017;11:1169-79.
2. Logan I, Bowlus CL. The geoepidemiology of autoimmune intestinal diseases. *Autoimmun Rev* 2010;9:A372-8.
3. Molodecky NA, Soon IS, Rabi DM, *et al.* Increasing Incidence and Prevalence of the Inflammatory Bowel Diseases With Time, Based on Systematic Review. *Gastroenterology* 2012;142:46-54.e42.
4. Van Limbergen J, Russell RK, Drummond HE, *et al.* Definition of phenotypic characteristics of childhood-onset inflammatory bowel disease. *Gastroenterology* 2008;135:1114-22.
5. Wagtmans MJ, Verspaget HW, Lamers CB, *et al.* Gender-related differences in the clinical course of Crohn's disease. *Am J Gastroenterol* 2001;96:1541-6.
6. Ponsioen CY, de Groof EJ, Eshuis EJ, *et al.* Laparoscopic ileocaecal resection versus infliximab for terminal ileitis in Crohn's disease: a randomised controlled, open-label, multicentre trial. *Lancet Gastroenterol Hepatol* 2017;2:785-92.
7. Travis SPL, Stange EF, Lémann M, *et al.* European evidence based consensus on the diagnosis and management of Crohn's disease: current management. *Gut* 2006;55:i16-35.
8. Rankin GB, Watts HD, Melnyk CS, *et al.* National Cooperative Crohn's Disease Study: extraintestinal manifestations and perianal complications. *Gastroenterology* 1979;77:914-20.
9. Lakatos PL, Lakatos L, Kiss LS, *et al.* Treatment of extraintestinal manifestations in inflammatory bowel disease. *Digestion* 2012;86 Suppl 1:28-35.
10. Severs M, van Erp SJH, van der Valk ME, *et al.* Smoking is Associated With Extra-intestinal Manifestations in Inflammatory Bowel Disease. *J Crohn's Colitis* 2016;10:455-61.
11. Boonstra K, Weersma RK, van Erpecum KJ, *et al.* Population-based epidemiology, malignancy risk, and outcome of primary sclerosing cholangitis. *Hepatology* 2013;58:2045-55.
12. Kappelman MD, Horvath-Puho E, Sandler RS, *et al.* Thromboembolic risk among Danish children and adults with inflammatory bowel diseases: a population-based nationwide study. *Gut* 2011;60:937-43.
13. Grainge MJ, West J, Card TR. Venous thromboembolism during active disease and remission in inflammatory bowel disease: a cohort study. *Lancet* 2010;375:657-63.
14. Dignass A, Lindsay JO, Sturm A, *et al.* Second European evidence-based consensus on the diagnosis and management of ulcerative colitis Part 2: Current management. *J Crohn's Colitis* 2012;6:991-1030.
15. Dignass A, Van Assche G, Lindsay JO, *et al.* The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Current management. *J Crohn's Colitis* 2010;4:28-62.
16. Frolkis AD, Dykeman J, Negrón ME, *et al.* Risk of surgery for inflammatory bowel diseases has decreased over time: a systematic review and meta-analysis of population-based studies. *Gastroenterology* 2013;145:996-1006.
17. Allez M, Karmiris K, Louis E, *et al.* Report of the ECCO pathogenesis workshop on anti-TNF therapy failures in inflammatory bowel diseases: definitions, frequency and pharmacological aspects. *J Crohns Colitis* 2010;4:355-66.
18. van der Sloot KWJ, Amini M, Peters V, *et al.* Inflammatory Bowel Diseases. *Inflamm Bowel Dis* 2017;23:1499-509.
19. van der Heide F, Dijkstra A, Weersma RK, *et al.* Effects of active and passive smoking on disease course of Crohn's disease and ulcerative colitis. *Inflamm Bowel Dis* 2009;15:1199-207.
20. Molodecky NA, Kaplan GG. Environmental risk factors for inflammatory bowel disease. *Gastroenterol Hepatol (N Y)* 2010;6:339-46.
21. Sartor RB. Microbial Influences in Inflammatory Bowel Diseases. *Gastroenterology* 2008;134:577-94.
22. Kostic AD, Xavier RJ, Gevers D. The microbiome in inflammatory bowel disease: current status and the future ahead. *Gastroenterology* 2014;146:1489-99.

23. Atarashi K, Tanoue T, Oshima K, *et al.* Treg induction by a rationally selected mixture of Clostridia strains from the human microbiota. *Nature* 2013;500:232-6.

24. Morgan XC, Tickle TL, Sokol H, *et al.* Dysfunction of the intestinal microbiome in inflammatory bowel disease and treatment. *Genome Biol* 2012;13:R79.

25. Imhann F, Vich Vila A, Bonder MJ, *et al.* Interplay of host genetics and gut microbiota underlying the onset and clinical presentation of inflammatory bowel disease. *Gut* 2018;67(1):108-119.

26. Anderson CA, Boucher G, Lees CW, *et al.* Meta-analysis identifies 29 additional ulcerative colitis risk loci, increasing the number of confirmed associations to 47. *Nat Genet* 2011;43:246-52.

27. Zhernakova A, van Diemen CC, Wijmenga C. Detecting shared pathogenesis from the shared genetics of immune-related diseases. *Nat Rev Genet* 2009;10:43-55.

28. Uniken Venema WT, Voskuil MD, Dijkstra G, *et al.* The genetic background of inflammatory bowel disease: from correlation to causality. *J Pathol* 2017;241:146-58.

29. de Lange KM, Moutsianas L, Lee JC, *et al.* Genome-wide association study implicates immune activation of multiple integrin genes in inflammatory bowel disease. *Nat Genet* 2017;49:256-61.

30. Liu JZ, van Sommeren S, Huang H, *et al.* Association analyses identify 38 susceptibility loci for inflammatory bowel disease and highlight shared genetic risk across populations. *Nat Genet* 2015;47:979-86.

31. Jostins L, Ripke S, Weersma RK, *et al.* Host–microbe interactions have shaped the genetic architecture of inflammatory bowel disease. *Nature* 2012;491:119-24.

32. Cleynen I, Boucher G, Jostins L, *et al.* Inherited determinants of Crohn's disease and ulcerative colitis phenotypes: a genetic association study. *Lancet* 2016;387:156-67.

33. van der Valk ME, Mangen M-JJ, Leenders M, *et al.* Healthcare costs of inflammatory bowel disease have shifted from hospitalisation and surgery towards anti-TNFα therapy: results from the COIN study. *Gut* 2014;63:72-9.

34. Khamis RY, Ammari T, Mikhail GW. Gender differences in coronary heart disease. *Heart* 2016;102:1142-9.