Epidemiology of Irritable Bowel Syndrome - hereditary and non-hereditary factors

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2018

Document Version:
Publisher's PDF, also known as Version of record

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Hereditary and non-hereditary factors

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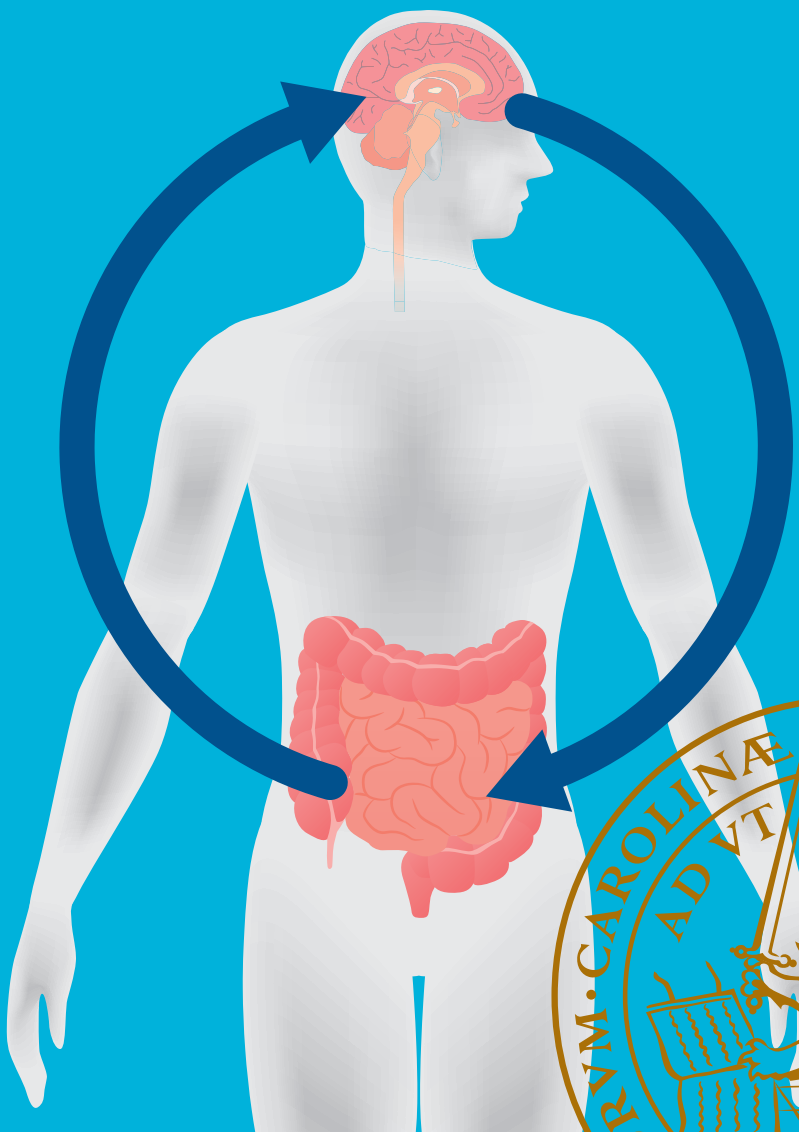

Irritable Bowel Syndrome (IBS) is a common, chronic, relapsing gastro-intestinal disorder with a global prevalence of 10-15 %. It has a great negative impact on patients` health related quality of life and the economic burden on society is substantial. In the present thesis aspects of risk factors in secondary specialist care as well as in primary care has been highlighted. Strong evidence of a genetic cause of IBS has been shown in family studies of first-, second and third-degree relatives and in adoptees. A low prevalence of IBS in primary care has also been shown suggesting an underestimation of IBS among general practitioners. Certain perinatal risk factors like caesarean and low birth weight and a family history of depression, anxiety and IBS increases the risk of IBS in young adulthood.

Rasmus Wæhrens received his medical degree from University of Copenhagen in 1999. He is a specialist in psychiatry and family medicine and works as a general practitioner.

Printed by Media-Tryck, Lund 2018 NORDIC SWAN ECOLABEL 3041 0903

LUND UNIVERSITY

FACULTY OF MEDICINE

Center for Primary Health Care Research
Department of Clinical Sciences

Lund University, Faculty of Medicine
Doctoral Dissertation Series 2018:52
ISBN 978-91-7619-619-9
ISSN 1652-8220

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UNIVERSITY

DOCTORAL DISSERTATION
by due permission of the Faculty of Medicine, Lund University, Sweden.
To be defended at Medelhavet, Wallenbergs Laboratory, Skåne University Hospital, Malmö. Wednesday 23 May 2018, 13:00

Supervisor
Associate Professor Bengt Zöller, Center for Primary Health Care Research, Clinical Research Centre, Faculty of Medicine, Lund University, Sweden

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Organization
LUND UNIVERSITY
Center for Primary Health Care Research
Clinical Research Centre
Faculty of Medicine, Lund University
Skåne University Hospital, Malmö

Author(s): Rasmus Wæhrens

Document name
DOCTORAL DISSERTATION

Date of issue May 23, 2018

Sponsoring organization

Title and subtitle
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Aims: The overall aims were to explore the role of hereditary and non-hereditary factors in IBS. In paper I, the epidemiology, number of visits, and comorbidity in IBS patients in primary care were described. In paper II, familial risks in first-, second-, and third-degree relatives of patients with IBS were determined. In paper III, familial risks of IBS in adoptees were studied. In paper IV, perinatal and familial risk factors for IBS were investigated.

Methods: A large primary care register was used to estimate the prevalence of IBS, number of visits, and comorbidities in IBS patients. In papers II-IV the Swedish national patient register (NPR) was used to identify patients with IBS. The NPR was linked to the Multi-generation register in order to calculate odds ratios for IBS in relatives of patients with IBS and in adoptees with adoptive parents or biological parents with IBS. Falconer's regression was used to determine heritability in paper III. In paper IV the Swedish Medical Birth Registry was used to identify 1,963,685 individuals born between 1973-1992. These individuals were followed for incidence of IBS in the NPR until 2010. The importance of perinatal and familial factors for development of IBS in adult age (18-38 years) was analysed.

Results: In paper I a low prevalence (1.2%) of IBS was observed. A high number of visits by IBS patients to their general practitioner was found. IBS has increased the number of comorbidities diagnosed. In paper II Odds Ratios (ORs) for first-, second-, and third-degree relatives of probands with IBS were increased significantly both in primary and specialist care. Spouses of IBS patients also had an increased risk of IBS, although lower than in biological first degree relatives. In paper III an increased risk of IBS was found in adoptees of biological parents with IBS, but not in adoptees with IBS of adoptive parents with IBS . The heritability was estimated by the use of Falconer's regression to be 19.5% ± 8.5%. In paper IV several significant perinatal risk factors for IBS in adulthood were identified: caesarean, low birth weight, being second in birth order. Foetal growth >=1 was borderline significant. Regarding socioeconomic factors, maternal age at < 20 years of age, having a divorced/widowed mother, maternal education 10-11 years and also 12-14 years were significant risk factors. Concerning inherited factors, a parental history of IBS, a parental history of anxiety, and also of depression were significant risk factors for IBS in adults. Though perinatal and socioeconomic factors were of low effect size the combination of several risk facors may result in high risk of IBS.

Conclusion: The results in the present thesis adds epidemiological evidence to the current knowledge of the pathogenesis and risk factors of IBS. A low prevalence of IBS was seen in patients in primary care, which suggests failure to diagnose IBS in primary health care. Family history of IBS is a risk factor for IBS. Biological (genetic) factors are of greater importance than environmental familial factors in adoptees with IBS. Perinatal factors may play a role in the aetiology of IBS in the long-term. The findings have implications for future directions in the research of IBS.

Keywords
Irritable Bowel Syndrome, epidemiology, genetics, adoption, perinatal, environment, multi-level analysis

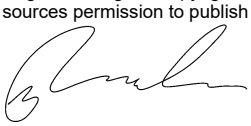
Classification system and/or index terms (if any)

Supplementary bibliographical information | Language English

ISSN and key title 1652-8220. Lund University, Faculty of Medicine
Doctoral Dissertation Series 2018:52 | ISBN 978-91-7619-619-9

Recipient's notes | Number of pages | Price

Security classification

Signature  Date April 17, 2018

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Cover photo: the Rome IV criteria from 2016 define IBS as a disorder of Gut-Brain interaction.

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ISBN 978-91-7619-619-9
ISSN 1652-8220
Lund University, Faculty of Medicine Doctoral Dissertation Series 2018:52

Printed in Sweden by Media-Tryck, Lund University
Lund 2018

To my wife, Maria and our son Anton

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List of publications

I. **Waehrens R**, Ohlsson H, Sundquist J, Sundquist K, Zöller B. Low prevalence of irritable bowel syndrome in primary health care in four Swedish counties. *Scand J Prim Health Care 2013; 31 (3): 132-7.*

II. **Waehrens R**, Ohlsson H, Sundquist J, Sundquist K, Zöller B. Risk of irritable bowel syndrome in first-degree, second-degree and third-degree relatives of affected individuals: a nationwide family study in Sweden. *Gut 2015; 64 (2): 215-21.*

III. **Waehrens R**, Zöller B, Sundquist J, Sundquist K, and PirouziFard M. A Swedish national adoption study of risk of irritable bowel syndrome (IBS). *BMJ Open Gastroenterology 2017; 4 (1).*

IV. **Waehrens R**, Li X, Sundquist J, Sundquist K, and Zöller B. Perinatal and familial risk factors for irritable bowel syndrome in a Swedish national cohort. *Scand J Gastroenterol 2017; 10: 1-8.*

Abbreviations

ORs	Odds Ratios
95% CI	95% Confidence Interval
CDR	Cause of Death Register
GP	General Practitioner
GWAS	Genome-Wide Association Study
HR	Hazard ratio
HRQOL	Health Related Quality Of Life
IBS	Irritable bowel syndrome
ICD	International classification of diseases
LUTS	Lower Urinary Tract Symptoms
MGR	Multi-Generation Register
NPR	National Patient Register
SES	Socioeconomic status
SNPs	Single Nucleotide Polymorphisms
TPR	The Swedish total population register

Chapter I.

Introduction

Overview

Irritable Bowel Syndrome (IBS) is a common chronic functional gastrointestinal disorder that is diagnosed according to the Rome symptom based diagnostic criteria. Prior to the latest Rome IV criteria, IBS was defined as a functional gastrointestinal disorder. The latest Rome IV criteria (2016) has defined IBS as a disorder of brain-gut axis and moved away from the term functional as it is imprecise and possibly stigmatising (Drossman, 2016; Ford et al, 2017).

Chaudhury and Truelove (1962), who examined 130 patients admitted to the department of clinical medicine Radcliffe Infirmary, Oxford, made the first thorough description of patients with symptoms suggestive of IBS in 1962. The diagnosis was Irritable Colon Syndrome and the patients were categorised according to two distinct clinical entities, with the large majority in the group with pain of colonic origin and variable bowel habit called spastic colon. The other group had painless diarrhoea. Two-thirds of the patients were women and psychological factors played a significant role in the onset of the disorder or in causing exacerbations in four out of five patients. This group had a worse prognosis except for those who experienced a major positive change in their life, after which their symptoms improved. In around one in five patients with IBS, gastroenteritis of various origin, although half presumed infectious origin, was the cause of the upcoming symptoms. Clinical examinations revealed varied abdominal tenderness. A considerable number of patients were examined with sigmoidoscopy including colonic biopsy and all patients underwent barium enema and measurement of the haemoglobin and erythrocyte sedimentation rate. All the results were normal (Chaudhury & Truelove, 1962).

The diagnosis of IBS has changed over time (Table 1). The first symptom-based criteria came with the criteria described by Manning et al in 1978. They asked 109 unselected patients referred to gastroenterological or surgical clinics, with abdominal pain or a change in bowel habits or both, to fill out a questionnaire before the consultation, with the intention to identify symptoms that could distinguish IBS from organic disease. Of the 109 patients, 79 received a definite

diagnosis of which 14 were excluded because of diverticular disease that could be regarded as organic or functional. Of the remaining 65 patients, 32 had IBS and 33 had organic disease. They found that four symptoms: pain relief after defecation, more frequent *and* looser stools after onset of pain, and distension were significantly more often present in patients with IBS than organic disease. Two more symptoms: passage of mucus and the sensation of incomplete evacuation were more often present in IBS than in organic disease but not as often as the first four symptoms. The more of the first four symptoms were present the more likely the diagnosis of IBS and when combining with the last two the likelihood increased even more. (Manning et al, 1978).

Kruis and colleagues (1984) created a scoring system which consisted of the case history, physical examination, and basic paraclinical investigations including erythrocyte sedimentation rate and blood count for the diagnosis of IBS in order to safely separate patients with some organic disease from patients with IBS. When the patients scored positively on abdominal pain, flatulence and irregularities of bowel movement, the diagnosis of IBS was highly significant and able to exclude the diagnosis from an organic disease in the abdomen, especially when including symptoms for at least two years (Kruis et al, 1984).

However, a continuous practice of investigating patients in order to exclude other disorders and the lack of well-defined criteria and clinical trials led to the release of a consensus document. By using the Delphi method (Dalkey & Helmer, 1963), in which an international group of experts, in this case in gastrointestinal disorders, worked together via e-mail and later gathered in a meeting in Rome, to reach consensus on symptom based diagnostic criteria on functional gastrointestinal disorders in five different anatomic domains. The first Rome criteria for IBS were described in 1990 as the Rome I criteria. This criteria differed from the Manning criteria in that the change in stool consistency or frequency could be more hard or less frequent stools, and softer or looser and more frequent stools. Abdominal bloating or distension and also mucus per rectum were replaced as diagnostic symptoms and instead as symptoms that may support the diagnosis. A time duration of at least three months with symptoms was included in the diagnosis. A meta-analysis, which was published in 2008, found one eligible study reporting on the accuracy of the Rome I criteria with a sensitivity of 71% and specificity of 85% (Ford et al., 2008). In 1999 the Rome II criteria and in 2006 the Rome III criteria were applied, respectively.

Table 1.
Criteria for Diagnosing IBS: Manning and Rome I-IV criteria

Manning criteria (1978)
Two or more of the following symptoms:
Abdominal distension
Pain relief with defecation
Frequent stools with pain
Looser stools with pain
Passage of mucus
Sensation of incomplete evacuation
Rome I Criteria (1990):
At least three months of continuous or recurrent abdominal pain:
Relieved with defecation or associated with change in stool consistency
With at least two of the following on at least 25% of days:
Altered stool frequency
Altered stool form
Altered stool passage
Passage of mucus
Bloating or abdominal distension
Rome II criteria (1999):
At least 12 weeks in the past 12 months:
Of continuous or recurrent abdominal pain or discomfort
With at least two of the following:
Relief with defecation
Altered stool form
Altered stool frequency
Onset of symptoms more than 12 months before diagnosis
Rome III criteria (2006)
At least three days per month in past 12 weeks of continuous or recurrent abdominal pain or discomfort
With at least two of the following:
Relief with defecation
Altered stool form
Altered stool frequency
Onset of symptoms more than six months before diagnosis
Rome IV criteria (2016):
Recurrent abdominal pain, on average, at least 1 day/week in the last 3 months, associated with two or more of the following criteria:
Related to defecation
Associated with a change in frequency of stool
Associated with a change in form (appearance) of stool.
Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

The newer criteria also included how often symptoms occur and when the onset of symptoms started. A study was conducted to validate the Rome III criteria and compared this criteria with the Manning, the Rome I and the Rome II criteria for IBS. Of the 4224 patients enrolled in the study, a total of 1981 underwent a complete colonoscopy. The authors concluded that the existing diagnostic criteria performed only modestly in distinguishing IBS from organic disease. Importantly,

the Rome III criteria did not perform better than any of the previous symptom-based criteria (Ford et al, 2013).

Part of the reason for making symptom-based criteria was to help the physician in making a positive diagnosis and thus also to minimise investigations that would turn out to be unnecessary. Guidelines for IBS still recommend this and state that IBS is not a diagnosis of exclusion. (Spiller et al., 2007; Ford et al, 2014; Quigley et al, 2015).

In primary health care, where the majority of patients with symptoms suggestive of IBS are evaluated, symptom based criteria are not always followed. A more pragmatic evaluation is often used for the diagnosis of the patient's symptoms with a focus on alteration in bowel movements together with discomfort and bloating and also including a family history of IBS, psychosocial complaints, frequent consultations for other problems including functional complaints, somatization behaviour, and recent major life events as supportive features (Rubin et al, 2006). A Rome Foundation report has supported this notion and shown that a tentative diagnosis of IBS in primary care is often made but still patients undergo additional testing like colonoscopy and are treated with varied therapies because of insecurity with causes of IBS and treatment effectiveness (Hungin et al, 2014). A more recent multinational European study evaluated general practitioners' use of Rome criteria. A positive diagnosis was made by 32% of the general practitioners, and 31% referred the patient for endoscopy. Psychological factors were the most frequent potential aetiologic factors selected. In a study evaluating the IBS diagnosis in primary care, three out of four patients were diagnosed with Rome III criteria for IBS (Engsbro et al, 2013). Another study with patients diagnosed with IBS according to the Rome III criteria and randomly assigned to either a positive diagnostic strategy or a strategy of exclusion found the positive strategy to be non-inferior to an exclusion strategy and with lower costs (Begtrup et al, 2013). Thus the question remains open as to whether the use of Rome criteria in primary care is of value.

Different subtypes of IBS have been described (Longstreth et al, 2006). IBS-C constitutes IBS patients with constipation. IBS with diarrhoea is called IBS-D. IBS-M is a mix of IBS-C and IBS-D. Unclassified IBS have insufficient stool abnormalities to be classified as IBS-C, IBS-D, or IBS-M.

Prevalence

According to a meta-analysis of the prevalence of IBS, the pooled global prevalence was 11.2% in 80 studies containing a total of 260960 individuals (Lovell & Ford, 2012). The included studies had the following distribution: 21

studies from Northern Europe, 19 from Southeast Asia, 10 from North America, 9 from Southern Europe, 8 from Middle East, 4 from Southern Asia, 4 from South America, and 3 from Australasia, and 2 studies from Africa. The prevalence varied with diagnostic criteria and also between countries: the lowest prevalence was 1.1% and the highest was 45%. According to different diagnostic criteria, IBS was more prevalent when diagnosed with the Manning criteria (14%) as compared with the Rome I criteria (8.8%) and Rome II criteria (9.4%). The prevalence was also higher among women than men and lower for those above 50 years of age compared with those younger than 50 years of age. IBS frequency did not vary with socioeconomic status (SES). However, only four studies reported information about SES (Lovell & Ford, 2012). Lovell & Ford (2012) reported the prevalence for Sweden to be 19.0% using Manning criteria, 14.0% using Rome I criteria, and 13.0% using Rome II criteria; the Swedish studies were based on questionnaires. In this thesis, Waehrens et al (2013) reported a prevalence of 1.2% in a Swedish register based primary health care study. Other register based studies have also found a lower prevalence of IBS (Thompson et al, 2000; Sandler et al, 1990). A UK Primary Care study found a prevalence of 2.5% and a US survey and register study found a prevalence of 1.6%. All included studies in the meta-analysis by Lovell & Ford (2012) were based on questionnaires or interviews. A British questionnaire based study by Wilson et al (2004) found that 56% of patients had visited their general practitioner during the last six months and that only 46% of IBS patients according to Rome II criteria had obtained a diagnosis of IBS. Thus, register based prevalence studies of IBS are likely to underestimate the true burden of IBS compared to questionnaire studies.

Pathophysiology

A number of heterogeneous mechanisms have been associated with IBS (Ford et al, 2017). IBS has been suggested to be a brain–gut disorder due to the association with psychosocial stress and psychiatric diseases like anxiety and depressive disorders. Inflammation has also been associated with IBS (Törnblom et al, 2005) along with infections in the intestines. After gastroenteritis, many patients (10-20%) will have persistent IBS like symptoms. The molecular mechanisms of post infectious IBS are most likely different from IBS due to non-infectious causes. For instance, patients with post-infectious IBS are more prone to have a slight intestinal inflammation in the large intestine. Alterations of the intestinal microbiome have also been associated with IBS. Other suggested causes of IBS are an altered sensory function (intestinal hypersensitivity) and motor function, i.e. a fast intestinal transit in IBS with diarrhoea and a prolonged intestinal transit in IBS with constipation. Intestinal permeability has been suggested to be changed in

IBS patients with diarrhoea. Altered gut immune activation is also associated with IBS.

Thus, a number of suggested mechanisms have been associated with IBS. It is therefore likely that IBS will turn out to be composed of many different disorders, which the recent studies of the genetics of IBS have indicated (Beyder et al, 2014; Holliday et al, 2014; Henström et al, 2018; Garcia-Etxebarria et al, 2018).

Genetics

IBS aggregates in families (Whorwell et al, 1986; Kalantar et al, 2003; Saito et al, 2008; Saito et al, 2010). Familial aggregation may be related to genes and/or shared familial environment. However, twin studies suggest a genetic contribution to IBS although there are some divergences among published twin studies regarding the contribution of genetic factors (Morris-Yates et al, 1998; Levy et al, 2001; Mohammed et al, 2005; Bengtson et al, 2006; Lembo et al, 2007). In the present thesis, Waehrens et al (2015) have shown an increased familial risk of IBS not only among first-degree relatives but also among second-degree and third-degree relatives thus indicating a genetic component contributing to the familial aggregation of IBS in families (Waehrens et al, 2015). In an adoption study, the heritability was 19.5%±8.5%, which indicates a low to moderate contribution of genetic factors (Waehrens et al, 2017).

There is now substantial evidence that the genetic architecture for IBS is complex and heterogeneous. IBS genetics span from complex polygenic conditions with combinations of common genetics variants to cases with rare single gene variants (D'Amato M, 2013; Henström & D'Amato, 2016).

In 2014 a pilot GWAS study was published by Holliday et al that found a genome-wide significant association with IBS ($p \sim 9x10\text{-}9$) of 21 perfectly correlated SNP on chromosome 10 on exon 10 of the protocadherin 15 gene (PCDH15). The diarrhoea predominant subtype (IBS-D) was also associated with a group SNP spanning a 500-kb region on chromosome 4 (Holliday et al, 2014). This region on chromosome 4 harbours several potentially interesting genes: FGF2 gene (fibroblast growth factor 2), the NUDT6 gene, and the SPRY1 gene. In 2015 a Swedish GWAS by Ek et al of twins identified a genome wide significant locus also in all replication cohorts and in a meta-analysis. This represents a major breakthrough in IBS research. The identified locus includes the genes KDELR2 (KDEL endoplasmic reticulum protein retention receptor 2) and GRID2IP (glutamate receptor, ionotropic, delta 2 (Grid2) interacting protein) (Ek et al, 2015).

A candidate gene study reported by Beyder et al in 2014 found that missense mutation in SCN5A gene are associated with IBS. The SCN5A gene encodes the α-subunit of the voltage-gated sodium channel NaV1.5. This gene has been associated with cardiac arrhythmias and patients with mutations in this gene have been reported to have an increased prevalence of IBS (Locke GR 3rd, 2006). However, the SCN5A gene is not only present in the heart but also in the gastrointestinal channel. These findings indicate a role of sodium channelopathies in IBS. Moreover, the findings of Beyder et al (2014) are a classic case of pleiotropy, i.e. one gene or one mutation affects multiple phenotypes (cardiac arrhythmias and IBS)(Beyder et al, 2014).

A candidate gene approach has also recently been successful. Henström et al (2018) found an association with functional variants in the sucrase-isomaltase gene (SI) and IBS. In addition, a common missense variant (Val15Phe; SNP rs9290264) was also associated with IBS. Garcia-Etxebarria et al (2018) also found an increased prevalence of rare sucrose-isomaltase pathogenic variants in IBS patients. Patients with homozygous deficiency of SI develop congenital sucrase–isomaltase deficiency (CSID) early in life (Garcia-Etxebarria, 2018). In the study by Henström et al (2018) heterozygous carriers of known rare CSID variants had a two times increased risk for IBS. These findings show that heterozygous carriers for a recessive disorder such as CSID are not always silent but symptoms may occur. Moreover, the findings of SI mutations in IBS indicate that the molecular cause of IBS is heterogeneous and when more knowledge is accumulated the previously ¨innocent¨ and ¨functional¨ disorder IBS will turn out to have several different causes. Moreover, this opens up for tailored treatment strategies for IBS (Henström et al, 2018).

Other completely different types of genes may also be involved. IBS is linked to comorbidities such as depression and anxiety. The NPSR1 protein is a receptor for neuropeptide S. This neuropeptide is related to anxiety, response to stress and fear, inflammation, and nociception (Henström & D'Amato, 2016). Recently, polymorphism in the NPSR1 has been shown to influence recurrent abdominal pain (RAP) in children, and RAP is one of the main symptoms of functional gastrointestinal disorders (FGID) such as IBS and functional abdominal pain (FAP) (Henström et al, 2014).

Chapter II.

Aims

The general aim of the present thesis was to investigate possible hereditary as well as non-hereditary risk factors for Irritable Bowel Syndrome in the Swedish population in order to shed new light on the relative influence of familial and inherited factors and various environmental risk factors.

Specific aims

- To examine the prevalence of IBS in Swedish primary health care. Another aim was to study the number of visits for IBS patients (article I).
- To assess the familial risk of IBS in first-degree, second-degree, and third-degree relatives, and spouses in a nationwide family study in order to estimate the relative influences of genetics and shared environment on risk of IBS (article II).
- To determine the risk and heritability of IBS in adoptees with a biological parent affected by IBS and to examine the risk of IBS in adoptees with an adoptive parent affected by IBS in a nationwide family study (article III).
- To explore the association between perinatal and familial factors and IBS in a national cohort study (article IV).

Chapter III.

Material and Methods

Design

The four papers included in this thesis by Waehrens et al were all register based studies (Table 2). The registers used in this thesis are maintained by Statistics Sweden and the National Board of Health and Welfare (Webster, 2014). Two different primary health care registers were included in papers I, II and IV. Papers II, III and IV also included the nationwide national patient register (NPR). An overall review of the four papers and their study design is presented in Table 2.

In all of the four included studies the unique Swedish 10-digit personal identification number, which is given at birth or immigration to all inhabitants in Sweden, was used to connect the used registers on the individual level (Ludvigsson et al, 2009). To secure anonymity the personal identification numbers were replaced with anonymised serial numbers by Statistics Sweden.

Table 2.
Overview of the four papers about irritable bowel syndrome included in this thesis.

	Paper I	**Paper II**	**Paper III**	**Paper IV**
Design	Cross sectional study	Case-cohort family study	Adoption family study	Retrospective Cohort study
Participants	919954	51952 IBS patients	2288 IBS patients	1963685
Data	Primary health care Register data	Register data	Register data	Register data
Statistical analysis	Logistic Regression	Conditional logistic regression	Conditional Logistic Regression Falconer's regression	Cox Regression
Study period	2001-2007	1987-2010	1964-2012	1973-2010

Primary Health Care Databases

Primary Health Care Databases

In article I (partially also in paper II) the study population was from a Swedish primary health care database that includes 71 primary health care centres from four Swedish counties: Stockholm (n=687 310 patients), Värmland (n=145 943 patients), Gotland (n=84 898 patients), and Uppsala (n=12 790 patients). The primary health care database holds individual level data from a total of 919954 patients who visited their general practitioner (GP) during the period 2001–2007.

In study III a larger Primary Care Register (PCR) was used (Sundquist et al, 2017; Waehrens et al, 2017a), which contains individual-level data from 1989 to 2016 from 12 Swedish counties. The PCR includes 7 908 367 individuals. The twelve counties were: Blekinge, Värmland, Kalmar, Uppsala, Västernorrland, Norrbotten, Halland, Kronoberg, Skåne, Östergötland, Stockholm, and Västra Götaland. On the 31st of December 2016 these 12 counties covered 77.7% of the Swedish population (https://www.scb.se/hitta-statistik/statistik-efter-amne/befolkning/befolkningens-sammansattning/befolkningsstatistik/pong/tabell-och-diagram/kvartals--och-halvarsstatistik--kommun-lan-och-riket/kvartal-4-2016/).

Nationwide registers

In articles II, III and IV data on all Swedish citizens and all cases of IBS were extracted from a number of nationwide registers including the Swedish multi-generation register (MGR) (Ekbom, 2011), the Total Population Register (TPR) (Ludvigsson et al, 2016), national patient register (NPR) (Ludvigsson et al, 2011), the Swedish Cause of Death Register (CDR) (Brooke et al, 2017), as well as a Primary Health Care Register (Sundquist et al, 2017; Waehrens et al, 2017a). The NPR consists of the inpatient register (IPR), which is also called the Hospital discharge register, and also since 2001 an outpatient register (OPR) (Ludvigsson et al, 2011). The registers were linked in order to identify individuals in Sweden diagnosed with IBS. This linkage was based on the unique individual Swedish 10-digit personal ID number introduced in 1947 and assigned at birth or immigration to all Swedish residents for life, information on which is nearly 100% complete (Ludvigsson et al, 2009). These numbers were replaced with random serial numbers upon data extraction to preserve anonymity.

Multi-Generation Register

The Swedish Multi-generation Register contains information on family relationships, specifically data on biological parents and siblings and also adoptions (Ekbom, 2011). All Swedish inhabitants born after 1932 and registered in Sweden at any time since 1961 are recorded as index cases. Information is available for mothers for 97% and for fathers in 95% of index cases. In December 2005, the Multi-generation Register contained information about 9,371,000 persons (Ekbom, 2011). The Multi-generation-register was used in articles II, III and IV.

Total Population Register

The Total Population Register (TPR) contains annual data on name, place of residence, sex, age, civil status, place of birth, death, citizenship, immigration (date, country, grounds for settlement), emigration, migration within Sweden, family relations (married couples, child-parent), and marital status (Ludvigsson et al, 2016).

Swedish National Patient Register (TPR)

The Swedish National Patient Register (TPR) includes data for inpatients and outpatients from specialist public care. However, primary care is not included. The Swedish National Inpatient Register (IPR), also called the Hospital Discharge Register, was started in 1964. The IPR includes all hospital discharge diagnoses. The IPR has had complete national coverage since 1987. Diagnoses in the IPR are coded according to the Swedish international classification of disease (ICD) system, first introduced in 1964 (adapted from the WHO ICD classification system). ICD-7 was used between 1964 and 1968. From 1969 until 1986 ICD version 8 was used. Between 1987 and 1997 ICD version 9 was used and since 1997 ICD version 10 has been used. Diagnosis coding in the register is based upon a physician´s clinical diagnosis. Currently, more than 99% of all somatic and psychiatric hospital discharges are registered in the IPR. The validity of the National Inpatient Register is generally high (Ludvigsson et al, 2011). It was used in articles II, III and IV.

The Swedish National Outpatient Register, also called the Outpatient Care Register, contains information on diagnoses from all specialist outpatient clinics in Sweden from 2001 to 2012. Compared with the IPR, coverage of hospital-based outpatient care is considerably lower (about 80%). In the outpatient register, data from private caregivers are missing. The coverage of data from public caregivers

in outpatient care is almost 100%). (Ludvigsson et al, 2011). It was used in articles II, III and IV.

Swedish Cause of Death Register

The Swedish Cause of Death Register contains data on date and cause of death of all Swedish citizens in Sweden as well as abroad. Data includes deaths in hospitals, nursing homes and private homes from 1952 to 2012. Reporting to the Cause of Death Register is mandatory and data are collected first at the time of death of the reporting physician. Cause of death is described afterwards in detail (at the latest three weeks after death is confirmed) in the death certificate completed by the patient's usual physician or the physician who last saw the patient before death. (Brooke et al, 2017). The Cause of death register was used in article IV.

Lisa Register

The Lisa Register – the Longitudinal Integration database for health insurance and labour market studies - from Statistics Sweden (SCB), contains annual data on education status from 1990. It also contains the Swedish Standard Classification of Occupations 1996, which is a national version of the International Standard Classification of Occupations. The register was used in article III. (https://www.scb.se/vara-tjanster/bestalla-mikrodata/vilka-mikrodata-finns/longitudinella-register/longitudinell-integrationsdatabas-for-sjukforsakrings--och-arbetsmarknadsstudier-lisa/).

Swedish Medical Birth Register

The Swedish Medical Birth Register includes data on all deliveries in Sweden including live births and stillbirths and mode of delivery (Källén, 2005) from 1973 onwards. It also contains data on the mother: age, maternal diagnosis, maternal medical drug use, single or multiple birth, duration of pregnancy, infant birth weight, body length, and head circumference. The register was used in article IV.

Small Area Market Statistics (SAMS)

From 1991 data has been used to define a municipal subarea when you need to characterise a neighbourhood; the code comprises the county, the municipality and unique SAMS area (9200 in whole Sweden) (https://www.geodata.se/GeodataExplorer/GetMetaData?UUID=f61fabe1-e440-4823-81d4-51c5ab946ce9).

Diagnostic definitions

Diagnoses of Irritable Bowel Syndrome and comorbid conditions are based on the ICD (International Classification of Diseases) codes of the World Health Organization (WHO).

Article I

In article I cases of IBS diagnosed in the primary care database were identified by the International Classification of Diseases (ICD-10) code K58. Diagnosis of IBS is based on symptom based diagnostic criteria.

Comorbidities in article I were defined by the following ICD-10 codes: depression (F32, F33, and F412); LUTS (R30); migraine (G43); headache (R519 and G442); and fibromyalgia (M797). However, fibromyalgia was not included in the analyses as no IBS patients in the database were also diagnosed with fibromyalgia.

Article II

IBS was diagnosed by ICD-9 code 564B and ICD-10 code K58. IBS patients with gastrointestinal differential diagnosis, that is, coeliac disease, inflammatory bowel disease and colorectal cancer were excluded (Table 3). Other functional gastrointestinal disorders and comorbidities were defined according to Table 3.

Table 3.
Definition of functional gastrointestinal disorders, comorbidites, and excluding diagnoses used in article II

	ICD-9	ICD-10
Other functional gastrointestinal disorders		
Functional constipation	564A	K59.0
Functional diarrhoea	564F	K59.1
Functional dyspepsia	536W	K30
Fecal incontinence	787G	R15
Comorbidities		
Anxiety	300A-D, 308, 309	F40-F43
Depression	296B, 311	F32, F33
Migraine	346	G43, G44.0, G44.1
Headache	R51, G44.2	784A, 307W
Micturition Pain	788B	R30
Pain	625	N94
Excluding diagnoses		
Celiac disease	579A	K900
Inflammatory bowel disease	555, 556	K50, K51
Colorectal cancer	153, 154	C18, C19, C20, C21

Article III

Cases of IBS in the Swedish Hospital Discharge Register, Outpatient Care Register and Primary Healthcare register were identified by the following International Classification of Diseases (ICD) codes: ICD-7 573.10, 573.21, 573.22; ICD-8 564.10, 564.11, 564.19; ICD-9 564B (IBS) and ICD-10 K58 (IBS). Patients with IBS with possible gastrointestinal differential diagnosis: coeliac disease ICD-7 286; ICD-8 269.00; ICD-9 579A; ICD-10 K900; inflammatory bowel disease (IBD) ICD-7572; ICD-8 563; ICD-9 555, 556; ICD-10 K50, K51; and colorectal cancer ICD-7 153,154; ICD-8 153,154; ICD-9 153, 154. and ICD-10 C18, C19, C20, C21.

Article IV

IBS was identified using primary and all secondary diagnoses from the International Classification of Diseases (ICD), revisions 9 and 10 (codes ICD-9 564B; and ICD-10 K58) in the Swedish Patient Register (inpatients and outpatients). Exclusion was done for IBS patients with potential differential diagnosis of coeliac disease (ICD-9 579A and ICD-10 K900), inflammatory bowel disease (ICD-9 555 and 556, and ICD-10 K50 and K51), and colorectal cancer (ICD-9 153 and 154 and ICD-10 C18, C19, C20, C21) (all primary and secondary diagnosis). In order to study the risk of incident IBS in young adulthood, patients with a prior diagnosis of IBS before the age of 18 years were excluded (564.19 in ICD-8; 564B in ICD-9; and K58 in ICD-10).

Statistical analyses

Article I

In article I logistic regression was used to investigate the association between IBS, gender, age, number of visits to a general practitioner, and comorbidities. Odds ratios (ORs) and 95% confidence intervals (CI) were calculated. Calculations were performed using SAS version 9.2.

Article II

Family studies are important for determining a genetic contribution to a disease (Burton et al, 2005). Although familial clustering might be caused by non-genetic mechanisms such as shared environmental exposures, it is seldom worthwhile to pursue a genetic cause if a disease does not cluster in families, which is a key concept in genetic epidemiology (Burton et al, 2005). In article II a case-cohort approach was used. ORs and corresponding 95% CI were calculated for first-, second- and third-degree relatives as well as spouses of cases with IBS and compared with relatives and spouses of controls without IBS. All IBS proband-relative pairs were matched to five control pairs. Matching was made on the basis of birth year, country of birth, level of education and sex. Analyses were conducted with the use of conditional logistic regression and performed using SAS version 9.3.

Article III

Adoption studies are a strong design to separate genetic from non-genetic causes of familial clustering (Risch, 2001). In article III a cohort study and a case-control study was used. In the cohort study the ORs were estimated with logistic regression for IBS in adoptees with biological parents affected by IBS compared with biological parents unaffected by IBS. ORs were also determined for IBS in adoptees with adoptive parents affected by IBS compared with adoptive parents unaffected by IBS.

In the case-control study matching of one case with five controls were made. ORs for IBS in adoptees with an affected biological parent were compared with ORs for IBS in adoptees with an affected adoptive parent. We also stratified ORs for age under 45 years and above 45 years of age. Analyses were conducted using conditional logistic regression.

The heritability in biological parents of adoptees with IBS was investigated with the use of Falconer's method (Falconer, 1965; Falconer & Mackay, 1996). and by using tetrachoric correlation (Frisell et al, 2013) with population estimates varying from 0.5% to 20%.

Article IV

In article IV Hazard Ratios (HRs) and corresponding 95% CIs were estimated with Cox regression for associations between perinatal and familial variables, and IBS.

Two models were used for adjustment: the first was adjusted for birth year and sex, and the second was further adjusted for foetal growth, gestational age at birth, caesarean, maternal age at delivery, maternal marital status, maternal and paternal education, parental history of IBS, parental history of depression and parental history of anxiety.

Birthweight and birth length was estimated in separate models as alternatives to the standardised foetal growth variable. A Chi-squared test was used to compare differences between those who developed IBS and those who did not. Statistical tests were two-sided and used an alfa-level of 0.05.

Chapter IV.

Ethical considerations

Study I was approved by the Ethics Committee of the Karolinska Institute, Huddinge Sweden. Study II was approved by the Ethics Committee of Lund University, Sweden and also approved by the Karolinska Institute, Huddinge, Sweden. Studies III and IV were approved by the Ethics Committee of Lund University, Sweden. All studies were performed in compliance with the Helsinki Declaration. Ethical considerations and aspects of registry-based research in Sweden and the other Nordic countries have been reviewed by Ludvigsson et al (2015).

Chapter V.

Results

Article I

Prevalence of Irritable Bowel Syndrome in Primary Care

In paper I, a total of 919954 individuals in a primary health care database with data from four counties in the period 2001-07 were included of which 10 987 (1.2%) individuals received a diagnosis of IBS (Table 4). The age distribution is presented in Figure 1.

Of the individuals without IBS 47% were male compared with IBS patients, where 29% were male. Of patients without IBS, 46% visited their doctor more than six times in the period compared with 81% with IBS. Only 5% of patients with IBS visited their doctor for IBS four or more times. Patients with IBS received a diagnosis of depression, migraine, lower urinary tract symptoms and headache 3-4 times more often than patients without IBS.

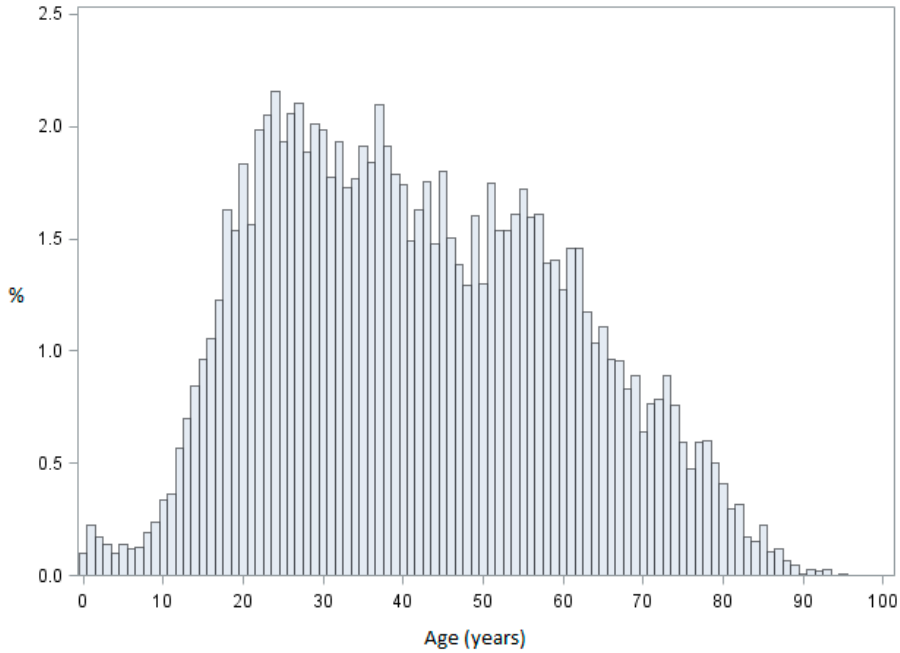

Figure 1:
The age distribution of individuals with IBS (n=10 987).

Table 4.
Descriptive statistics for all 919 954 individuals in the primary health care database

	All patients	Patients without IBS	Patients with IBS
Number of patients	919 954 (100)	908 967 (98.8)	10 987 (1.2)
Age (years)			
0-24	323 221 (35)	320 984 (35)	2 237 (20)
25-44	271 991 (30)	267 948 (30)	4 043 (37)
45-64	210 108 (23)	206 874 (23)	3 234 (29)
65-74	62 506 (7)	61 563 (7)	943 (9)
75-84	40 344 (4)	39 892 (4)	452 (4)
85+	11 110 (1)	11 038 (1)	72 (1)
Men	430 759 (47)	427 560 (47)	3 199 (29)
Number of GP visits			
1-2	270 724 (29)	270 020 (30)	704 (6)
3-5	217 744 (24)	216 373 (24)	1 371 (12)
6+	431 486 (47)	422 574 (46)	8 912 (81)
Depression (F32, F33, F412)	44 992 (5)	43 345 (5)	1 647 (15)
Lower urinary tract symptoms (R30)	3 257 (0.4)	3 154 (0.4)	103 (1)
Migraine (G43)	12 047 (1)	11 659 (1)	388 (4)
Headache (R519, G442)	8 699 (1)	8 315 (1)	384 (4)

In the first logistic regression analysis (model A), age and gender were included; patients in the age groups 25-44, 45-64 and 65-74 had the highest ORs (Table 5). In the second analysis (Models B1-B5) controlling for age and gender, all comorbidities were associated with IBS. The OR for IBS was high among the patients with IBS visiting their doctor six or more times. In the third analysis (Model C), adjustments were made for age, gender, number of visits to the doctor and comorbidities. Associations were similar to the second analysis. Six or more visits to the doctor showed the strongest association with IBS.

Table 5.
Results from logistic regression analysis of odds of IBS using data for the 919 954 individuals in the primary health care database

	Model A	**Models B1-B5**	**Model C**
Gender (males vs. females)	0.47 (0.45-0.49)	-	0.54 (0.52-0.58)
Age (years)			
0-24	1 (Ref)	-	1 (Ref)
25-44	2.12 (2.02-2.24)	-	1.85 (1.75-1.95)
45-64	2.23 (2.11-2.35)	-	1.61 (1.52-1.70)
65-74	2.16 (2.00-2.33)	-	1.39 (1.28-1.50)
75-84	1.52 (1.38-1.69)	-	0.93 (0.84-1.03)
85+	0.82 (0.65-1.04)	-	0.56 (0.44-0.70)
Number of GP visits			
1-2	-	1 (Ref)	1 (Ref)
3-5	-	2.41 (2.20-2.64)	2.36 (2.16-2.59)
6+	-	7.65 (7.08-8.26)	6.91 (6.39-7.47)
Depression (F32, F33, F412)	-	2.76 (2.61-2.91)	1.81 (1.71-1.91)
Lower urinary tract symptoms (R30)	-	2.54 (2.08-3.09)	1.79 (1.47-2.19)
Migraine (G43)	-	2.15 (1.94-2.39)	1.34 (1.21-1.49)
Headache (R519, G442) M (men)	-	4.50 (3.58-5.65)	2.76 (2.19-3.47)
Headache (R519, G442) F (women)	-	2.95 (2.63-3.33)	1.79 (1.59-2.02)

Article II

Risk of Irritable Bowel Syndrome in first-, second- and third-degree relatives

In paper II patients with a diagnosis of IBS were retrieved from the hospital discharge register, the outpatient care register and from a primary health care register covering four counties. A total of 51 952 patients were diagnosed with IBS. Patients were excluded if they had a concomitant coeliac disease (2.2%), inflammatory bowel disease (6.4%), and colorectal cancer (0.6%).

Mean age of probands of first-degree relatives were for siblings 40.9 (standard deviation (SD)=16.1), offspring 48.2 (SD=13.2), parents 37.5 (SD=15.6) (Table 6). Among probands between 28.4 – 30.1% had a high education and between 71.7 – 74.6% were women.

Mean age of probands of second-degree relatives were for maternal half-siblings 33.1 (SD13.5), paternal half-siblings 34.0 (SD13.5), niece/nephew 47.7 (SD13.2). 17.7% of probands of maternal half-siblings had a high education, 21.6% of probands of paternal half-siblings had a high education and 29.2 % of probands of nieces/nephews (Table 6).

Table 6.
Descriptive statistics for the probands, i.e. age, sex, and education.

	Mean Age of Proband*	High Education among proband	Women among proband
First degree			
Sibling	40.9 (16.1)	28.4 %	71.9 %
Offspring	48.2 (13.2)	29.0 %	74.6 %
Parent	37.5 (15.6)	30.1 %	71.7 %
Second degree			
Maternal half sib	33.1 (13.5)	17.7 %	73.3 %
Paternal half sib	34.0 (13.5)	21.6 %	72.9 %
Niece/Nephew	47.7 (13.2)	29.2 %	72.1 %
Third degree			
Cousins	28.6 (9.5)	26.8 %	69.9 %
Non biological			
Spouses	53.0 (13.9)	26.9 %	71.3 %

In Table 7 descriptive statistics of the 60 489 siblings are shown. Siblings of probands when compared with siblings of controls more often had functional constipation, functional diarrhoea, functional dyspepsia, and faecal incontinence; all results were statistically significant. Of the 60 489 siblings, 6806 (11%) had an ICD diagnosis of functional constipation (ICD-9 564A or ICD-10 K590) and/or

functional diarrhoea (ICD-9 564F or ICD-10 K591). However, to fulfil the diagnostic criteria for functional constipation or functional diarrhoea, there should be insufficient criteria for IBS according to Rome II and Rome III criteria, that is, an IBS-diagnosis cannot exist together with these diagnoses. However, these patients could have a possible IBS, and if these two diagnoses were made within a short time interval, the patients are more likely to have the same diagnosis on both occasions. We checked the mean time difference between IBS and functional constipation and functional diarrhoea. The mean time difference between diagnosis of IBS and functional constipation was 42 days with an SD of 1971 days (median −57 days and IQR −715 and 699 days). The time difference in diagnosis between IBS and functional diarrhoea was three days with an SD of 1271 days (median −48 days and IQR −308 and 150 days). Moreover, the OR for the remaining siblings of probands with IBS was 1.70 (95% 1.55-1.85), which was similar to the OR 1.75 (95 % CI 1.62-1.89) for siblings with a diagnosis of IBS and functional and/or functional diarrhoea (Table 7).

Table 7
Descriptive statistics of other functional gastrointestinal disorders and comorbidities for the 60,489 sibling pairs included in the analysis.

	Proband*	Control**	P-value #	Proband-sibling*	Control-sibling **	P-value ##	P-value ###
Other functional gastrointestinal disorders							
Functional constipation	5.9 %	1.0 %	<0.001	1.2 %	0.9 %	<0.001	<0.001
Functional diarrhoea	6.0 %	0.4 %	<0.001	0.6 %	0.4 %	<0.001	<0.001
Functional dyspepsia	7.2 %	1.1%	<0.001	1.3 %	0.9 %	<0.001	<0.001
Fecal incontinence	0.9 %	0.2 %	<0.001	0.2 %	0.1 %	0.0152	<0.001
Comorbidities							
Anxiety	11.5 %	4.3 %	<0.001	5.3 %	3.9 %	<0.001	<0.001
Depression	8.7 %	3.4 %	<0.001	4.0 %	3.0 %	<0.001	<0.001
Migraine	2.9 %	1.2 %	<0.001	1.4 %	1.0 %	<0.001	<0.001
Headache	8.3 %	2.6 %	<0.001	3.4 %	2.23 %	<0.001	<0.001
Micturition Pain	1.5 %	0.4 %	<0.001	0.4 %	0.3%	<0.001	<0.001
Pain	10.6 %	3.2 %	<0.001	4.2 %	3.0 %	<0.001	<0.001

*Proband (affected) and proband-siblings belong to the proband-sibling pair. **Control (not affected) and control-sibling belong to the control-sibling pair. ICD=International classification of disease.
*** Pain associated with female genital organs and menstrual cycle
#P-value from a chi-square test between proband and controls
##P-value from a chi-square test between proband-sibling and control-sibling
###P-value from a chi-square test between proband and proband-siblings

The distribution of the time difference in days between IBS and functional constipation or functional diarrhoea is shown in Figure 2 and 3. In Figures 2 and 3 a value below 0 means that functional constipation/diarrhoea diagnosis was registered before a diagnosis of IBS. A value above 0 means that the functional constipation/diarrhoea diagnosis was registered after a diagnosis of IBS.

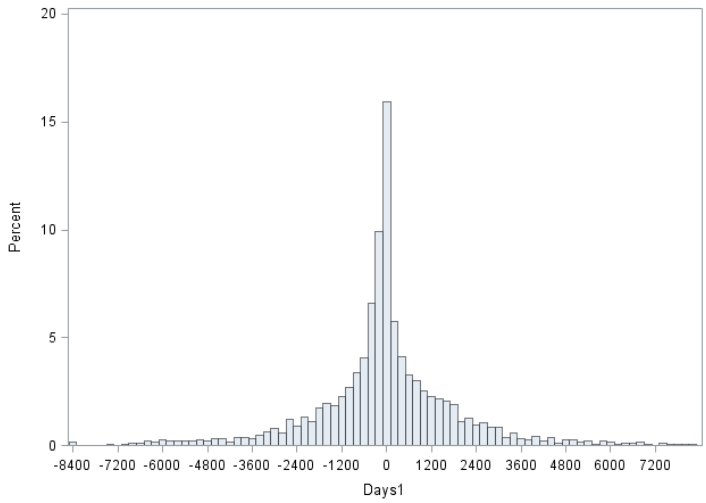

Figure 2.
Distribution of time at diagnosis for functional constipation (ICD-9 564A and ICD-10 K590) in relation to time at IBS diagnosis.

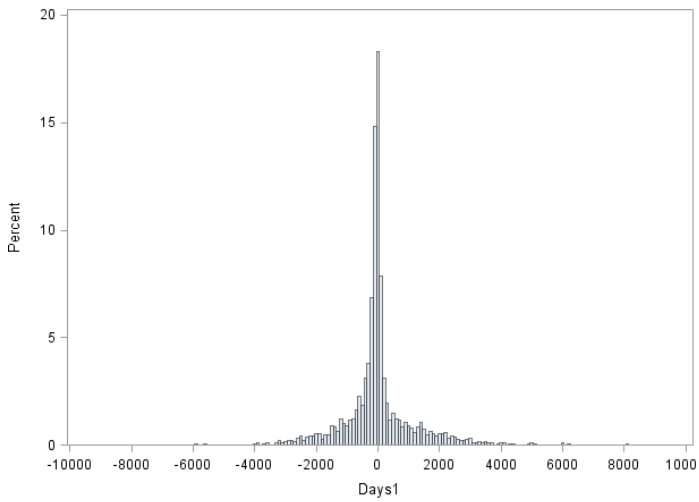

Figure 3.
Distribution of time at diagnosis for functional diarrhoea (ICD-9 564F and ICD-10 K591) in relation to time at IBS diagnosis.

ORs of first-, second- and third-degree relatives and also spouses of patients with IBS, being diagnosed with IBS, were calculated (Table 8). For all first-degree relatives significant ORs were found; for siblings, ORs were 1.75 (95% CI 1.63-1.89), for offspring ORs were 1.82 (95% CI 1.67-1.97) and for parents ORs were 1.90 (95% CI 1.76-2.05). For second-degree relatives ORs for paternal half-siblings were significantly increased to 1.78 (95% CI 1.48-2.15), but not for maternal half-siblings 1.10 (95% CI 0.88-1.39). Nieces and nephews had an increased OR for IBS 1.27 (95% CI 1.18-1.38). For third-degree relatives ORs for cousins were increased 1.11 95% CI 1.04-1.18). For spouses ORs were increased 1.51(1.24-1.84) (Table 8).

Table 8.
Odds ratios (ORs) of IBS in relatives of probands diagnosed with IBS in Sweden between 1987 and 2010 compared to relatives of matched controls.

Relation to proband	No. of pairs	No. of concordant pairs*	OR (95% CI)
First-degree relatives			
Sibling	60,489	724 (1.2%)	1.75 (1.63–1.89)
Offspring	64,168	604 (0.9%)	1.82 (1.67–1.97)
Parent	73,316	727 (1.0%)	1.90 (1.76–2.05)
Second-degree relatives			
Maternal half-sibling	8,290	73 (0.9%)	1.10 (0.88–1.39)
Paternal half-sibling	11,147	115 (1.0%)	1.78 (1.48–2.15)
Niece/nephew	86,475	600 (0.7%)	1.27 (1.18–1.38)
Third-degree relatives			
Cousin	129,593	1,021 (0.8%)	1.11 (1.04–1.18)
Non biological relatives			
Spouse	12,816	100 (0.8%)	1.51 (1.24–1.84)

In Table 9, the sex-specific familial risks odds for IBS are presented. There were no major differences between sexes. The importance of age and sex was investigated with the insertion of interactions terms in the models. There were no significant interactions between sex and IBS (data not shown in table).

Table 9
Odds ratios of IBS of all probands who were diagnosed with IBS during 1987-2010 in Sweden compared to relatives to matched controls stratified on gender of proband.

Relation to proband	Male OR (95 % CI)	Female OR (95 % CI)
First degree		
Sibling	1.84 (1.60 – 2.11)	1.72 (1.57 – 1.88)
Child	1.90 (1.62 – 2.24)	1.79 (1.63 – 1.97)
Parent	1.80 (1.57 – 2.08)	1.94 (1.78 – 2.12)
Second degree		
Maternal half sib	1.24 (0.79 – 1.95)	1.07 (0.81 – 1.39)
Paternal half sib	2.11 (1.50 – 2.95)	1.57 (1.33 – 2.09)
Niece/Nephew	1.26 (1.09 – 1.47)	1.28 (1.16 – 1.41)
Third degree		
Cousins	1.21 (1.09 – 1.35)	1.06 (0.99 – 1.15)
Non biological		
Spouses	1.48 (1.12 – 1.96)	1.54 (1.16 – 2.04)

Regarding age, the familial aggregation was significantly stronger at younger ages but only among cousins (Table 10), that is, the OR for IBS was higher for young individuals than for older individuals among cousins. Otherwise there were no significant interactions between age and IBS.

Table 10.
Odds ratios of IBS of all probands who were diagnosed with IBS during 1987-2010 in Sweden compared to relatives to matched controls including interaction terms for age at IBS diagnosis.

Relation to proband	OR (95 % CI)	Age At IBS*IBS
First degree		
Sibling	1.74 (1.61 – 1.87)	0.99 (0.99 – 1.00)
Child	1.87 (1.70 – 2.05)	1.00 (0.99 – 1.00)
Parent	1.82 (1.67 – 1.98)	0.99 (0.99 – 1.00)
Second degree		
Maternal half sib	1.11 (0.88 – 1.39)	0.99 (0.97 – 1.01)
Paternal half sib	1.78 (1.48 – 2.15)	1.00 (0.98 – 1.01)
Niece/Nephew	1.29 (1.17 – 1.41)	1.00 (0.99 – 1.01)
Third degree		
Cousins	1.11 (1.04 – 1.18)	0.99 (0.99 – 0.0999)
Non biological		
Spouses	1.51 (1.23 – 1.84)	1.00 (0.98 – 1.01)

In order to determine for shared environmental factors, the interaction between age difference between relatives in a pair and IBS in relatives was determined. There was no interaction between age difference between probands and proband-relatives and IBS except among paternal half-siblings (left part of Table 11). Moreover, there was no interaction between year difference in time of diagnosis between proband and proband–relative (right part of Table 11) and IBS in relatives.

Table 11.
Odds ratios of IBS of all probands who were diagnosed with IBS during 1987-2010 in Sweden compared to relatives to matched controls including interaction terms for age difference in year between relatives and for differences in year of diagnosis between relatives.

Relation to proband	OR (95 % CI)	Difference in year	OR (95 % CI)	Difference in year of diagnosis
First degree				
Sibling	1.80 (1.57 – 2.07)	0.99 (0.97 – 1.02)	1.74 (1.59 – 1.94)	1.00 (0.98 – 1.02)
Child	1.57 (1.03 – 2.41)	1.01 (0.99 – 1.02)	1.92 (1.70 – 2.16)	0.99 (0.97 – 1.01)
Parent	1.66 (1.13 – 2.43)	1.01 (0.99 – 1.02)	1.97 (1.77 – 2.20)	0.99 (0.98 – 1.01)
Second degree				
Maternal half sib	1.79 (1.04 – 3.07)	0.95 (0.89 – 1.01)	0.99 (0.71 – 1.39)	1.03 (0.97 – 1.09)
Paternal half sib	1.10 (0.73 – 1.66)	1.04 (1.01 – 1.08)	1.76 (1.34 – 2.31)	1.00 (0.96 – 1.04)
Niece/Nephew	1.48 (1.13 – 1.95)	0.99 (0.98 – 1.00)	1.37 (1.22 – 1.54)	0.98 (0.96 – 1.00)
Third degree				
Cousins	1.12 (1.01 – 1.24)	1.00 (0.99 – 1.01)	1.13 (1.03 – 1.24)	0.99 (0.98 – 1.01)
Non biological				
Spouses			1.80 (1.34 – 2.41)	0.95 (0.90 – 1.02)

In a sensitivity analysis, the familial odds ratios of having IBS in relatives of probands with at least two IBS diagnoses were increased. A total of 13136 individuals had a diagnosis of IBS at least twice. ORs when including only individuals registered twice for IBS were for siblings 2.57 (95% CI 2.06-3.19), offspring 2.66 (95% CI 2.06-3.43), parents 3.63 (95% CI 2.84-4.64), cousins 1.24 (95% CI 1.02-1.52), and for spouses 1.17 (95% CI 0.56-2.45). The number of individuals was not enough to calculate risks for half-siblings. In conclusion, the ORs for biological relatives were even higher but were lower for spouses compared to those in Table 8.

Article III

Risk of Irritable Bowel Syndrome in adoptees

A total of 30 693 adoptees (born between 1951 and 1995), 51 634 adoptive parents and 49 912 biological parents were included (Table 12). IBS patients with a concomitant diagnosis of coeliac disease, inflammatory bowel disease and colorectal cancer were excluded. After exclusion, a total of 2288 IBS cases were identified of which 776 were adoptees, 840 biological parents, and 660 adoptive parents. A total of 1678 IBS patients were females (73%). More adoptees had a high education (29.34%) than adoptive parents (17.67%) and biological parents (9.96%).

Table 12
Descriptive statistics of 30 693 adoptees and their adoptive (n=51 634) and biological parents 49 912 (132,239 individuals in total).

	Adoptees (n = 30 693)	**Adoptive parents (n = 51 634)**	**Biological parents (n = 49 912)**
£Sex Female	14 883 (48.49%)	22 547 (43.67%)	29 706 (59.52%)
£IBS Female	776 (2.53%) 552 (1.80)	660$ (1.28%) 433 (0.84)	840¤ (1.68%) 693 (1.39)
£High education (12 years or more)	9 004 (29.34%)	9 067 (17.67%)	4 973 (9.96%)
‡Age at IBS diagnosis (median and interquartile range)	43 (35 – 49)	71 (63 – 78)	62 (55 -69)
+Age at end of follow-up (median and interquartile range)	49 (43 – 54)	76 (68 – 83)	68 (60 – 75)

£number of observations (%);$ 4 adoptees had two adoptive parents with IBS; ¤ 8 adoptees had two biological parents with IBS.

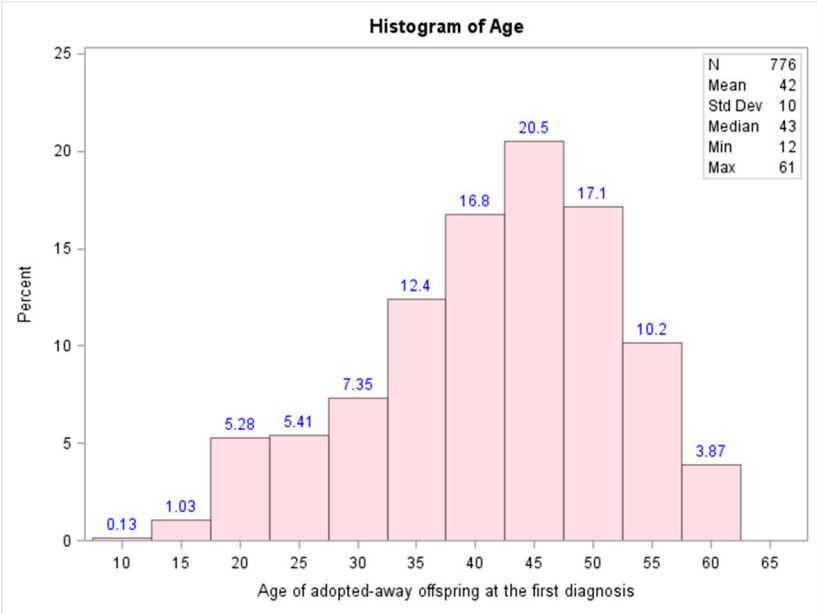

Figure 4.
Age distribution for Swedish born (1951–1995) adoptees at first time diagnosis of irritable bowel syndrome.

In Table 13 the median birth year of adoptees 1963 (IQR, 1957 – 1968), of biological parents 1939 (IQR, 1932 – 1946) and for adoptive parents 1928 (IQR, 1921 – 1938) is shown. Adoptees' median age at IBS diagnosis was 43 years with an interquartile range (IQR) of 35-49 (also shown in figure 4). Adoptive parents median age at IBS diagnosis was 71 (IQR 63-78) and for biological parents the median age was 62 (IQR 55-69).

Table 13
The distribution of the birth years for adoptees and their adoptive and biological parents are shown.

	n	Min	Max	Mean	SD	Median	Q1-Q3
Adopted-offspring	30 693	1951	1995	1964	9	1963	1957-1968
Adoptive parents	51 634	1888	1979	1930	12	1928	1921-1938
Biological parents	49 912	1884	1980	1939	11	1939	1932-1946

Table 14 shows the descriptive statistics for the 30693 adoptees with regards to IBS status. Adoptees without IBS were female in 47.9% of cases and with IBS were female in 71.1% of cases, which was highly significant. No significant difference in high education was found between the two groups. A total of 1.35%

had a high socioeconomic status in adoptees without IBS and 0.52% with IBS. Occupation demanding university competence was found in 18.9% of adoptees without IBS and in 15.2% with IBS, which was significant. No significant difference in median age was found between the two groups (49 versus 48 years).

Table 14
Descriptive statistics of 30 693 adoptees with and without diagnosis of irritable bowel syndrome (IBS).

	No IBS (n = 29 917)	**IBS (n = 776)**	**P value**
Sex Female	14 331 (47.90%)	552 (71.13%)	<0.0001*
High education (12 years or more)	8 756 (29.27%)	248 (31.96%)	0.104*
NDI& (High socioeconomic status)	403 (1.35%)	4 (0.52%)	0.053**
Occupation ‡	5 657 (18.91%)	118 (15.21%)	*0.009
Age at end of follow-up (median and interquartile range)	49 (43 – 54)	48 (43 – 54)	0.239***

In Table 15 the calculated ORs with the corresponding 95% CI are presented for the cohort design. With no adjustments (model 1) the OR for IBS in adoptees of biological parents, of which at least one had IBS was increased, was 1.66 (95% CI, 1.17 – 2.35). The OR with adjustments (model 2) was also significantly increased to 1.63 (95% CI, 1.14 – 2.32). The estimated OR for IBS in adoptees with an affected adoptive parent was not significantly increased neither in the non-adjusted model (OR 0.77; 95% CI, 0.44 – 1.34) or in the adjusted model (OR 0.75; 95% CI 0.43 – 1.32).

Table 15
Odds ratio determined with logistic regression for IBS in adoptees with an affected biological or adoptive parent (Cohort design).

		Biological parents		**Adoptive parents**	
Risk factors	REF	Model 1^{+}	Model 2$^{\#}$	Model 3^{+}	Model 4$^{\#}$
IBS	0	1.66 (1.17 – 2.35)	1.63 (1.14 – 2.32)	0.77 (0.44 – 1.34)	0.75 (0.43 – 1.32)
Year of birth		1.01 (1.00 – 1.02)	1.01 (1.00 – 1.02)	1.01 (1.00 – 1.02)	1.01 (1.00 – 1.02)
Sex		2.68 (2.29 – 3.14)	2.61 (2.23 – 3.06)	2.68 (2.29 – 3.14)	2.61 (2.23 – 3.06)
County (region)		1.00 (0.99 – 1.01)	1.00 (0.99 – 1.01)	1.00 (0.99 – 1.01)	1.00 (0.99 – 1.01)
Education	Male	1.25 (1.13 – 1.39)	1.16 (1.04 – 1.29)	1.25 (1.13 – 1.39)	1.16 (1.04 – 1.29)

In Table 16 the results of the case-control study are presented. IBS in the adoptees was significantly associated with IBS in biological parents with an OR of 1.67 (95% CI, 1.06 – 2.62). In adoptees with IBS, who had an adoptive parent with IBS, the OR was 0.88 (95 % CI, 0.48 – 1.63), which is not statistically significant.

Table16.
Results for the matched case-control study (1:5). Odds ratios (ORs) for IBS among adoptees with an affected biological or adoptive parent. Age stratified ORs for IBS are also shown.

	All[£]	Age <= 45 years[&]	Age > 45 years[#]
ORs for IBS in adoptees with an affected biological parent	1.67 (1.06 – 2.62)	1.70 (0.93 – 3.08)	1.63 (0.82 – 3.25)
ORs for IBS in adoptees with an affected adoptive parent	0.88 (0.48 – 1.63)	1.03 (0.48 – 2.21)	0.69 (0.24 – 1.96)

Data are presented as OR (95 % CI=confidence interval). [£]Cases (n = 569) and controls (n = 2 845); [&] cases (n = 315) and controls (n = 1 575); [#] cases (n = 254) and controls (n = 1 270).

Using Falconer's regression, the heritability was determined to be 19.5%+-8.5 %. In Table 17 the heritability with different population frequencies ranging from 0.5% to 20% was determined by the use of tetrachoric correlation. The heritability was 18.3% as in the present population with 1.73% prevalence and varied from 16% in a population with 0.5% prevalence to 27% in a population with 20% prevalence.

Table 17
Heritability of IBS based on estimated population prevalence and tetrachoric correlation in case-control study according to Frisell et al.

Exposed cases	Unexposed cases	OR	Prevalence	Tetrachoric correlation	Heritability
26	543	1.67	0.5	0.08	16%
26	543	1.67	1.0	0.09	17%
26	543	1.67	3.0	0.10	20%
26	543	1.67	5.0	0.11	22%
26	543	1.67	10.0	0.12	24%
26	543	1.67	15.0	0.125	25%
26	543	1.67	20.0	0.133	27%

Article IV

Perinatal and familial risk factors for IBS

A total of 1 963 685 individuals in the Swedish Medical Birth Registry born between 1973 and 1992 were included of which 24 633 had received a diagnosis of IBS (Table 18). A total of 48.6% of the study population were females and 71.9% of IBS patients were females. A significant trend towards higher foetal growth and risk of IBS in young adulthood was found and also a significant trend towards lower birth weight as well as lower birth length and risk of IBS. Lower maternal age at delivery and lower paternal and maternal education were also associated with increased risk of IBS. An association between a parental history of IBS, anxiety and depression and risk of IBS was also found. Caesarean was also associated with risk of IBS.

Table 18
Baseline characteristics of individuals in the Swedish Birth Registry who were live-born from 1973 through 1992 and living in Sweden at age of 18 years according to incident irritable bowel syndrome (IBS) during follow-up from 18 years of age through 2010. Chi-square trend test was used to compare perinatal and familial factors between those who were affected and not affected by IBS during follow-up.

	Population (N=1,963,685)	%	IBS (N=24633)		No IBS (N=1,939,052)	
Sex						
Male	1010143	51.4	6923	28.1	1003220	51.7
Female	953542	48.6	17710	71.9	935832	48.3
Foetal growth (SD)			<0.001			
<-2	26725	1.4	211	0.9	26514	1.4
-2 to <-1	72844	3.7	496	2.0	72348	3.7
-1 to <1	1684586	85.8	21597	87.7	1662989	85.8
≥1	179530	9.1	2329	9.5	177201	9.1
Per additional 1 SD (trend test)			<0.001			
Gestational age at birth (weeks)						
<37	89300	4.5	1150	4.7	88150	4.5
37-41	1687272	85.9	20984	85.2	1666288	85.9
≥42	187113	9.5	2499	10.1	184614	9.5
Per additional 1 week (trend test)			<0.001			
Birthweight (g)						
<2500	59420	3.0	897	3.6	58523	3.0
2500-3999	1561919	79.5	20020	81.3	1541899	79.5
≥4000	342346	17.4	3716	15.1	338630	17.5
Per 1000 g (trend test)			<0.001			
Birth length (cm)						
<48	175733	8.9	2552	10.4	173181	8.9
48-52	1461652	74.4	18591	75.5	1443061	74.4
≥53	316845	16.1	3387	13.7	313458	16.2
Unknown	9455	0.5	103	0.4	9352	0.5
Per cm (trend test)			<0.001			
Multiple birth status						
Singleton	1938594	98.7	24363	98.9	1914231	98.7
Twin or higher order	25091	1.3	270	1.1	24821	1.3
Trend test			<0.001			
Birth order						
1	822291	41.9	10261	41.7	812030	41.9
2	721346	36.7	9289	37.7	712057	36.7
≥3	420048	21.4	5083	20.6	414965	21.4
Per 1 higher birth order (trend test)		0.0	<0.001			
Maternal age at delivery (years)		0.0				
<20	60737	3.1	934	3.8	59803	3.1
20-24	465279	23.7	6224	25.3	459055	23.7
25-29	738391	37.6	9300	37.8	729091	37.6
30-34	487050	24.8	5833	23.7	481217	24.8
≥35	212228	10.8	2342	9.5	209886	10.8
Per each higher category (trend test)			<0.001			
Maternal marital status						
Married/cohabiting	1377314	70.1	17705	71.9	1359609	70.1
Never married	419262	21.4	4191	17.0	415071	21.4
Divorced/widowed	167109	8.5	2737	11.1	164372	8.5

Trend test			<0.000			
Maternal education (years)						
≤9	594773	30.3	7791	31.6	586982	30.3
11-Oct	709863	36.1	8846	35.9	701017	36.2
14-Dec	170224	8.7	2055	8.3	168169	8.7
≥15	488825	24.9	5941	24.1	482884	24.9
Per each higher category (trend test)			<0.001			
Paternal education (years)						
≤9	733325	37.3	9667	39.2	723658	37.3
11-Oct	534947	27.2	6276	25.5	528671	27.3
14-Dec	242792	12.4	3206	13.0	239586	12.4
≥15	452621	23.0	5484	22.3	447137	23.1
Per each higher category (trend test)			<0.001			
Caesarean						
No	1799711	91.6	22652	92.0	1777059	91.6
Yes	163974	8.4	1981	8.0	161993	8.4
Per each category (trend test)			<0.001			
Parental history of IBS						
Yes	206792	10.5	642	2.6	32417	1.7
No	1756893	89.5	23991	97.4	1906635	98.3
Trend test			<0.001			
Parental history of anxiety						
Yes	206792	10.5	3059	12.4	203733	10.5
No	1756893	89.5	21574	87.6	1735319	89.5
Trend test			<0.001			
Parental history of depression						
Yes	58217	3.0	831	3.4	57386	3.0
No	1905468	97.0	23802	96.6	1881666	97.0
Trend test			<0.001			

Gender and birth year

Gender was the most important predictor for IBS. In the model adjusting for birth year and sex, the HR for being a male was 0.36 (95% CI 0.35-0.37; p< 0.001), which remained significant when adjusting for all other factors (p < 0.001) (Table 19). Lower birth year was also associated with a lower risk of IBS (HR=0.96, 95% CI 0.96-0.96, p<0.001).

Perinatal factors

Several perinatal factors were associated with IBS. Foetal growth < - 2 standard deviations (SD) was a risk factor for IBS in model 1, but was not significant in model 2 adjusting for all factors. Foetal growth > 1 SD above the mean was associated with an increased risk of IBS in model 1 HR 1.07 (95% CI 1.03-1.12) and remained borderline significant in model 2 HR 1.06 (95% CI 1.00-1.11). Birth weight < 2500 grams was associated with an increased risk of IBS in both model 1 HR 1.18 (95% CI 1.10-1.26) and model 2 HR 1.11 (95% CI 1.01-1.22). Caesarean

was associated with an increased risk of IBS in both model 1 HR 1.12 (95% CI 1.07-1.18) and model 2 HR 1.10 (95% CI 1.05-1.15)

Socioeconomic factors.

Several socioeconomic factors were associated with IBS. Maternal age < 20 years of age was associated with an increased risk of IBS in young adulthood in both model 1 HR 1.09 (95% CI 1.02-1.17) and model 2 HR 1.09 (95% CI 1.02-1.17). Maternal age => 35 years of age was a protective factor for IBS in both model 1 HR 0.95 (95 % CI 0.91-1.00, p = 0.03) and model 2 HR 0.95 (95 % CI 0.90-1.00, p = 0.03). Having a divorced/widowed mother increased the risk of IBS significantly in both model 1 HR 1.15 (95% CI 1.10-1.19) and model 2 HR 1.12 (95% CI 1.08-1.17). Maternal education 10-11 years was associated with an equally increased risk of IBS in Model 1 and 2 HR 1.04 (95% CI 1.10-1.08). Maternal education 12-14 years was not associated with an increased risk in model 1 HR 1.05 (95% CI 1.00-1.10, p = 0.073) but associated with an increased risk when adjusting for all factors in model 2 HR 1.06 (95% CI 1.01-1.11).

Inherited factors

Inherited factors were also associated with IBS. A parental history of IBS was associated with an increased risk of IBS in both model 1 HR 1.58 (95% CI 1.46-1.71) and model 2 HR 1.54 (95% CI 1.42-1.66. Parental history of anxiety increased the risk of IBS in both model 1 HR 1.25 (95% CI 1.20-1.30) and model 2 HR 1.21 (95% CI 1.17-1.26). An increased risk of IBS with a parental history of depression was observed in both model 1 HR 1.18 (95% CI 1.10-1.27) and model 2 HR 1.09 (95% CI 1.02-1.17) (table 19).

Table 19

Age- and sex-adjusted and multivariable hazard ratios (HR) with 95% confidence interval (CI) and p-values for incident irritable bowel syndrome (IBS) during follow-up in a nationwide Swedish birth cohort (1973-1992) from the age of 18 years through until 2010 (ages 18 to 38 years).

	Adjusted Model 1[a]				Adjusted Model 2[b]			
	HR	**95% CI**		***P* value**	**HR**	**95% CI**		***P* value**
Sex								
Male	0.36	0.35	0.37	<0.001	0.36	0.35	0.37	<.0001
Female	1.00				1.00			
Birth Year	0.96	0.96	0.96	<0.001	0.96	0.96	0.96	<0.001
Foetal growth (SD)								
<-2	1.20	1.05	1.38	<0.001	1.12	0.96	1.32	0.16
-2 to <-1	1.03	0.94	1.13	0.577	1.01	0.92	1.11	0.81
-1 to <1	1.00				1.00			
≥1	1.07	1.03	1.12	<0.001	1.06	1.00	1.11	0.05
Gestational age at birth (weeks)								
<37	1.10	1.03	1.16	0.002	0.96	0.88	1.05	0.35
37-41	1.00				1.00			
≥42	0.98	0.94	1.02	0.383	0.97	0.93	1.02	0.20

Birthweight (g)								
<2500	1.18	1.10	1.26	<0.001	1.11	1.01	1.22	0.02
2500-3999	1.00				1.00			
≥4000	0.98	0.95	1.02	0.307	0.98	0.94	1.02	0.26
Birth length (cm)								
<48	1.08	1.03	1.12	<0.001	1.02	0.97	1.07	0.43
48-52	1.00				1.00			
≥53	1.01	0.97	1.05	0.711	1.03	0.98	1.07	0.26
Unknown	1.16	0.95	1.40	0.141	1.08	0.88	1.31	0.47
Multiple birth status								
Singleton	1.00				1.00			
Twin or higher order	0.92	0.81	1.03	0.146	0.91	0.81	1.03	0.13
Birth order								
1	1.00				1.00			
2	1.02	1.00	1.05	0.095	1.04	1.01	1.08	0.01
≥3	0.99	0.96	1.03	0.676	1.02	0.98	1.06	0.27
Maternal age at delivery (years)								
<20	1.09	1.02	1.17	0.013	1.09	1.02	1.17	0.02
20-24	1.02	0.98	1.05	0.363	1.02	0.98	1.05	0.40
25-29	1.00				1.00			
30-34	0.99	0.96	1.02	0.5013	0.99	0.96	1.02	0.48
≥35	0.95	0.91	1.00	0.0343	0.95	0.90	1.00	0.03
Maternal marital status								
Married/cohabiting	1.00				1.00			
Never married	1.01	0.98	1.05	0.603	0.99	0.96	1.03	0.67
Divorced/widowed	1.15	1.10	1.19	<0.001	1.12	1.08	1.17	<.0001
Maternal education (years)								
≤9	1.00				1.00			
10-11	1.04	1.01	1.08	0.008	1.04	1.01	1.08	0.01
12-14	1.05	1.00	1.10	0.073	1.06	1.01	1.11	0.03
≥15	1.00	0.97	1.04	0.959	1.02	0.98	1.06	0.31
Paternal education (years)								
≤9	1.00				1.00			
10-11	1.04	1.01	1.07	0.025	1.03	1.00	1.07	0.06
12-14	1.02	0.98	1.06	0.301	1.03	0.99	1.07	0.15
≥15	1.00	0.97	1.04	0.802	1.02	0.99	1.06	0.22
Caesarean								
No	1.00				1.00			
Yes	1.12	1.07	1.18	<0.001	1.10	1.05	1.15	<0.001
Parental history of IBS								
No	1.00				1.00			
Yes	1.58	1.46	1.71	<0.001	1.54	1.42	1.66	<.0001
Parental history of anxiety								
No	1.00				1.00			
Yes	1.25	1.20	1.30	<0.001	1.21	1.17	1.26	<.0001
Parental history of depression								
No	1.00				1.00			
Yes	1.18	1.10	1.27	<0.001	1.09	1.02	1.17	0.02

[a]Adjusted for birth year and sex. [b]Adjusted for birth year, sex, and all other factors in table. Birthweight and birth length were each examined in separate models as alternatives to the standardized foetal growth variable. The reference category for all variables is indicated by an HR of 1.00. SD = standard deviation. Birth year was modelled as a continuous variable.

Multiple risk factors

There was no multiplicative interaction between risk factors. The HRs for a combination of risk factors may therefore be calculated by multiplication of the HRs for the individual risk factors. Figure 5 shows the HRs for men (1-5) and women (6-10) with increasing numbers of risk factors compared with men (reference=1) with no risk factors. Men born via caesarean section, those living alone, those with a family history of anxiety, and those with a family history of IBS had a HR of 2.30 compared with men without these risk factors. Women born via caesarean section, those living alone, those with a family history of anxiety, and those with a family history of IBS had a HR of 6.38 compared with men without these risk factors.

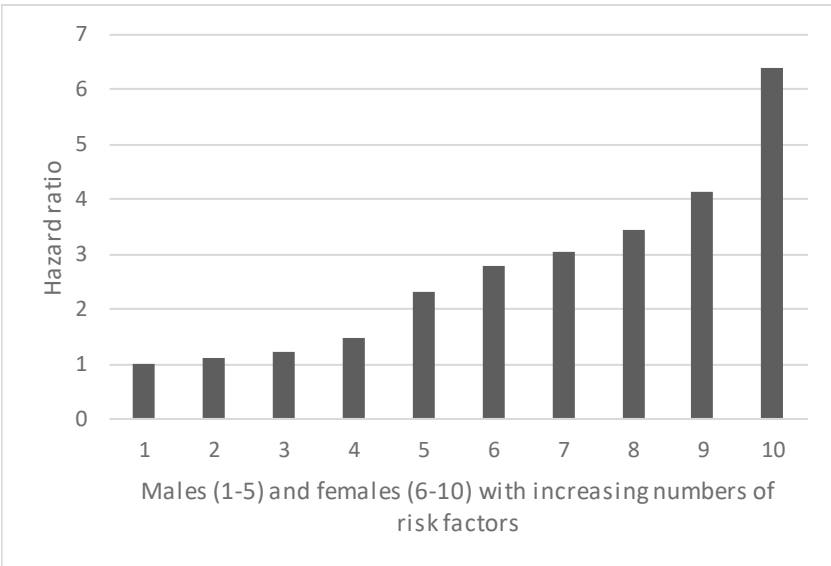

Figure 5
HRs for men (1-5) and women (6-10) with increasing numbers of risk factors

Chapter VI

Discussion

Article I: Low prevalence of IBS in Primary Care

In paper I a low prevalence of IBS was found in Swedish Primary Health Care. This may be due to GPs not being very familiar with the diagnostic criteria of IBS and GPs viewing IBS as an exclusion diagnosis. Patients and their GP do not always agree on the reason for the patient's symptoms and GPs often consider IBS to be a psychological disorder (Franke et al, 2009; Spiegel et al, 2010; Harkness et al, 2013; Bradley et al, 2018). Patients with IBS visited their GP more often than patients without IBS, but it was rarely because of IBS. An association with depression, headache, migraine, LUTS and depression was seen, which is in line with a previous study showing that people with IBS have lower health-related quality of life (HRQOL) scores than those without IBS (General et al, 2008). Thus, it seems like IBS patients with classical IBS comorbidities are identified. It is possible that the low detection rate of IBS in primary care is related to gender disparities because women are more affected by IBS than men. It is well-known that gender disparities exist for cardiovascular disorders (McSweeney et al, 2012).

Recent genetic studies have shown that the genetic architecture for IBS is complex and heterogeneous (D'Amato M, 2013; Henström & D'Amato, 2016). If GPs think of IBS as a psychological disorder (Franke et al, 2009; Spiegel et al, 2010; Harkness et al, 2013; Bradley et al, 2018), IBS patients with functional variants in the sucrase-isomaltase gene (SI) and IBS might be misinterpreted (Henström et al, 2018).

Strengths of paper I are the use of a database that contains information on all visits to primary care in four counties; it eliminates selection bias. A limitation is the fact that we do not know what criteria were used to diagnose patients with IBS. A pragmatic approach to diagnosis, involving clinical judgement rather than specific criteria, is usually adopted in primary care (Franke et al, 2009). IBS is used by many GPs as a diagnosis after exclusion of other conditions (Spiegel et al, 2010). The IBS diagnosis has not been validated in the primary care database. However, a systematic review validating a general practice research database in the UK found a positive predictive value of 77 % on IBS diagnosis (Khan et al, 2010). The

prevalence of IBS in this paper is close to a prevalence of 2.5% from a previous primary care study (Thompson et al, 2000).

Article II: Family history and IBS

In paper II increased risks of IBS in first-degree, second-degree, and third-degree relatives of probands with IBS were observed. The odds tended to be higher in more closely related relatives, which is typical for a complex or polygenic trait (Lander & Schork. 1994). Second-degree and third-degree relatives usually do not grow up together thus suggesting a genetic cause rather than an environmental cause due to shared familial household. In the present study the odds ratios for paternal half-siblings of IBS were significantly increased but not for maternal half-siblings. Paternal half-siblings are very seldom brought up together and maternal half-siblings are very often brought up together. These findings lend support to a genetic contribution to IBS. However, the low and non-significant association among maternal half-siblings is unclear. We also found an increased risk in spouses of probands with IBS, which indicates a non-genetic contribution to IBS. Spouses share the same environment including health-related behaviours such as diet and physical activity and life events. A large cross-sectional study in primary care found increased odds of hypertension, hyperlipidaemia, asthma, peptic ulcer disease and depression in partners of patients with these diseases (Hippisley-Cox et al, 2002). Diet is often shared within a household and diet could contribute to the observed increased risks in spouses (Pachucki et al, 2011). Possible other shared environmental familial factors could be infections. IBS after infections has been documented in a meta-analysis (Dai et al, 2012).

Several studies have now shown that the conclusion of this study was correct, i.e. IBS has a genetic basis. A number of genetic variants have been identified as a cause of IBS (D'Amato M, 2013; Henström & D'Amato, 2016). The genetic studies of IBS show a large diversity of involvement of genes associated with IBS. The growing list of diverse genetic loci associated with IBS is illustrative (D'Amato M, 2013; Henström & D'Amato, 2016). For instance, genes with different functions such as the protocadherin 15 gene (PCDH15), the KDELR2 gene (KDEL endoplasmic reticulum protein retention receptor 2), the GRID2IP gene (Glutamate Receptor, Ionotropic, Delta 2 [Grid2] Interacting Protein), SCN5A gene, the sucrase-isomaltase gene (SI), the NPSR1 gene, and a loci at chromosome 4 harbouring genes such as the FGF2 gene (fibroblast growth factor 2), the NUDT6 gene, and the SPRY1 gene (Holliday et al, 2014; Beyder et al, 2014; Garcia-Etxebarria et al, 2018; Henström et al, 2014).

All of the above mentioned gene variants may have contributed to the increased familial risks observed in the present study. It is likely that even more variants will be detected in future gene studies. However, it will be of importance in future clinical and family studies to identify if there are different types of IBS subtypes segregating in different families. This might increase the statistical power of genetic studies not being diluted by different molecular causes of IBS.

Another important conclusion from paper II, which was not stressed in the original publication, is that other functional gastrointestinal disorders cluster in sibling pairs where one sibling has IBS. The same is true for classical IBS comorbidities such as anxiety, depression, migraine, headache, micturition pain, and pain associated with female genital organs and menstrual cycle. This suggests that some of the genetic variants associated with IBS that have been defined and others that remain to be identified are likely to be involved also in these disorders.

The study has limitations. It is not representative of all patients in Sweden with IBS. The prevalence of IBS is much lower than in questionnaire based studies. Many of the patients were from the hospital discharge register and the hospital outpatient register. Most of the patients with IBS are treated in primary care and around half of the patients are not diagnosed because they do not seek medical help (Williams et al, 2003). Since the diagnosis of IBS is based on health care seeking this may introduce a selection bias. Nevertheless, we linked the specialist treatment registers to a primary care database and found ORs for probands that were similar in the primary care database. A further limitation is the lack of information on the diagnosis of IBS. The diagnostic criteria used are not known. The hospital discharge register has a high diagnostic validity (85-95%), which makes the diagnosis more likely to be correct (Ludvigsson et al, 2011). As an example, the diagnosis of coeliac disease was correct in 86% of patients and in 74% of patients with Inflammatory Bowel Disease the diagnosis was correct. (Ludvigsson et al, 2011). The fact that only 9% of patients with IBS developed a diagnosis of Coeliac Disease, Inflammatory Bowel Disease or colorectal cancer is also an indication that the diagnosis of IBS is correct. Moreover, the Swedish Patient Register has been validated for IBS. The diagnosis was correct in 70% of cases and in a further 9.6% of cases a diagnosis of IBS was probable. Only 5% of cases had an incorrect diagnosis of IBS (Jossan et al, 2014).

The study has strengths as well. An important problem with case-control studies is recall bias, which is eliminated because of the study design. The nationwide design and the use of several national registers of high quality is a major strength. The study is the largest family study. Usage of the Swedish personal identification number is also of value as that makes it possible to cover nearly 100% of the Swedish healthcare system (Ludvigsson et al, 2009).

Article III: Risk of IBS in adoptees

This is the first heritability study of IBS in adoptees. An increased risk of IBS was found in adoptees of biological parents with IBS but not in adoptees of adoptive parents with IBS. The heritability was determined with the use of Falconer's method to be 19.5% +-8.5%. In twin studies, a heritability of 25% (Svedberg et al, 2008) and of 48% (Bengtson et al, 2006) has been reported. The study adds to existing evidence of genetic factors being important in IBS. The present study does not reveal any of the molecular causes of IBS that appear to be diverse (D'Amato M, 2013; Henström & D'Amato, 2016). Just as in study II, in this thesis a number of diverse genetic loci are likely to contribute to the observed heritability in the present study. Speculatively, it is possible that certain subtypes of IBS have higher or lower heritability but this remains to be studied.

A limitation of the study is, just as with the other studies, that we do not know whether IBS was diagnosed according to the Rome criteria or not. The Swedish Patient Register has been validated for IBS. The diagnosis was correct in 70% of cases and in a further 9.6% of cases the diagnosis of IBS was probable. Only 5% of cases had an incorrect diagnosis of IBS (Jossan et al, 2014). However, the diagnosis of IBS has not been evaluated in the primary care register. In an English primary care register the diagnosis of IBS had a positive predictive value of 77% (Khan et al, 2010). The age and sex distribution in the present study is equivalent to other studies of IBS (Longstreth et al, 2006; Khan and Chang, 2010, Lovell and Ford, 2012a). This may suggest that the ICD code mostly identifies patients with IBS in the registers used. The present study cannot rule out that shared familial environmental factors play a part because most adoptees were adults at the first time of diagnosis. Whether the effect of familial environmental factors is impaired or not after adoptees become adults and move from the adoptive parents is not known. Increased risk in spouses of individuals with IBS has been observed in a previous study, which suggests an effect of shared adult familial environment (Waehrens et al, 2015). Strengths of the study are the use of nationwide specialist care registers and also a large primary health care database including information on all primary care visits from well-defined areas. This approach minimised any selection bias.

Article IV: Perinatal and familial risk factors for IBS

Perinatal risk factors associated with IBS were caesarean section, low birth weight and foetal growth >= 1 SD above the mean, although foetal growth remained only borderline significant when the model was adjusted not only for birth year and sex but also for all other factors. Caesarean section as a risk factor for adult IBS has not been confirmed in other studies, where delivery method was found not to be associated with IBS (Koloski et al, 2015; Raslau et al, 2016). The gut microbiota seems to be altered in patients with IBS compared to controls with a change in diversity in the bacteria composition (Bennet et al, 2015; Dupont, 2016). Caesarean section has an effect on the composition of the microbiota of a newborn. Vaginally born newborns are colonised with their mother's bacteria and gut microbiota shows a greater diversity and abundance, when compared to newborns delivered by caesarean (Rutayisire et al, 2016). The same review has shown that the difference in gut microbiota between vaginally newborns and newborns born by caesarean disappears within the first six months (Rutayisire et al, 2016). Different reasons for caesarean are seen, both acute conditions like placenta praevia and foetal distress, but also because the mother does not wish to give birth vaginally. Thus, it is difficult to exclude the theory that IBS is associated with various indications for caesarean. Low birth weight has been shown in two other studies to be associated with increased risk of IBS in adulthood, one calculated the risk to be increased only in newborns with a birth weight <= 1500 g (Bengtson et al, 2006) and the other showed that lower birth weight was a risk factor, although it did not include enough subjects meeting the criteria for birth weight <= 2500g to be examined unlike our study (Raslau et al, 2016).

A parental history of IBS, as well as anxiety and depression were shown to be risk factors for adult IBS. Young maternal age was a risk factor. Maternal marital status as divorced or widowed increased the risk of IBS in adulthood. A family history of IBS has been associated with IBS in some studies (Kanazawa et al, 2004; Pace et al, 2006; Waehrens et al, 2015). The association between parental history of depression and anxiety has been shown in another study with self-reporting from individuals with IBS and controls for a family history of mental illness (Knight et al, 2015). Waehrens et al (2015) have found an association in sibling pairs between IBS and depression and anxiety. It is likely that common familial factors, both genetic and non-genetic, could predispose to IBS and anxiety/depression.

A strength of the study was our ability to investigate the association between perinatal risk factors and risk of IBS in ages 18-38 years old, with the use of a

nationwide birth cohort, with all data from nationwide registers. Limitations include the use of specialist treated IBS patients and not cases from primary care, where most patients with abdominal problems are seen. The patients in specialist treated care are often more severely affected and the diagnosis is more likely to be correct. We do not know if other risk factors are more important in less severe cases. Another limitation of the study is that the diagnostic criteria of IBS have changed. From 1978 with the Manning criteria to 2016 with the Rome IV criteria, five different diagnostic criteria have been used (Manning et al, 1978; Drossman, 2016). The diagnostic criteria have been shown to affect the prevalence and incidence of IBS. The Manning criteria often gives higher prevalence numbers than the Rome criteria (Hillilä and Färkkilä, 2004; Olafsdottir et al, 2010). The follow-up period of 1991-2010 in the study was during the period where the Rome criteria were used, which indicates a strength, since the Rome criteria are often more strict. The Swedish Patient Register has been validated for IBS. The diagnosis was correct in 70% of cases and in a further 9.6% of cases the diagnosis of IBS was probable. Only 5% of cases had an incorrect diagnosis of IBS (Jossan et al, 2014).

Article I-IV limitations of changing criteria of IBS

The criteria for diagnosing IBS have changed several times (Manning et al, 1978; Kruis et al, 1984; Ford et al, 2008; Engsbro et al, 2013; Drossman, 2016; Ford et al, 2017). However, in paper II the OR was not very different compared to main analysis (both proband and relatives (1987-2010) when the probands diagnosis of IBS was determined in the hospital discharge register and the Outpatient Care Register (1987-2010), but the relatives diagnosis of IBS was determined in the Outpatient Care Register (2001-2010). Moreover, when the probands were diagnosed in the Outpatient Care Register and the hospital discharge register (1987-2010), and the relatives were diagnosed in the primary healthcare database (2001-2007), the ORs for siblings were 1.90 (95% CI 1.58 to 2.28) and 2.09 (95% CI 1.75 to 2.50) for offspring. When the probands were diagnosed in the primary healthcare database (2001-2007) and the relatives in the Outpatient Care Register and the hospital discharge register (1987-2010), the ORs for siblings were 1.82 (95% CI 1.52 to 2.18), and for offspring 1.82 (95% CI 1.49 to 2.21). Thus, the familial ORs did not change to any major degree with different time periods. Moreover, the sex and age distribution and associated comorbidities are similar to those in other studies of IBS. This indirectly suggests that the used ICD codes for IBS mostly identifies IBS patients.

Article I-IV limitations of low IBS prevalence

An important limitation with all four articles in the present thesis is the low prevalence of IBS not only in specialist care but also in primary care. This is not unique for the present study but is in fact similar to other register based studies (Thompson et al, 2000).

A number of IBS patients are therefore likely to be misclassified as non-IBS patients and may dilute the control group but also change the exposure (family history versus no family history). Two types of misclassification might be possible (Szatmari & Jones, 1999). Differential misclassification is when the information errors differ between different groups. This means that the bias is different for exposed and non-exposed. Differential misclassification can bias the results in any direction. However, it is likely that the results are due to non-differential misclassification. The IBS patients identified in the present thesis appear to have the same age, sex, and comorbidity distribution as in the literature (Khan & Chan, 2010). Non-differential misclassification is when the information is incorrect, but is the same across different groups. This usually introduces a non-differential bias that attenuates the results and in family studies may reduce the observed relative risk towards the null value. Thus, the results in this thesis may underestimate the true familial risks (Szatmari & Jones, 1999). It is also possible that some of the identified perinatal and socioeconomic factors in study IV could be even more strongly associated with IBS.

As reviewed by Spiller et al (2007), the main predictors of health-care seeking among IBS patients have been reported to be abdominal pain or distension, pain severity, symptoms according to the Rome II criteria. However, psychological and social factors also play an important role in health care seeking. Thus, the results in the present thesis may not be valid for all IBS patients without such symptoms. It is possible that the present thesis reflects an IBS phenotype with more abdominal pain and distension but also more psychological and social factors involved (Spiller et al, 2007). In genetic epidemiology this is not always a disadvantage because a more severe phenotype usually has a stronger genetic background than more mild phenotypes (Lander & Schork, 1994).

Chapter VII

Conclusion

The present thesis highlights various aspects of risk factors for IBS in a nationwide setting in secondary specialist care as well as a large setting in primary care. For the first time it is shown in a nationwide setting that IBS is inherited in first-, second- and third-degree relatives of patients with IBS (Paper II) and that the risk of IBS in adoptees is increased if at least one biological parent has IBS, but not increased if at least one adoptive parent has IBS (Paper III). This provides strong evidence of a genetic cause of IBS, though increased risks among spouses also suggest that shared household environment may contribute to IBS risks. Moreover, IBS shares a familial background and possibly a genetic background with several gastrointestinal functional disorders and several IBS associated comorbidities.

It is also shown that the prevalence of IBS is low in Swedish primary care and that patients with IBS more often consult their GP but not for IBS (Paper I). This confirms previous register based studies and suggests that IBS might be underestimated in primary care by general practitioners.

The fourth article indicates that perinatal risk factors, socioeconomic factors, and familial risk factors such as caesarean, low birth weight, high foetal growth, young maternal age, a parental history of IBS, anxiety and depression may affect the risk of IBS in young adults (Paper IV).

Future perspectives

In the present thesis it has been shown that heredity plays an important role concerning the risk of IBS and several related gastrointestinal functional disorders and IBS related comorbidities. Recent genetic studies have shown that the genetic loci associated with IBS are diverse and suggest a complex and mechanistically heterogonous cause of IBS. This gives hopes for the future because a specific and tailored treatment might be available for many IBS patients when the molecular mechanisms are clarified. However, before the molecular mechanisms are clarified it will be important to determine in clinical studies if there are clinical different types of IBS segregating in different families. In register based studies it could be possible to identify if there are IBS families with different types of functional gastrointestinal disorders/comorbidities. Another track of research initiated with this thesis could be to clarify the importance of perinatal factors for IBS in clinical and not only register based settings.

Populärvetenskaplig sammanfattning (summary in Swedish)

IBS – irriterat tarm – är en vanlig, kronisk tarmsjukdom karakteriserat av återkommande magsmärtor minst en gång i veckan under de senaste tre månaderna, som är relaterat till tömning av tarm och associerat med en ändring i antalet avföringar och/eller form av avföringen. Symptomen ska ha börjat minst sex månader innan diagnosen sätts.

IBS sjukdomen har stor påverkan på den enskilda patienten och IBS inverkar i hög grad på det dagliga livet. IBS patienten är ofta frustrerat över att inte ha kontroll över symptomen och kan vara rädd att det kan vara allvarligt. Livskvaliteten för den enskilda IBS patienten är påverkat i betydlig grad och ofta sämre än hos patienter med andra sjukdomar så som diabetes, reflux sjukdom och njursvikt. Patienter har ofta fler sjukdagar och IBS sjukdomen kostar mycket för samhället. IBS patienter har ofta fler andra symptom och sjukdomar än patienter utan IBS.

Förekomsten av IBS är 10-15 % i befolkningen och är ofta baserat på undersökningar av patienter, som fått diagnosen på sjukhus eller baserat på enkäter, som skickas ut till en icke selekterad grupp av människor i befolkningen. Hälften av alla med IBS besöker inte läkaren för deras problem. Familjeläkaren ser ofta IBS som en uteslutningsdiagnos och inte som en positiv diagnos baserat på kända kriterier, som riktlinjer rekommenderar. Behandlingen av sjukdomen är ofta att lindra symptomen och de flesta behandlingar är inte mycket bättre än placebo behandling. Familjeläkaren och patienten är inte alltid överens om orsaken och vad som måste göras för att avhjälpa symptomen. Detta gör sjukdomen till ett lidande för den enskilda patient och hanteringen av IBS patienter till en utmaning för familjeläkaren.

Det har gjorts få undersökningar av hur ofta IBS diagnosticeras i primärvården, trots att det är där patienter med misstänkt IBS oftast ser en läkare. Den första studien i denna avhandling (artikel I) har visat på att bara 1,2 % har fått diagnosen bland en population på knappt en miljon individer, som är anknuten till en vårdcentral i perioden 2001-07 i Stockholm, Värmland, Gotland och Uppsala. Det innebär att familjeläkarna ofta försummar diagnosen IBS. Drygt två av tre patienter med IBS är kvinnor. Studiet har också visat på att patienter med IBS oftare söker läkare än patienter utan IBS, men att orsaken vanligtvis inte är på grund av IBS. Med hjälp av logistisk regression kan man justera för orsaker, som kan ha betydelse för resultatet. Studie I undersökte om patienter med IBS oftare har depression, migrän, huvudvärk och symptom från nedre urinvägar (trängningar, frekventa vattenkastningar, små mängder vid vattenkastning, nattliga

vattenkastningar, svag stråle, sveda, känsla av ofullständig tömning) och justerat för ålder och kön i en analys och för ålder, kön, antal besök till läkare och samsjuklighet. I bägge analyser har vi sett att patienter med IBS oftare har nämnde sjukdomar än patienter utan IBS.

Resultatet tyder på att läkare i primärvården inte tillräckligt ofta ställer diagnosen IBS hos deras patienter. Det kan vara på grund av bristande kunskaper om de diagnostiska kriterierna för IBS. Det kan vara på grund av osäkerhet om vad man kan göra för att hjälpa patienten och att IBS uppfattas som ett komplext tillstånd, där psykologiska orsaker spelar in och att det då kan ta tid att hantera. IBS är en sjukdom som oftare drabbar kvinnor, varför även genus perspektivet kan vara en bidragande förklaring.

Orsaken till IBS är inte känd. Många undersökningar har pekat på störningar i rörelsemönstret i tarmen, på ökad känslighet i tarmen, på ändrat tarmflora, på infektioner i tarmen. Sambandet mellan hjärnan och tarmen har blivit allt mer tydlig och i de senaste diagnostiska kriterierna från 2016 IBS har ändrats från att vara en funktionell störning dvs. utan känd biologisk bakgrund till en hjärn-tarm störning.

Ärftlighet av en sjukdom kan undersökas med olika metoder. Tvilling studier, där man jämför enäggstvillingar, som är bärare av helt samme genmaterial och tvääggstvillingar, som är bärare av hälften av samma genmaterial, har visat på olika resultat. Några har visat på större risk för IBS hos enäggstvillingar, medan andra inte har kunnat hitta en skillnad. Familjestudier, där man undersöker om risken att få IBS är ökat hos släktingar till individer med IBS har visat på en ökad risk för släktingar till individer med IBS, men med lite varierande resultat. Andra-grads-släktingar (halv-syskon, fastrar, mostrar, farbröder, morbröder, syskonbarn) och tredje-grads släktingar (kusiner) delar ofta inte samma hushållsmiljö och en ökad risk för IBS hos andra- och speciellt tredje-grads släktingar till individer med IBS kan tyda på en genetisk orsak. Adoptionsstudier där man jämför risken att få en sjukdom hos den adopterade om de biologiska föräldrarna (genetik) har sjukdomen jämfört med om de biologiska föräldrarna inte har sjukdomen. På samma sett kan man studera uppväxt faktorers betydelse om adoptions föräldrarna (miljö) har sjukdomen jämfört med om de inte har sjukdomen.

I den andra studien undersöktes om IBS oftare diagnosticeras hos första-, andra- och tredje-grads släktingar till patienter med IBS jämfört hos de som inte har en släkting med IBS. Register användes som täcker hela Sverige, där diagnosen har ställts på sjukhus i såväl öppenvård som slutenvård. Även en större primärvårdsdatabas har använts för att jämföra familjära risker i specialistvård med primärvård. Studien var en matchad fall-kontroll studie. Studien visade att risken för IBS är ökat hos båda första-, andra- och tredje-grads släktingar till patienter med IBS jämfört med första-, andra- och tredjegrads-släktingar till

individer utan IBS. Det observerades också att make/maka till patienter med IBS har en ökad risk för IBS. Resultaten tyder på en genetisk orsak till IBS, speciellt eftersom båda andra- och tredjegrads-släktingar har en ökat risk för IBS. Att make/maka också har en ökad risk tyder på att det även finns en icke-genetisk orsak, som bland annat kan ha bakgrund i levnadsvanor, aktiviteter i det dagliga livet och positiva och negativa livshändelser.

I den tredje studien observerades att adopterade barn i vuxenålder har större risk att få IBS om de biologiska föräldrarna har IBS jämfört med om de biologiska föräldrarna inte har IBS. Ingen statistisk säkerställd riskökning observerades om adoptivföräldrarna hade IBS. Detta tyder på att det finns en genetisk orsak till IBS eftersom bortadopterade inte delar miljö med biologiska föräldrarna, men med adoptiv föräldrarna.

I den fjärde studien undersöktes olika perinatala faktorer och familjära faktorer för att se om de ökar risken att få IBS hos unga vuxna i åldern 18-38 år. Studien är rikstäckande och följde patienterna från födelsetidpunkten och fram till ung vuxenålder. Kejsarsnitt, låg födelsevikt och ökad växt i fosterlivet har visat sig öka risken för IBS i vuxenålder. Ålder under 20 år hos mamman, skilsmässa/änkestånd, medellång utbildning (10-11 år och 12-14 år) hos mamma, föräldrar med IBS, föräldrar med ångest/depression ökade risken att drabbas av IBS som vuxen.

Slutsatsen i denna avhandling är att IBS är en under diagnosticerad sjukdom i primärvården, att en familjehistoria med IBS kan vara en risk faktor för IBS, att genetiska faktorer spelar en viktig roll för risken att drabbas av IBS även om miljöfaktorer, perinatala och socioekonomiska också kan ha betydelse för utvecklingen av IBS.

Acknowledgements

I wish to express my appreciation and my sincere gratitude to the following persons:

First and foremost, my head supervisor Bengt Zöller for his everlasting enthusiasm, engagement and being an invaluable source of inspiration in the research process. His immense knowledge, talent and insight in the research field has sparked my interest in continuing the work with the dissertation and afterwards. Always available, no matter the hour and day, for questions and valuable discussions. He is the reason that the thesis became a reality.

Co-supervisor Jan Sundquist for being an inspiration and a motivator, for having a positive attitude and for believing in me. Always supportive and constructive; it has had a great impact on the way through the years of research.

Co-supervisor Kristina Sundquist for being a great researcher and for concise and constructive criticism during the writing and for the enthusiasm that has had a positive influence on me during hard times.

Co-supervisor MirNabi Pirouzifard, for invaluable support in biostatistics and for helping in increasing my understanding somewhat in the field.

Xinjun Li for help with biostatistics in the fourth paper. Always available with exact answers to difficult questions.

Henrik Ohlsson for his help with biostatistics in the first articles. He has a great understanding of the field.

Patrick Reilly for his excellent help with proof reading and making sure that the translation in articles and thesis kept a high level.

Martin Lindström, my mentor, for great talks and interesting discussions in the medical research field and other exciting fields as well. A great intellectual and inspiring person.

Helene Brandt for valuable help with the databases and for her enthusiasm and her continuing kindness and cooperativeness.

Klas Cederin for his help with the databases and for sharing his great knowledge in the concept of SAMS.

Emelie Stenman for her big help with all important practical questions and for her positive, enthusiastic and kind nature.

Helene Rosenqvist for invaluable help with all aspects of administrative support.

My beloved wife, Maria and our wonderful son, Anton. For your everlasting love. You make my life meaningful.

My parents, Elsebeth and Jens, for their love - always believing in me and being a support, whenever it is needed.

The staff at the Center for Primary Health Care Research for the great working atmosphere and their kind attitude.

Jonas Palm and Gunilla Albertén at Media-Tryck for their great help with the making of this thesis.

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Paper I

Scandinavian Journal of Primary Health Care, 2013; 31: 132–137

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ORIGINAL ARTICLE

Low prevalence of irritable bowel syndrome in primary health care in four Swedish counties

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Abstract

Objective. Few large-scale studies have examined the prevalence of irritable bowel syndrome (IBS) and the number of visits among IBS patients in a primary health care setting. The aim of this study was to assess the prevalence of IBS in primary health care in four Swedish counties. Another aim was to study the number of visits among the IBS patients. *Design.* A register-based study. *Setting.* A primary health care database with information on patients from 71 primary health care centres in the Swedish counties of Stockholm, Uppsala, Värmland, and Gotland. *Subjects.* The primary health care database contains individual-level data for 919 954 patients for the period 2001–2007. *Main outcome measures.* Prevalence of IBS diagnosis. *Results.* 10 987 patients had a diagnosis of IBS, which corresponds to a prevalence of 1.2%. IBS was most common in the 25–44 years age group (37% of IBS patients); 71% of IBS patients were female, and 81% of IBS patients visited their GP six or more times, compared with 46% of non-IBS patients. However, 95% of the IBS patients visited their GP three times or fewer for IBS. *Conclusion and implications.* The prevalence of IBS was low among Swedish primary health care patients. This might suggest that IBS patients are insufficiently diagnosed in Swedish primary health care.

Key Words: *Epidemiology, gender, general practice, irritable bowel syndrome, prevalence, primary health care, Sweden*

Introduction

Irritable bowel syndrome (IBS) is a functional gastrointestinal (GI) disease characterized by chronically recurring abdominal pain or discomfort and altered bowel habits [1,2]. It has been reported to be one of the most common gastrointestinal disorders, with a worldwide prevalence of 2.5% to 25% [1,2]. The pathogenesis of IBS remains incompletely understood [1,2]. The pathophysiology is probably multifactorial, with involvement of both genetic and environmental factors. Suggested mechanisms include psychosocial factors, abnormal gastrointestinal motility, visceral hypersensitivity, mucosal inflammation after gastroenteritis, and small intestinal bacterial overgrowth [1,2]. Four different sets of diagnostic criteria for IBS have been used: the Manning criteria, the Rome I criteria, the Rome II criteria, and the Rome III criteria [1,2]. The existence of these different criteria poses problems for the comparison of prevalence studies over time. Moreover, in primary health care a more pragmatic approach to diagnosis, involving clinical judgement rather than specific criteria, is usually adopted [3].

Population-based surveys from Europe and the US have shown the prevalence of IBS to be 7–12.5% [4–8]. The prevalence was higher among females than males: the gender ratio was about 2:1 [4–8]. In another population-based survey, the prevalence of IBS varied from 5.1% to 16.2% depending on whether the diagnosis of IBS was based on the Manning or Rome I or II criteria [9]. In a community survey in the US, the overall prevalence of IBS was 14.1% [10]. Of the IBS patients identified in that study, only 23% had previously been medically diagnosed [10]. Among 3111 patients seen by 36 general practitioners (GPs) at six locations in and around Bristol, UK, only 2.5% were judged to have IBS [11]. This is a much lower prevalence than those obtained in most population-based studies [4–10]. Rather, it is more similar to the figure of 1.6% obtained in an

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(Received 30 November 2011; accepted 22 April 2013)

ISSN 0281-3432 print/ISSN 1502-7724 online
DOI: 10.3109/02813432.2013.811949

- Few large-scale studies have examined the prevalence of irritable bowel syndrome (IBS) among unselected patients in primary health care.
- The prevalence of IBS diagnoses in Swedish primary health care was low (1.2%).
- IBS patients often visited their GP, but rarely because of IBS.

older nationwide study based on data from six systematic national health surveys and registers in the US [12].

The discrepancy in IBS prevalence between population-based studies and primary health care-based studies [4–12] may not only be due to diagnostic differences [3]. It might also be related to health-care-seeking behaviours of IBS patients, as reviewed by Spiller et al. [2]. In many studies, only around 50% of IBS patients are diagnosed [2]. The main predictors of health-care seeking among IBS patients are abdominal pain or distension, pain severity, symptoms according to the Rome II criteria, and psychological and social factors [2]. IBS patients tend to seek health care more often than non-IBS patients [2]. IBS has been reported to be a risk factor for becoming a frequent health care attender [13]. Frequent health care attenders often have psychosocial problems [13,14]. In line with this, IBS has been associated with comorbidities such as depression, anxiety, fibromyalgia, headache, migraine, and lower urinary tract symptoms (LUTS) [2,15,16].

There have been few recent large-scale primary health care register studies of IBS. This study was conducted to examine the prevalence of IBS and number of visits among IBS patients using a large primary health care database. Our hypothesis was that there would be age and gender effects on the prevalence of IBS and that certain comorbidities would be associated with IBS.

Material and methods

This study was approved by the Ethics Committee of the Karolinska Institute, Huddinge, Sweden (reference number 12/2000, 2000-03-06 and 2002-11-18) and was performed in compliance with the Helsinki Declaration. The study population was from a primary health care database covering 71 primary health care centres in the Swedish counties of Stockholm (n = 687 310), Värmland (n = 145 943), Gotland (n = 84 898), and Uppsala (n = 12 790). The primary health care database contains individual-level data from a total of 919 954 individuals who visited their GP during the period 2001–2007.

Cases of IBS diagnosed by GPs were identified by the International Classification of Diseases (ICD-10) code K58. Five comorbidities known to be associated with IBS were selected in order to evaluate whether the patients with IBS diagnoses in the present study had the same comorbidity patterns as those described in previous literature [2,15,16]. These comorbidities were defined by the following ICD-10 codes: depression (F32, F33, and F412); LUTS (R30); migraine (G43); headache (R519 and G442); and fibromyalgia (M797). However, fibromyalgia was not included in the analyses as no IBS patients in the database were also diagnosed with fibromyalgia. Age, gender, and number of GP visits were also included in the analysis.

Statistical analysis

Logistic regression was used to investigate the associations between IBS and gender, age, number of GP visits, and comorbidities. Odds ratios (ORs) and corresponding 95% confidence intervals were calculated. Three main models were used in the logistic regression analysis of the data in the primary health care database, with IBS as the outcome. In model A, only age and gender were included and their associations with IBS were analysed. In the B models (B1–B5), associations between number of GP visits and different comorbidities among the IBS patients were analysed. Gender and age were controlled for in all B models. In model B1, which was controlled for age, the association between number of GP visits and IBS was studied. Models B2, B3, B4, and B5 analysed the associations of IBS with depression, LUTS, migraine, and headache (including an interaction term with gender), respectively (with all models being controlled for gender and age). In model C, gender, age, number of GP visits, and comorbidities were included. All calculations were performed using SAS version 9.2.

Results

Primary health care database

Table I shows descriptive statistics for all 919 954 individuals included in the primary health care database, which contains information on all GP visits between 2001 and 2007. The age and gender distribution (47% male), number of GP visits, and four comorbidities known to be associated with IBS (depression, migraine, LUTS, and headache) are shown. Individuals aged 0–24 years constituted the largest age group, accounting for 35% of all patients. Depression was diagnosed in 5% of all patients, and 47% of all patients visited their GP six times or more.

Table I. Descriptive statistics for all 919 954 individuals in the primary health care database.

	All patients	Patients without IBS	Patients with IBS
Number of patients	919 954 (100)	908 967 (98.8)	10 987 (1.2)
Age (years):			
0–24	323 221 (35)	320 984 (35)	2 237 (20)
25–44	271 991 (30)	267 948 (30)	4 043 (37)
45–64	210 108 (23)	206 874 (23)	3 234 (29)
65–74	62 506 (7)	61 563 (7)	943 (9)
75–84	40 344 (4)	39 892 (4)	452 (4)
85+	11 110 (1)	11 038 (1)	72 (1)
Male	430 759 (47)	427 560 (47)	3 199 (29)
Number of GP visits:			
1–2	270 724 (29)	270 020 (30)	704 (6)
3–5	217 744 (24)	216 373 (24)	1 371 (12)
6+	431 486 (47)	422 574 (46)	8 912 (81)
Depression (F32, F33, F412)	44 992 (5)	43 345 (5)	1 647 (15)
Lower urinary tract symptoms (R30)	3 257 (0.4)	3 154 (0.4)	103 (1)
Migraine (G43)	12 047 (1)	11 659 (1)	388 (4)
Headache (R519, G442)	8 699 (1)	8 315 (1)	384 (4)

Note: Data are presented as n (%).

IBS in the primary health care database

Of the 919 954 patients, 10 987 (overall prevalence 1.2%) had a diagnosis of IBS (see Table I). Of the IBS patients, 29% (n = 3 199) were male (see Table I). The age distribution for IBS patients is shown in Table I and Figure 1. The mean age of IBS patients at first diagnosis was 41.9 years (SD 18.7 years; range 0–95 years) and 57% of IBS patients were younger than 45 years. IBS patients visited their GP frequently: 81% of IBS patients visited their GP six or more times between 2001 and 2007, compared with 47% of non-IBS patients. Some 15% of IBS patients had been diagnosed with depression by their GP (see Table I).

Yearly prevalence and incidence from 2001 to 2007

The 12-month prevalence did not vary greatly during the study period (2001–2007). The highest 12-month prevalence was 0.55% in 2004 and the lowest was 0.44% in 2001. The estimated yearly incidence,

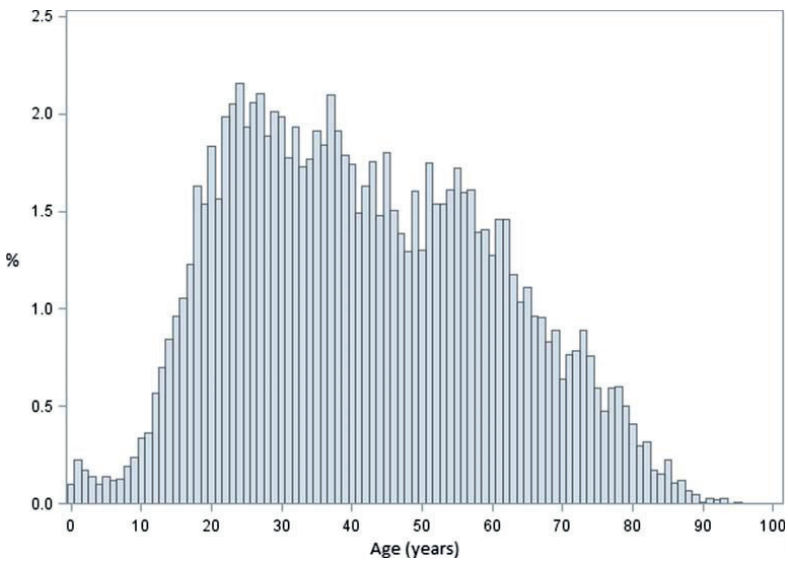

Figure 1. Age distribution of individuals with IBS (n = 10 987).

defined as first registration during the study period, also varied little during the study period. The highest yearly incidence was 4.4 per person-year in 2004 and the lowest was 3.7 per person-year in 2007.

Prevalence of IBS in the four different counties included in the study

The seven-year prevalences of IBS in the four different counties were 1.2% (95% CI 1.2–1.2) for Stockholm, 1.1% (95% CI 1.1–1.2) for Värmland, 1.0% (95% CI 0.9–1.1) for Gotland, and 2.9% (95% CI 2.5–3.1) for Uppsala.

Logistic regression analysis of factors associated with IBS

Table II shows the results of the logistic regression analysis. Three models were used. In model A, only age and gender were included. Male gender was associated with decreased odds of IBS. Individuals aged 25–44, 45–64, and 65–74 years had the highest ORs compared with the reference group (Table II).

In models B1–B5 (controlled for age and gender), all comorbidities were associated with IBS, with headache among males having the highest OR – higher than the OR for headache among females. No other significant gender differences were identified (data not shown). The OR for IBS was high among those who made six or more GP visits.

In model C, gender, age, number of GP visits, and comorbidities were included. The observed associations were similar to those obtained using models A and B. Six or more GP visits was the factor with the strongest association with IBS in model C.

Number of visits for IBS among IBS patients

In total 95% (10 462) of the IBS patients made between one and three GP visits for IBS. Only 5% (525) of the IBS patients made four or more visits for IBS. Males with IBS tended to have lower odds than females of four or more GP visits, but the difference was not significant (data not shown). In a multivariate model, only increasing age and depression were significantly associated with four or more GP visits for IBS (data not shown).

Discussion

Statement of principal findings

This is the first Swedish study to assess the prevalence of IBS using data from a large primary health care register. We found the prevalence of IBS to be only 1.2%, much lower than in many previously published studies [4–10]. However, our value is in line with a study that did not find IBS to be a common minor ailment in out-of-hours primary care [17]. Ninety-five percent of IBS patients visited their GP

Table II. Results from logistic regression analysis of odds of IBS using data for the 919 954 individuals in the primary health care database.

	Model A	Models B1–B5	Model C
Gender (male vs. female)	0.47 (0.45–0.49)	–	0.54 (0.52–0.58)
Age (years):			
0–24	1 (Ref)	–	1 (Ref)
25–44	2.12 (2.02–2.24)	–	1.85 (1.75–1.95)
45–64	2.23 (2.11–2.35)	–	1.61 (1.52–1.70)
65–74	2.16 (2.00–2.33)	–	1.39 (1.28–1.50)
75–84	1.52 (1.38–1.69)	–	0.93 (0.84–1.03)
85+	0.82 (0.65–1.04)	–	0.56 (0.44–0.70)
Number of GP visits:			
1–2	–	1 (Ref)	1 (Ref)
3–5	–	2.41 (2.20–2.64)	2.36 (2.16–2.59)
6+	–	7.65 (7.08–8.26)	6.91 (6.39–7.47)
Depression (F32, F33, F412)	–	2.76 (2.61–2.91)	1.81 (1.71–1.91)
Lower urinary tract symptoms (R30)	–	2.54 (2.08–3.09)	1.79 (1.47–2.19)
Migraine (G43)	–	2.15 (1.94–2.39)	1.34 (1.21–1.49)
Headache (R519, G442) (males)	–	4.50 (3.58–5.65)	2.76 (2.19–3.47)
Headache (R519, G442) (females)	–	2.95 (2.63–3.33)	1.79 (1.59–2.02)

Notes: Data are presented as OR (95% CI) for diagnosis of IBS. In model A, only age and gender were included. In the B models (B1–B5), associations of IBS with number of GP visits and different comorbidities were analysed. Gender and age were controlled for in all B models. In model B1, the association between number of GP visits and IBS was studied. Models B2–B5 analysed the associations of IBS with different comorbidities. In model C, gender, age, number of GP visits, and comorbidities were included.

three times or fewer during the study period. Similar to previous studies, the IBS patients in the present study visited primary health care more often for non-IBS problems than for IBS [2]. Moreover, IBS patients made more GP visits for other conditions than patients without IBS. IBS was associated with depression, migraine, LUTS, and headache, in accordance with previous studies [2,15,16] and in line with the notion that psychological factors may be involved in the pathogenesis of IBS [1,2]. Surprisingly, IBS was not associated with fibromyalgia, which was previously described in IBS patients in primary care [18]. As in other studies, the majority of IBS patients were young females [1,2].

Strengths and weaknesses of the study

One strength of this study is the use of a large primary health care database containing information on all primary health care visits in well-defined areas. This approach eliminated any selection bias. The study is, however, limited by the fact that the diagnostic criteria used are unknown. A pragmatic approach to diagnosis, involving clinical judgement rather than specific criteria, is usually adopted in primary care [3]. IBS is used by many GPs as a diagnosis after exclusion of other conditions [19]. Also, the diagnosis of IBS has not been validated in our database. A general-practice-based database in the UK has been extensively validated. The positive predictive value of an IBS diagnosis in the UK database was 77% [20]. The gender and age distribution and associated comorbidities are similar to those in other studies of IBS [1–12]. This may indirectly suggest that the ICD-10 code K58 mostly identifies IBS patients in the primary health care database. The fairly similar prevalences of IBS in the four different counties represented in the database are also reassuring of relatively good diagnostic validity.

Strengths and weaknesses in relation to other studies

Few large-scale studies have determined the prevalence of IBS in primary health care [11], which was the aim of the present study. Many studies estimating the prevalence of IBS are population-based studies with defined diagnostic criteria [4–10], which do not reflect a primary health care setting [11]. Strengths of these studies are, however, the use of predefined criteria such as the Manning or Rome criteria [1,2,4–10]. However, these criteria have some limitations as they have different sensitivities for IBS diagnosis. The IBS prevalence of 1.2% in the present study is more similar to the prevalence of 2.5% from a previous primary health care study [11] than those from population-based surveys [4–10]. Our results show that IBS patients visit their GP more often than non-IBS patients, which further supports the idea that people with IBS may use more health care resources than people without IBS [2,13]. As described in the literature, a significant number of children with IBS were also identified [21].

Meaning of the study

The low prevalence of IBS in this study may be due to GPs not being familiar with the Manning or Rome I, II, or III criteria [2,3,19]. Moreover, it has been shown that functional disorders are underreported in Swedish primary health care [22]. It has been suggested that GPs may have insufficient knowledge in diagnosing and handling functional disorders such as IBS [23]. GPs may also be reluctant to use stigmatizing diagnoses [23], and they may also find that there is insufficient time to manage patients with functional disorders [23]. This hypothesis is further underlined by the lack of an association between IBS and fibromyalgia in the present study, which contradicts a previous report [18].

The associations with comorbidities and an increased number of non-IBS GP visits are in line with previous research showing that people with IBS have lower health-related quality of life (HRQOL) scores [24] than those without IBS. This suggests that IBS patients may be insufficiently diagnosed and inadequately treated in primary care in Sweden. This explanation is more likely than the alternative one: that the actual prevalence of IBS is low in Swedish primary health care.

In conclusion, the prevalence of IBS diagnoses was low in this study from Swedish primary health care. IBS patients visited their GP often, but rarely because of IBS.

Unanswered questions and future research

This study suggests clinically relevant topics for research on IBS in primary health care, and raises the question as to why the prevalence of IBS diagnoses is so low in primary health care. As well as answering this question, future studies may also highlight the role of patient questionnaires in the diagnosis of IBS in primary health care.

Acknowledgements

The authors wish to thank the CPF's Science Editor, Stephen Gilliver, for his useful comments on the text. The registers used in the present study are

maintained by Statistics Sweden and the National Board of Health and Welfare.

Declaration of interests

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

This work was supported by grants awarded to Kristina Sundquist and Jan Sundquist by the Swedish Research Council (2008-3110 and 2008–2638) and ALF funding awarded to Kristina Sundquist and Jan Sundquist, as well as by the Swedish Council for Working Life and Social Research (2006-0386, 2007-1754 and 2007-1962), Formas (2006-4255-6596-99 and 2007-1352), King Gustaf V and Queen Victoria's Foundation of Freemasons (Jan Sundquist), and funding awarded to Bengt Zöller by Region Skåne (REGSKANE-124611), ALF funding, and the Swedish Heart-Lung Foundation

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Paper II

ORIGINAL ARTICLE

Risk of irritable bowel syndrome in first-degree, second-degree and thirddegree relatives of affected individuals: a nationwide family study in Sweden

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▸ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/gutjnl-2013-305705).

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Received 19 July 2013
Revised 12 March 2014
Accepted 19 March 2014
Published Online First 2 April 2014

ABSTRACT

Objectives IBS aggregates in families, but the familial risk of IBS has only been determined in first-degree relatives and spouses. This nationwide study aimed to determine the familial risk of IBS in first-degree, second-degree, and third-degree relatives and spouses of affected individuals in order to estimate the relative influences of genes and shared family environment.

Methods We performed a case-cohort study. The Swedish Multigeneration Register was linked to the Hospital Discharge Register for the period 1987–2010 and the Swedish Outpatient Care Register for 2001–2010. ORs for IBS were calculated for relatives of individuals who had been diagnosed with IBS compared with relatives of individuals unaffected by IBS as the reference group. ORs were also determined for IBS cases diagnosed in primary healthcare in four Swedish counties (2001–2007).

Results The ORs for IBS were 1.75 in siblings (95% CI 1.63 to 1.89), 1.82 in offspring (1.67 to 1.97), 1.90 in parents (1.76 to 2.05), 1.10 in maternal half-siblings (0.88 to 1.39), 1.78 in paternal half-siblings (1.48 to 2.15), 1.27 in nieces/nephews (1.18 to 1.38), 1.11 in cousins (1.04 to 1.18), and 1.51 in spouses (1.24 to 1.84) of probands diagnosed with IBS. The OR for probands diagnosed in primary healthcare was 1.82 in siblings (1.52 to 2.18), and 1.82 in offspring (1.49 to 2.21).

Conclusions The increased IBS risk among first-degree relatives and also second-degree and third-degree relatives indicates a genetic component of the familial clustering of IBS. However, a non-genetic contribution is also suggested by the increased risk among spouses.

Significance of this study

What is already known on this subject?
- IBS is known to aggregate in families.
- Familial aggregation may be due to shared genetic or environmental factors.

What are the new findings?
- IBS aggregates in Swedish families, and a non-genetic familial contribution is suggested by the increased risk among spouses.
- A genetic contribution to the familial aggregation of IBS in Sweden is suggested by the increased familial risks among first-degree relatives and also second-degree and third-degree relatives.
- This the largest register-based family study of IBS, and the first nationwide one.

How might it impact on clinical practice in the foreseeable future?
- Family history of IBS is a potential useful predictor for IBS.
- Genetic studies in order to identify IBS-associated genetic variants might be worthwhile.

INTRODUCTION

IBS is a chronic functional bowel disorder characterised by abdominal pain or discomfort. It is relieved by defecation, and its onset coincides with a change in defecation frequency or stool consistency.[1 2] It is one of the most common gastrointestinal conditions.[3] Although a number of disease mechanisms have been suggested, the pathophysiology of IBS is still poorly understood.[1 2] IBS has been shown to aggregate in families.[4–7] This may be due to shared genes or shared family environmental exposures.[8 9] Twin and adoptee studies can help to disentangle genetic and environmental influences.[9] Twin studies support the concept that IBS has genetic and environmental contributions.[10–14] Conflicting data from twin studies exist. For instance, a study by Mohammed *at al* reported that there was no significant difference in casewise concordance rates between the MZ (monozygotic) and DZ (dizygotic) twins (28% vs 27%), suggesting that genetic factors are of little or no influence on IBS, and that the predominant influences are environmental.[12] By contrast, Levy *et al* found that the concordance for IBS was significantly greater in MZ (17.2%) than in DZ (8.4%) twins (p=0.0030), supporting a genetic contribution to IBS.[11] However, Levy *et al* also found that the proportion of dizygotic twins with IBS who have mothers with IBS (15.2%) was greater than the proportion of dizygotic twins with IBS who have co-twins with IBS (6.7%, p<0.001).[11] Levy *et al* concluded that although heredity contributes to the development of IBS, social learning has an equal or greater influence.[11] By contrast, the twin studies by Morris–Yates *et al*[10] and Lembo *et al*[14] suggested that a substantial proportion of the liability for functional bowel disorders and IBS may be under genetic control. Bengtson *et al*[13] found support for

To cite: Waehrens R, Ohlsson H, Sundquist J, *et al*. *Gut* 2015;**64**: 215–221.

a genetic contribution to IBS but also for a significant influence of restricted fetal growth on the development of IBS later in life. Another approach to estimate the familial non-genetic contribution is to study spouses, who share adult environments but not genetic factors.[9] However, Saito *et al* found no increase in IBS risk among spouses.[7] While family studies suggest a genetic contribution, definitive disease-causing genes remain to be determined for IBS; in spite of that many case-control studies have been carried out.[15]

A further possibility to study the influence of genetic and non-genetic familial factors is to study first-degree, second-degree and third-degree relatives.[16] First-degree relatives share 50% of their genes, in addition to environmental exposures common to their family. Second-degree relatives (half-siblings and uncles/aunts/nieces/nephews) share 25% of their genes, and third-degree relatives (eg, first cousins) share 12.5% of their genes. An increased disease risk in second-degree and third-degree relatives of affected individuals supports the interpretation that genetic factors influence familial aggregation, since individuals outside the nuclear family are less likely to share the same environmental exposure.[16 17] Half-siblings are special in terms of family environmental exposures. According to national census data, 83% of maternal half-siblings in Sweden were registered as living in the same household, compared with only 3% of paternal half-siblings.[18] To our knowledge, no nationwide studies have examined the familial aggregation in first-degree, second-degree and third-degree relatives of patients with IBS.

Our aim was to estimate the familial risk of IBS in first-degree, second-degree and third-degree relatives in a nationwide family study in order to estimate the relative influences of genetics and shared environment on risk of IBS. The study was based on the Swedish Hospital Discharge Register and the Swedish Outpatient Care Register. We also determined familial risks when cases (or controls) were diagnosed in a primary healthcare database from four Swedish counties,[19] while controls (or cases) were diagnosed in the Hospital Discharge Register and Outpatient Care Register. The findings of the present study could be potentially useful for IBS prediction in families, or as a basis for future molecular biological studies.

METHODS

To assess IBS among individuals in Sweden, comprehensive registers and nationwide healthcare data from five sources were linked.[17 20–24] Linkage was also made to a primary healthcare database from four Swedish counties.[19] This linkage was based on the unique individual Swedish 10-digit personal ID numbers assigned at birth or immigration to all Swedish residents for life, information on which is nearly 100% complete. These numbers were replaced with serial numbers to preserve anonymity. We used data from six sources:

1. The Swedish Multigeneration Register, which contains information on family relationships. The register contains information on index persons registered in Sweden between 1 January 1961 and 31 December 2008 and born between 1 January 1932 and 31 Decemcber 2008.
2. The Total Population Register, which contains annual data on education and marital status from 1990 to 2010. The total population registry holds data on sociodemographic factors including data on education and marital status.
3. The Swedish Hospital Discharge Register, which contains all hospital diagnoses for all people in Sweden from 1987 to 2010. Every record has the main discharge diagnosis.
4. The Outpatient Care Register, which contains information on diagnoses from all specialist outpatient clinics in Sweden from 2001 to 2010.
5. The Swedish Cause of Death Register, which contains data on date and cause of death from 1987 to 2010.
6. The primary healthcare database covering 71 primary healthcare centres in the counties of Stockholm (n=687 310), Värmland (n=145 943), Gotland (n=84 898), and Uppsala (n=12 790).[19] The primary healthcare database contains individual-level data from totally 919 954 individuals, who visited their general practitioner in the period 2001–2007.

Variable definition

Cases of IBS in the Swedish Hospital Discharge Register and Outpatient Care Register were identified by the following ICD (International Classification of Diseases) codes: ICD-9 564B (IBS); and ICD-10 K58 (IBS). The validity in the Hospital Discharge Register is generally 85–95%.[21 24] The present study is not representative of all Swedish IBS patients, and may introduce a selection bias as the diagnosis of IBS is based on healthcare seeking. Therefore, we linked the nationwide Registers to a primary healthcare database in order to determine whether the calculated familial ORs were different or not when different data sources were used.[19] We also determined comorbidities known to be associated with IBS in order to evaluate whether patients with IBS diagnosis in the present study had the same comorbidity patterns as previously described.[1 2 3 4 25] We also exclude IBS patients with gastrointestinal differential diagnosis, that is, coeliac disease, inflammatory bowel disease and colorectal cancer. ICD codes are presented in online supplementary table S1.

Sample

The analyses were based on a database (see above) containing information on the entire Swedish population, including relationships.[17] In the database we double-entered all sibling pairs, all maternal half-sibling pairs, all paternal half-sibling pairs, all cousin pairs, and all spouse pairs. We also single-entered all parent–offspring pairs, all offspring–parent pairs, and all aunt/uncle–niece/nephew pairs. We also required that the proband and the relative were alive after 1986. We selected pairs where at least one member of the pair (which we defined as the proband) was diagnosed with IBS. In total, 56 813unique individuals were diagnosed with IBS during the period 1987–2010. Totally, 11% of the cases were found in the Hospital Discharge Register (1987–2010) and 89% in the Outpatient Care Register (2001–2010). Potential differential diagnoses (ie, coeliac disease, IBD, and colorectal cancer) to IBS were checked for. Among IBS probands, 2.2% suffered from coeliac disease. The corresponding figures were 6.4% for IBD and 0.6% for colorectal cancer. Thus, 9% of IBS probands diagnosed in the Hospital discharge register and outpatient care register may, instead of IBS, have their symptoms explained by coeliac disease, IBD or colorectal cancer. Probands and relatives with IBS diagnosis as well as a concomitant diagnosis of coeliac disease, IBD, or colorectal cancer were therefore excluded. A total of 51 952 IBS individuals remained after exclusion of those individuals with coeliac disease, IBD, or colorectal cancer.

Statistics

The statistical methods used have previously been described.[17] We used a case-cohort approach in order to investigate our research question. We conducted eight main analyses; proband–sibling, proband–offspring, proband–parent, proband–maternal

half-sibling, proband–paternal half-sibling, proband–niece/nephew, proband–cousin, and proband–spouse. In all analyses, we studied all IBS proband–relative pairs (one affected proband and one proband relative) that could be matched to five control pairs (one control without IBS and one control relative) from the Swedish population. The proband–relative in the proband–relative pair and the control–relative in the control–relative pair may or may not be affected by IBS. For example, in the proband–sibling analysis, we selected all sibling pairs where at least one sibling was diagnosed with IBS, and matched each such pair to five control pairs. The control pairs were chosen randomly from individuals who lived in Sweden at the time of the proband's diagnosis of IBS. Furthermore, both individuals in the control pair also had to have lived in Sweden sometime during the period 1987–2010. Control pairs were matched based on birth year, sex, country of birth, and level of education (the year before the date of diagnosis). The matching was done on the proband and on the entire pair. The matching was conservative as the control in the control pair was allowed to develop IBS during the follow-up time (but not before or at the time for inclusion). For the proband–spouse analysis, we only had information on marital status from 1990 onwards. This limited our study period to 1991–2010 as we defined marital status the year before IBS diagnosis. In this analysis the control individual also had to be registered as being married the same year as the case proband. For descriptive statistics, see table 1.

In order to test the trend that there was a higher risk of IBS in relatives who were more closely related, we included all types of proband–relative pairs in one dataset. Each pair was assigned their genetic resemblance (ie, 0.5 for sibling-pairs, parent–offspring pairs, child–parent pairs, and 0.25 for half-sibling pairs, niece/nephew pairs, 0.125 for cousin pairs and 0 for spouse pairs). We conducted the same analysis as described previously, but we also included an interaction term between the genetic resemblance and IBS in relatives. The hypothesis was that if this interaction term was not significant, there existed no trend of higher risk in IBS in relatives who were more closely related.

In order to investigate possible sex differences in the familial clustering of IBS, we stratified the data by sex and included an interaction term between sex of proband–relative and IBS (1 for males and 0 for females).

In an additional model, in order to investigate the potential effect of possible age in the familial clustering of IBS, we included an interaction between the defined predictor variable (eg, IBS in sibling) and age at diagnosis of IBS in the proband (centred at the mean value). The matching does not interfere with the interaction analyses. We also tested for interaction between IBS in relative and age difference between the relatives in a pair. Interaction was also tested between IBS in relative and the difference (in years) in diagnosis of IBS between proband and proband relative. We examined linear effects for these differences.[26]

We also performed a sensitivity analysis where we only investigated probands that were registered twice for IBS in the registers. This analysis was performed in the same way as the analyses explained above.

Analyses were conducted using conditional logistic regression. As an example, in the proband–sibling analysis, IBS in sibling (yes/no) was used as the independent variable. As a particular proband could be included several times, we adjusted for non-independence by using a robust sandwich estimator. In all analyses, less than 2% of the proband pairs could not be matched to five controls and were excluded from the analysis. Approximately 70% of these excluded pairs were born outside Sweden. We present ORs and corresponding 95% CIs. All calculations were performed using SAS V.9.3.

Table 1 Descriptive statics for the probands, that is, age, sex, and education

	Mean age of proband*	High education among probands (%)	Women among probands
First-degree			
Sibling	40.9 (16.1)	28.4	71.9
Offspring	48.2 (13.2)	29.0	74.6
Parent	37.5 (15.6)	30.1	71.7
Second-degree			
Maternal half-sibling	33.1 (13.5)	17.7	73.3
Paternal halfsibling	34.0 (13.5)	21.6	72.9
Niece/nephew	47.7 (13.2)	29.2	72.1
Third-degree			
cousins	28.6 (9.5)	26.8	69.9
Non-biological			
spouses	53.0 (13.9)	26.9	71.3

*SDwithin brackets.

RESULTS

Descriptive statistics and comorbidities

A total of 51 952 individuals were diagnosed with IBS (excluding individuals with a concomitant coeliac disease, IBD, and colorectal cancer) during the study period (1987–2010). Table 1 presents the descriptive statistics for proband siblings, that is, age, sex and educational attainments. Table 2 presents other functional gastrointestinal disorders (for a detailed description, see below) and comorbidities of all 60 489 sibling pairs included in the study. Other functional gastrointestinal disorders and comorbidities were more common in probands than controls, and in probands than proband–relatives. Other functional gastrointestinal disorders and comorbidities were also more common in proband–relatives than control–relatives.

Of the 60 489 siblings, 6806 (11%) had an ICD diagnosis of functional constipation (ICD-9 564A or ICD-10 K590) and/or functional diarrhoea (ICD-9 564F or ICD-10 K591). However, to fulfil the diagnostic criteria for functional constipation or functional diarrhoea, there should be insufficient criteria for IBS according to Rome II and Rome III criteria, that is, an IBS-diagnosis cannot exist together with these diagnoses. However, these patients could have a possible IBS, and if these two diagnoses were made within a short time interval, the patients are more likely to have the same diagnosis at both occasions. We checked the mean time difference between IBS and functional constipation and functional diarrhoea. The mean time difference between diagnosis of IBS and functional constipation was 42 days with a SD of 1971 days (median −57 days and IQR −715 and 699 days). The time difference in diagnosis between IBS and functional diarrhoea was 3 days with a SD of 1271 days (median −48 days and IQR −308 and 150 days). The distribution of the time difference in days between IBS and functional constipation or functional diarrhoea is shown in online supplementary figure S1 and S2.

Familial risks for IBS

We found familial clustering of IBS, with significant ORs for all first-degree biological relationships (table 3). The OR of IBS for full siblings (50% genetic similarity) was 1.75 (95% CI

Table 2 Descriptive statistics of other functional gastrointestinal disorders and comorbidities for the 60 489 sibling pairs included in the analysis

	Proband* (%)	Control† (%)	p Value‡	Proband-sibling* (%)	Control-sibling† (%)	p Value§	p Value¶
Other functional gastrointestinal disorders							
Functional constipation	5.9	1.0	<0.001	1.2	0.9	<0.001	<0.001
Functional diarrhoea	6.0	0.4	<0.001	0.6	0.4	<0.001	<0.001
Functional dyspepsia	7.2	1.1	<0.001	1.3	0.9	<0.001	<0.001
Fecal incontinence	0.9	0.2	<0.001	0.2	0.1	0.0152	<0.001
Comorbidities							
Anxiety	11.5	4.3	<0.001	5.3	3.9	<0.001	<0.001
Depression	8.7	3.4	<0.001	4.0	3.0	<0.001	<0.001
Migraine	2.9	1.2	<0.001	1.4	1.0	<0.001	<0.001
Headache	8.3	2.6	<0.001	3.4	2.23	<0.001	<0.001
Micturition pain	1.5	0.4	<0.001	0.4	0.3	<0.001	<0.001
Pain associated with female genital organs and menstrual cycle	10.6	3.2	<0.001	4.2	3.0	<0.001	<0.001

*Proband (affected) and proband-siblings belong to the proband-sibling pair.
†Control (not affected) and control-sibling belong to the control-sibling pair.
‡p Value from a χ^2 test between proband and controls.
§p Value from a χ^2 test between proband-sibling and control-sibling.
¶p Value from a χ^2 test between proband and proband-siblings.
ICD, International classification of disease.

1.63 to 1.89), which was higher than that for maternal half-siblings who share 25% genetic similarity (OR 1.10, 95% CI 0.88 to 1.39) and have similar family environmental exposures. Nieces/nephews of proband cases had an OR of 1.27 for IBS. Nieces/nephews share 25% genetic similarity with the proband but do not usually share family environmental exposures. The OR was also significantly increased for paternal half-siblings. The OR for maternal half-siblings (who have 25% genetic similarity and often share family environmental exposures) was lower than the OR for paternal half-siblings (who have 25% genetic similarity, but rarely share family environmental exposures). The OR for cousins, who have 12.5% genetic similarity but who usually do not share family environmental exposures to any major degree, was also increased. Spouses share adult family environmental exposures but are genetically unrelated. The OR for IBS in the spouse analysis was 1.51 (95% CI 1.24 to 1.84) (table 3).

In order to test the trend that there was a higher risk of IBS in relatives who were more closely related, we included all types of proband-relative pairs in one dataset. We conducted the same analysis as described previously but we also included an interaction term between the genetic resemblance and IBS in the relative. The interaction term was strong and highly significant (OR 3.36 95% CI 2.78 to 4.05; p<0.0001), that is, there was a strong association between genetic resemblance and familial ORs of IBS.

As the diagnosis of IBS may or may not be correct in the 6806 individuals with a diagnosis of functional constipation and/or functional diarrhoea we calculated familial risks for the remaining 53 683 siblings (89%) without a diagnosis of functional constipation and/or functional diarrhoea.The familial OR was 1.70 (95% CI 1.55 to 1.85), which is similar to the OR 1.75 (95% CI 1.63 to 1.89) in table 3, which was calculated without exclusion of cases with a possible IBS diagnosis (11%).

Table 3 ORs of IBS in relatives of probands diagnosed with IBS in Sweden between 1987 and 2010 compared to relatives of matched controls

Relation to proband	pairs, n	concordant pairs*, n (%)	OR (95% CI)
First-degree relatives			
Sibling	60 489	724 (1.2)	1.75 (1.63 to 1.89)
Offspring	64 168	604 (0.9)	1.82 (1.67 to 1.97)
Parent	73 316	727 (1.0)	1.90 (1.76 to 2.05)
Second-degree relatives			
Maternal half-sibling	8290	73 (0.9)	1.10 (0.88 to 1.39)
Paternal half-sibling	11 147	115 (1.0)	1.78 (1.48 to 2.15)
Niece/nephew	86 475	600 (0.7)	1.27 (1.18 to 1.38)
Third-degree relatives			
Cousin	129 593	1021 (0.8)	1.11 (1.04 to 1.18)
Non-biological relatives			
Spouse	12 816	100 (0.8)	1.51 (1.24 to 1.84)

*Number of pairs where both individuals were affected.

Table 4 Odds ratios of IBS of all probands who were diagnosed with IBS during 1987–2010 in Sweden compared to relatives to matched controls stratified on gender of proband.

Relation to proband	Males OR (95% CI)	Females OR (95% CI)
First-degree		
Sibling	1.84 (1.60 to 2.11)	1.72 (1.57 to 1.88)
Child	1.90 (1.62 to 2.24)	1.79 (1.63 to 1.97)
Parent	1.80 (1.57 to 2.08)	1.94 (1.78 to 2.12)
Second-degree		
Maternal half-sibling	1.24 (0.79 to 1.95)	1.07 (0.81 to 1.39)
Paternal half-sibling	2.11 (1.50 to 2.95)	1.57 (1.33 to 2.09)
Niece/nephew	1.26 (1.09 to 1.47)	1.28 (1.16 to 1.41)
Third-degree		
Cousins	1.21 (1.09 to 1.35)	1.06 (0.99 to 1.15)
Non-biological		
Spouses	1.48 (1.12 to 1.96)	1.54 (1.16 to 2.04)

Interaction between IBS, sex and age

In table 4, the sex specific familial risks odds for IBS are presented. There were no major differences between sexes. The importance of age and sex was investigated with the insertion of interactions terms in the models. There were no significant interactions between sex and IBS (data not shown in table). Regarding age, the familial clustering was significantly stronger at younger ages but only among cousins (see online supplementary table S2), that is, the OR for IBS was higher for young individuals than for older individuals among cousins. Otherwise there were no significant interactions between age and IBS.

Interaction between age difference or time of diagnosis and IBS

To test further for shared environmental factors, the interaction between age difference between relatives in a pair and IBS in relative was determined. There was no interaction between age difference between probands and proband–relatives and IBS except among paternal half-siblings (left part of online supplementary table S3). Moreover, there was no interaction between year difference in time of diagnosis between proband and proband–relative (right part of online supplementary table S3) and IBS in relative.

Sensitivity analysis

In a sensitivity analysis, we only included individuals registered with IBS in the registers at least twice. The ORs for cases with at least two IBS diagnoses were 2.57 (95% CI 2.06 to 3.19) for siblings, 2.66 (2.06 to 3.43) for offspring, 3.63 (2.84 to 4.64) for parents, 1.24 (1.02 to 1.52) for cousins, and 1.17 (0.56 to 2.45) for spouses. Thus, the ORs were even higher for biological relatives, but lower for spouses compared to those presented in table 3. Since only 13 136 individuals had the same diagnosis at least twice there were not enough cases to calculate risks for half-siblings.

Additional analysis in the Outpatient Care Register

We wanted to test whether the familial odds were affected by the use of different data sources, and used the Outpatient Care Register for this purpose. The probands diagnosis of IBS was determined in the hospital discharge register and the Outpatient Care Register, but the relative diagnosis of IBS was determined in the Outpatient Care Register. The OR for siblings was 1.72 (95% CI 1.59 to 1.87) and 1.79 (95% CI 1.64 to 1.96) for offspring, which is similar to the results in table 3.

Additional analysis in the primary healthcare database

When the probands were diagnosed in the Outpatient Care Register and the hospital discharge register, and the relatives were diagnosed in the primary healthcare database, the ORs for siblings were 1.90 (95% CI 1.58 to 2.28) and 2.09 (95% CI 1.75 to 2.50) for offspring. When the probands were diagnosed in the primary healthcare database and the relatives in the Outpatient Care Register and the hospital discharge register, the ORs for siblings were 1.82 (95% CI 1.52 to 2.18), and for offspring 1.82 (95% CI 1.49 to 2.21).

DISCUSSION

This is the first total population study to provide robust estimates of familial IBS odds in relatives at varying genetic and environmental distances from each other (full siblings, offspring, parents, maternal and paternal half-siblings, niece/nephews, cousins and spouses). The odds of IBS was significantly increased in the first-degree, second-degree and third-degree relatives of individuals diagnosed with IBS, with the odds of IBS tending to be higher in more closely related relatives. The present large nationwide register-based follow-up study confirms previous studies of familial aggregation of IBS among first-degree relatives.[4–7 10–14] However, previous family studies have been twin-studies, case-control studies of first-degree relatives, and based on contact to probands and relatives.[4–7 10–14] The present study has also a much larger sample size than previous studies. The results of the present study suggest a genetic, but also a non-genetic, contribution to the familial aggregation of IBS. This is in line with previous twin studies that also suggest genetic and environmental contribution to IBS.[10–14] The design of the present nationwide study is different and underlines a potential biological and genetic contribution to familial aggregation of IBS. For instance, second-degree and third-degree relatives usually do not share household (except for maternal siblings) and the increased familial ORs among these relatives suggest a genetic contribution. A genetic influence was further suggested by the finding that paternal half-siblings (3% of whom share households) had a significantly increased OR (1.78 95% CI 1.48 to 2.15). Moreover, a genetic influence on the odds of IBS was also suggested by the higher OR for full siblings (OR 1.75, 95% CI 1.63 to 1.89) than for maternal half-siblings (OR 1.10, 95% CI 0.88 to 1.39), because they share similar environmental exposures.

Spouses are genetically unrelated, but share adult environments and demographic characteristics except for sex.[27 28] Cardiovascular health-related behaviours, such as smoking, exercise and alcohol consumption correlate much more strongly among spouses than among siblings or between parents and offspring.[27 28] The increased odds of IBS among spouses in our study also suggests that familial adult non-genetic factors may contribute to the increased familial risk in the Swedish population. However, assortative mating could also contribute to the association among spouses. Thus, individuals with IBS may be more likely to marry individuals with similar health problems. Moreover, spouses of individuals with IBS may also be more likely to seek medical attention. A previous study of spouses found no increased risk of IBS.[7] The cause of this discrepancy between that study and the present study is unclear, but may be related to factors such as different study populations, diagnostic criteria and study sizes. Spouses share the same family environmental exposures, including diets, daily activities such as physical activity, and positive and negative life events. Spousal concordance has been shown in studies on food choice.[29] Shared environmental factors like diet could, therefore, contribute to the observed spousal odds of IBS. Several diseases have previously been reported to be shared among spouses, such as asthma, depression, hypertension, hyperlipidaemia and peptic ulcer.[30] Infection is another example of possible shared environmental familial factors. An increased risk of developing IBS after acute gastroenteritis has been verified in a meta-analysis.[31] Bacterial gastroenteritis and helminth and protozoan infections have been associated with IBS.[32] Moreover, a recent study by Zanini *et al* showed that even viral gastroenteritis increased the risk of IBS.[33] Other examples of shared familial adult environmental risk factors are adult life trauma, low socioeconomic status, chemical exposures and allergenic antigens.[28]

Strengths and weaknesses in relation to other studies

The present study has several limitations. It included specialist-treated inpatients (11%) and outpatients (89%) in Sweden. Many IBS patients are only treated by family physicians or may

not even be diagnosed. Thus, the present study is not representative of all Swedish IBS patients, and may introduce a selection bias as the diagnosis of IBS is based on healthcare seeking. However, we linked the nationwide hospital discharge register and the Outpatient Care Register to a primary healthcare database from four Swedish counties, and found similar familial OR for probands diagnosed in the primary healthcare database. However, the majority of IBS patients in the population may never be seen in primary care, and the results of this study may, therefore, also be a reflection of healthcare-seeking behaviour in families. This could potentially underestimate the familial clustering of IBS and, ideally, all relatives should be interviewed. Additionally, many controls are not without IBS, they are only without IBS diagnosis. This could result in an overestimation of familial odds. However, the estimated familial odds in the present study are somewhat lower than previously published.[5–7] A further weakness is the lack of diagnostic information. We do not know which diagnostic criteria were used. The validity of an IBS diagnosis in registers relative to the existing diagnostic criteria (Rome I, II or III) has not been evaluated, so we do not know the proportion of subjects who have received an IBS diagnosis from their physician, and who actually fulfils the diagnostic criteria for IBS. Additionally, 6086 (11%) of IBS patients also had a diagnosis of functional constipation or functional diarrhoea. An IBS-diagnosis should not exist together with these diagnoses according to Rome II and Rome III criteria. However, exclusion of these possible IBS cases did not change the familial ORs for siblings (1.70 vs 1.75). Moreover, the diagnostic criteria have changed over time. Nonetheless, the fact that the patients were identified in the Hospital Discharge Register, which has 85–95% validity, and the Outpatient Care Register (hospital-based specialised outpatient care) makes it more likely that the diagnoses are correct.[21 24] For instance, diagnoses in the Hospital Discharge Register were shown to be correct in 86% of patients with coeliac disease and 74% of patients with Crohn's disease and ulcerative colitis.[24] It is possible that the diagnostic accuracy is lower for functional diagnoses. Moreover, only 9% of IBS probands in the present study developed coeliac disease, inflammatory bowel disease, or colorectal cancer during follow-up and these IBS patients were all excluded from the study. A general practice-based database in the UK has been extensively validated. The positive predictive value for an IBS diagnosis (ICD 8th revision code 5641) in the UK database was 77%.[34 35] The validity of the IBS diagnosis made by hospital specialists are not expected to be lower. Moreover, the sex and age distribution and associated comorbidities are similar to those in other studies of IBS.[1–4 25] This indirectly suggests that the used ICD codes for IBS mostly identifies IBS patients. Moreover, the familial risks for IBS was similar among primary healthcare patients and patients from the Hospital Discharge Register for the period and Swedish Outpatient Care Register, which also is reassuring. Additionally, the large number of comparisons is a point worthy consideration. While some advocate correcting for multiple comparisons, others suggest that in observational studies this should not be recommended.[36]

The present study also has many strengths. Its design eliminates the risk of recall bias, which is an important problem in case-control studies. The study is also the largest family study of IBS and the only nationwide study of IBS. The nationwide design and the use of several well studied and high-quality national registers is also a very important strength.[17 20–24] The Swedish personal ID numbers (replaced by serial numbers) are a valuable tool for linking medical registers, and allow for almost 100% coverage of the Swedish healthcare system.[23] For instance, in 2001, serial numbers and main diagnoses were missing for only 0.4 and 0.9% of hospitalisations, respectively.[22]

In conclusion, the present nationwide study confirms that IBS aggregates in families, and suggests that genetic factors contribute to IBS risk among Swedish families, although disease-causing variants remain to be found in the Swedish population. However, a non-genetic contribution to the observed familial aggregation is also suggested by the clustering among spouses. Future studies could examine which shared familial factors are important for the development of IBS.

Acknowledgements The authors wish to thank the CPF's Science Editor Stephen Gilliver for his useful comments on the text. The nationwide registers used in the present study are maintained by Statistics Sweden and the National Board of Health and Welfare.

Contributors RW, HO, JS, KS, and BZ were involved in study design and execution, and finalising the paper. RW drafted the manuscript. All authors critically revised the paper and all authors approved the final draft submitted. All authors had full access to all the data (including statistical reports and tables) and take responsibility for the integrity of the data and the accuracy of their analysis.

Funding This work was supported by grants awarded to Dr Bengt Zöller from the Swedish Heart-Lung Foundation and Region Skåne (REGSKANE-124611), to KS from the Swedish Research Council, and to JS from the Swedish Council for Working Life and Social Research (2007–1754) and King Gustaf V and Queen Victoria's Foundation of Freemasons, as well as by ALF funding from Region Skåne awarded to Bengt Zöller, Jan Sundquist, and Kristina Sundquist.

Competing interests None.

Ethics approval The study was approved by the Ethics Committee of Lund University, Sweden (approval number 409/2008 Lund with complementary approvals dated September 1, 2009, and January 22, 2010) and by the Ethics Committee of the Karolinska Institute, Huddinge, Sweden (reference number 12/2000, 2000-03-06 and 2002-11-18), and was performed in compliance with the Helsinki Declaration.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The nationwide registers used in the present study are maintained by Statistics Sweden and the National Board of Health and Welfare.

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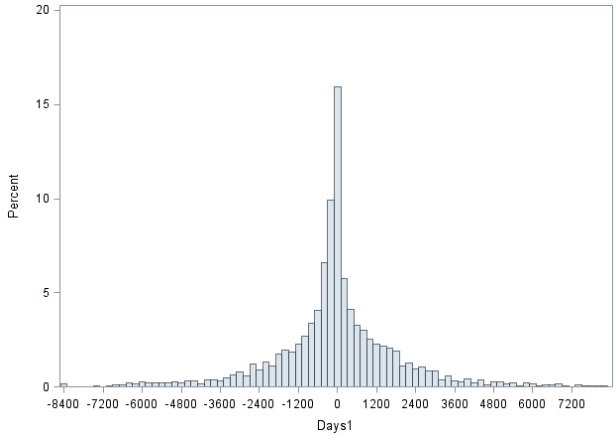
Supplementary Table 1. ICD codes for comorbidities and excluding diagnoses.		
	ICD-9	ICD-10
Other functional gastrointestinal disorders		
Functional constipation	564A	K59.0
Functional diarrhea	564F	K59.1
Functional dyspepsia	536W	K30
Fecal incontinence	787G	R15
Comorbidities		
Anxiety	300A-D, 308, 309	F40-F43
Depression	296B, 311	F32, F33
Migraine	346	G43, G44.0, G44.1
Headache	R51, G44.2	784A, 307W
Micturition Pain	788B	R30
Pain***	625	N94
Excluding diagnoses		
Celiac disease	579A	K900
Inflammatory bowel disease	555, 556	K50, K51
Colorectal cancer	153, 154	C18, C19, C20, C21

Supplementary Table 2. Odds ratios of IBS of all probands who were diagnosed with IBS during 1987-2010 in Sweden compared to relatives to matched controls including interaction terms for age at IBS diagnosis.

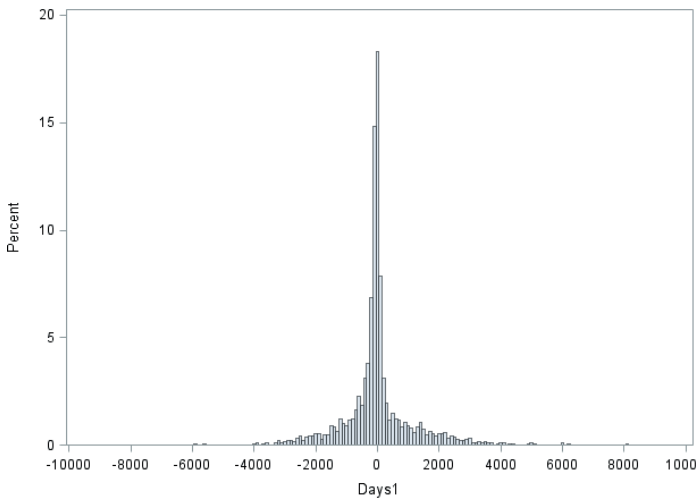
Relation to proband	**OR (95 % CI)**	**Age At IBS*IBS**
First degree		
Sibling	1.74 (1.61 – 1.87)	0.99 (0.99 – 1.00)
Child	1.87 (1.70 – 2.05)	1.00 (0.99 – 1.00)
Parent	1.82 (1.67 – 1.98)	0.99 (0.99 – 1.00)
Second degree		
Maternal half sib	1.11 (0.88 – 1.39)	0.99 (0.97 – 1.01)
Paternal half sib	1.78 (1.48 – 2.15)	1.00 (0.98 – 1.01)
Niece/Nephew	1.29 (1.17 – 1.41)	1.00 (0.99 – 1.01)
Third degree		
Cousins	1.11 (1.04 – 1.18)	0.99 (0.99 – 0.0999)
Non biological		
Spouses	1.51 (1.23 – 1.84)	1.00 (0.98 – 1.01)

Supplementary Table 3. Odds ratios of IBS of all probands who were diagnosed with IBS during 1987-2010 in Sweden compared to relatives to matched controls including interaction terms for age difference in year between relatives and for differences in year of diagnosis between relatives.

Relation to proband	**OR (95 % CI)**	**Difference in year**	**OR (95 % CI)**	**Difference in year of diagnosis**
First degree				
Sibling	1.80 (1.57 – 2.07)	0.99 (0.97 – 1.02)	1.74 (1.59 – 1.94)	1.00 (0.98 – 1.02)
Child	1.57 (1.03 – 2.41)	1.01 (0.99 – 1.02)	1.92 (1.70 – 2.16)	0.99 (0.97 – 1.01)
Parent	1.66 (1.13 – 2.43)	1.01 (0.99 – 1.02)	1.97 (1.77 – 2.20)	0.99 (0.98 – 1.01)
Second degree				
Maternal half sib	1.79 (1.04 – 3.07)	0.95 (0.89 – 1.01)	0.99 (0.71 – 1.39)	1.03 (0.97 – 1.09)
Paternal half sib	1.10 (0.73 – 1.66)	1.04 (1.01 – 1.08)	1.76 (1.34 – 2.31)	1.00 (0.96 – 1.04)
Niece/Nephew	1.48 (1.13 – 1.95)	0.99 (0.98 – 1.00)	1.37 (1.22 – 1.54)	0.98 (0.96 – 1.00)
Third degree				
Cousins	1.12 (1.01 – 1.24)	1.00 (0.99 – 1.01)	1.13 (1.03 – 1.24)	0.99 (0.98 – 1.01)
Non biological				
Spouses			1.80 (1.34 – 2.41)	0.95 (0.90 – 1.02)



Supplementary Figure 1. Distribution of time at diagnosis for functional constipation (ICD-9 564A and ICD-10 K590) in relation to time at IBS diagnosis. Values above 0 means that the functional constipation diagnosis was registered after the IBS diagnosis.



Supplementary Figure 2. Distribution of time at diagnosis for functional diarrhoea (ICD-9 564F and ICD-10 K591) in relation to time at IBS diagnosis. Values above 0 means that the functional constipation diagnosis was registered after the IBS diagnosis.

Paper III

BMJ Open Gastroenterology

A Swedish national adoption study of risk of irritable bowel syndrome (IBS)

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To cite: Waehrens R, Zöller B, Sundquist J, *et al*. A Swedish national adoption study of risk of irritable bowel syndrome (IBS). *BMJ Open Gastro* 2017;4:e000156. doi:10.1136/bmjgast-2017-000156

► Additional material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjgast-2017-000156).

Received 27 May 2017
Revised 29 July 2017
Accepted 29 August 2017

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ABSTRACT

Objectives Irritable bowel syndrome (IBS) clusters in families, but the familial risk of IBS has not been determined in adoptees. Studying adoptees and their biological and adoptive parents is a strong study design for separating genetic from environmental causes of familial clustering. This nationwide study aimed to separate the biological (genetic) and familial environmental contribution to the familial transmission of IBS.

Methods We performed a family study for Swedish-born adoptees born from 1951 until 1995, and their biological and adoptive parents. The Swedish Multigeneration Register was linked to the Hospital Register (inpatients and outpatients) for the period 1964–2012 and the Swedish Outpatient Care Register for 2001–2012, and the Swedish Primary Healthcare register for 1989–2012. ORs for IBS were calculated for adoptees with an affected biological parent with IBS compared with adoptees without a biological parent with IBS. The OR for IBS was also determined in adoptees with an adoptive parent with IBS compared with adoptees without an adoptive parent with IBS. Heritability h^2 (±SE) was also determined.

Results The ORs for IBS were 1.67 in adoptees (95% CI 1.06 to 2.62) of biological parents diagnosed with IBS. The ORs for IBS were 0.88 in adoptees (95% CI 0.48 to 1.63) of adoptive parents diagnosed with IBS. The heritability was 19.5%±8.5%.

Conclusions The present study indicates that biological (genetic) factors are important for the familial clustering of IBS. The heritability calculated is in the range from twin studies and suggests that heritability may be estimated in adoptees.

Summary box

What is already known about this subject?

- Irritable bowel syndrome (IBS) is known to aggregate in families.
- Familial aggregation may be due to genetic or environmental factors.

What are the new findings?

- IBS is transmitted to adoptees from their biological parents but not to a major degree from their adoptive parents.
- The present study suggests that biological (genetic) factors are important in the familial aggregation of IBS among adoptees.

How might it impact on clinical practice in the foreseeable future?

- History of IBS in a biological parent is a risk factor for IBS in adoptees.
- Genetic studies in order to identify IBS-associated genetic variants might be worthwhile.

INTRODUCTION

Irritable bowel syndrome (IBS) is a common chronic functional bowel disorder characterised by abdominal pain or discomfort.[1 2] IBS is believed to be a complex disorder or trait,[3] that is, any phenotype that does not show classic Mendelian recessive or dominant inheritance due to a single gene locus.[4] IBS clusters in families and[5–9] familial ORs for IBS among first relatives has been reported to range between 1.75 and 3.1.[6–9] The reason for this may be due to shared genes or shared family environmental exposures.[10 11] Twin and adoptee studies can help to disentangle genetic and environmental influences.[11] Twin studies support the concept that IBS has both genetic and environmental contributions.[12–17] The heritability, that is, the fraction of the phenotype variability that can be attributed to genetic variation, has been determined to be 56.9% for functional gastrointestinal disorder in general and between 19% and 48% for IBS in twin studies.[12–19] Furthermore, extended family studies may also support a genetic cause of familial clustering.[9] While family studies suggest a genetic contribution, recent genetic studies have been able to identify genetic variants linked to IBS.[20–22]

Determining the contributions of genetic and family environmental factors is difficult in family studies of IBS. This is because most children, including dizygotic (DZ) and monozygotic (MZ) twins, grow up in their biological families.[10 11] An important assumption in twin studies is that MZ and DZ twins show similarities because of shared environmental factors so that the difference in concordance rates between MZ and DZ twins is only a reflection of genetic factors.[11] However, studies suggest

that MZ twins are treated more similarly than DZ twins, which theoretically may inflate the estimated heritability determined in twin studies.[23] It may therefore be of value to have other methods than twin studies as a determinant of the heritability for IBS. Studying adoptees is an appropriate alternative for analysing the genetic and shared familial environmental influence on the transmission of IBS.[11 24 25] Studies of adoptees offer an opportunity to understand the genetic transmission of IBS because adoptees do not grow up in their biological families.[11] Transmission of IBS from biological parents to offspring would therefore be explained by biological (genetic factors) or early life factors rather than family environment. In addition, transmission of IBS from adoptive parents to their non-biological offspring would be explained by family environment rather than genetic factors. To the best of our knowledge, no study has examined the familial aggregation in adoptees with IBS with the aim to shed new light on the familial transmission of IBS.

This study used the Swedish Inpatient Register, the Swedish Outpatient Care Register, a Swedish Primary Healthcare Register and the Swedish Multigeneration Register. Our study had two primary aims: (1) to examine the risk and heritability of IBS in adoptees with a biological parent affected by IBS and (2) to examine the risk of IBS in adoptees with an adoptive parent affected by IBS.

METHODS

We linked comprehensive registers and nationwide healthcare data from multiple sources to assess IBS among individuals in Sweden.[26–31] This linkage was based on the unique individual Swedish 10-digit personal ID numbers assigned at birth or immigration to all residents in Sweden for life. This information is nearly 100% complete. These numbers were replaced with serial numbers to preserve anonymity. We used data from the following sources:

1. The Swedish Multigeneration Register; this contains information on family relationships including adoptions. The register contains information on index persons registered in Sweden from 1 January 1961 and born from 1 January 1932 onwards.
2. The Lisa Register from Statistics Sweden (SCB), which contains annual data on education status from 1990 to 2012. It also contains the Swedish Standard Classification of Occupations 1996, which is a national version of the International Standard Classification of Occupations.
3. The Swedish Hospital Discharge Register, which contains all hospital diagnoses for all people in Sweden from 1964 to 2012. The register has had nationwide coverage since 1987.
4. The Hospital Outpatient Care Register, which contains information on diagnoses from all specialist outpatient clinics in Sweden from 2001 to 2012.
5. The Swedish Cause of Death Register, which contains data on date and cause of death from 1964 to 2012.
6. A nationwide Primary Healthcare register, which contains data from 1989 to 2016 (with 7 908 367 individuals in registers from 12 regions) (see online supplementary tables 1 and 2 and supplementary figure 1).
7. The Migration register, which contains data on immigration and emigration from 1892 to 2012.
8. Census registers, including individual addresses, available every 5 years between 1960 and 1990.
9. From 1991 Small Area Market Statistics (SAMS) data has been used to define a municipal subarea when you need to characterise a neighbourhood; the code comprises the county, the municipality and unique SAMS area (9200 in whole Sweden). Neighbourhood Deprivation Index (NDI) was created according to Winkleby *et al* and was based on educational status; income; unemployment and social welfare recipient.[32] A z score was calculated for each SAMS neighbourhood. The z scores, weighted by the coefficients for the eigenvectors, were then summed to create the index. The index was categorised into three groups: below 1 SD from the mean (low deprivation), above 1 SD from the mean (high deprivation) and within 1 SD of the mean (moderate deprivation). Higher scores reflect more deprived neighbourhoods.[32]

Study approval

The study was approved by the Ethics Committee of Lund University, Sweden, and was performed in compliance with the Helsinki Declaration. Informed consent was waived as a requirement by the ethics committee.

Definition of IBS

Cases of IBS in the Swedish Hospital Discharge Register, Outpatient Care Register and Primary Healthcare register were identified by the following International Classification of Diseases (ICD) codes: ICD-7 573.10, 573.21, 573.22; ICD-8 564.10, 564.11, 564.19; ICD-9 564B (IBS) and ICD-10 K58 (IBS). Main and all secondary diagnoses were used. The validity in the Hospital Discharge Register is generally 85%–95%.[30] The present study may not be representative of all patients with IBS in Sweden and may introduce a selection bias as the diagnosis of IBS is based on healthcare seeking.[33] However, familial risk in Sweden is similar using these national specialist register and primary healthcare data.[9] We excluded patients with IBS with possible gastrointestinal differential diagnosis, that is, coeliac disease, inflammatory bowel disease (IBD) and colorectal cancer. ICD codes are presented in online supplementary tables 3; and (5) adoptees not linked to at least one biological and at least one adoptive parent.[9]

Sample

The analyses were based on a dataset containing information on the entire Swedish population, including parental relationships. The dataset contains all Swedish-born children that were adopted (born 1951–1995) with respective biological or adoptive parents. We

Table 1 Descriptive statistics of 30 693 adoptees and their adoptive (n=51 634) and biological parents 49 912 (132 239 individuals in total)

	Adoptees (n=30 693)	Adoptive parents (n=51 634)	Biological parents (n=49 912)
Sex*			
Female	14 883 (48.49%)	22 547 (43.67%)	29 706 (59.52%)
IBS*	776 (2.53%)	660† (1.28%)	840‡ (1.68%)
Female	552 (1.80)	433 (0.84)	693 (1.39)
High education* (12 years or more)	9004 (29.34%)	9067 (17.67%)	4973 (9.96%)
NDI (high socioeconomic status)	407 (1.33%)	4575 (8.86%)	2426 (4.86%)
Occupation§	5775 (18.82%)	5832 (11.29%)	3475 (6.96%)
Age at IBS diagnosis (median and IQR)	43 (35–49)	71 (63–78)	62 (55–69)
Age at end of follow-up (median and IQR)	49 (43–54)	76 (68–83)	68 (60–75)

*Number of observations (%).
†Four adoptees had two adoptive parents with IBS.
‡Eight adoptees had two biological parents with IBS.
§Chief or occupation with a requirement for in-depth university competence.
IBS, irritable bowel syndrome; NDI, Neighbourhood Deprivation Index.

excluded adoptees from the study if they had: (1) died before age 16 years (death year–birth year); (2) migrated from Sweden before age 16 years (migration year–birth year); (3) died before 1964; (4) gastrointestinal differential diagnosis, that is, patients with IBS with coeliac disease, IBD and colorectal cancer were excluded. ICD codes are presented in online supplementary tables 3; and (5) adoptees not linked to at least one biological and at least one adoptive parent. All adoptive children who had lived with a biological parent were excluded according to Census (1960–1990) or SAMS (from 1991). For those born between 1951 and 1959, the status in the 1960 census was used.

We also excluded adoptees that had lived with their adoptive grandparent, aunt/uncle and sibling or with step-parents and their biological parent. A total of 30 693 adoptees remained in the study after exclusions. They constitute the study population in the cohort study. These adoptees could be linked to 51 634 adoptive parents and 49 912 biological parents.

After exclusions, we identified 2288 (1.73%) IBS cases. A total of 776 IBS cases were found in adoptees, 840 IBS cases in biological parents and 660 IBS cases in adoptive parents. Of the 2288 IBS cases, 55.07% (1260) were found in the Primary Healthcare register and 44.93% (1028) in the Hospital register. Among the hospital-diagnosed IBS cases, 330 (32.10%) were from the Hospital Discharge register n=330 and 698 (67.90%) from the specialist Outpatient register. Of all IBS cases, 5.68% (n=130) were identified with ICD-8, 3.63% (n=83) with ICD-9 and 90.69% (n=2075) with ICD-10. No case was identified with ICD-7.

Statistical calculations

We collected data on adoptees and their biological and adoptive parents from 1964 to 2012 in order to assess the genetic and environmental influences in IBS disease. We used a cohort design and a case-control approach. We conducted two main analyses: one using biological parents and one using adoptive parents. We used case-control exact matching method (1:5) by drawing a sample of affected adoptees as cases and matched control groups of unaffected adoptees.[34] The control groups were matched based on sex, birth year, county of birth and level of education. In the case-control study, we connected both groups using connection codes to their biological and adoptive parents.[35] For the case-control study, analyses were conducted using conditional logistic regression. For the cohort study, we used logistic regression. In the multivariate model, we used adoptees' birth year, sex, education of adoptees and county (region) of birth of adoptees as covariates. The estimated parameters

Table 2 The distribution of the birth years for adoptees and their adoptive and biological parents are shown

	n	Minimum	Maximum	Mean	SD	Median	Q1–Q3
Adopted offspring	30 693	1951	1995	1964	9	1963	1957–1968
Adoptive parents	51 634	1888	1979	1930	12	1928	1921–1938
Biological parents	49 912	1884	1980	1939	11	1939	1932–1946

Q1–Q3=IQR range.

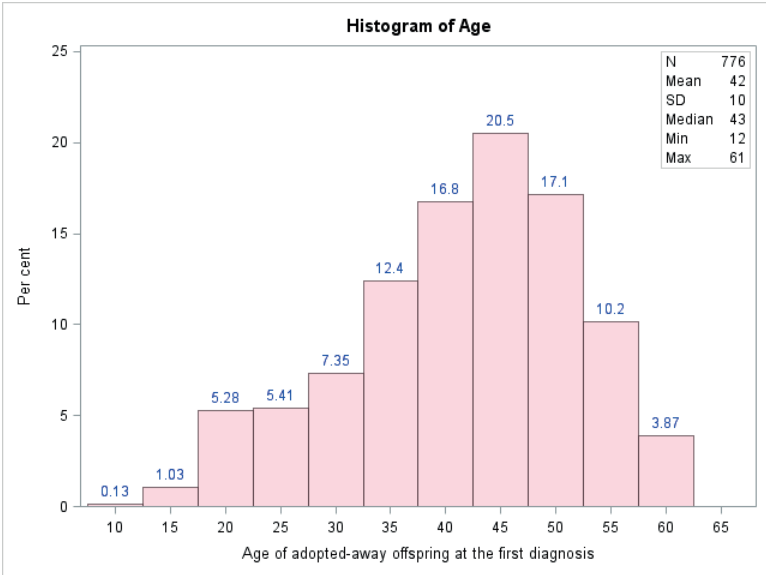

Figure 1 Age distribution for Swedish born (1951–1995) adoptees at first time diagnosis of irritable bowel syndrome.

were odds of an adoptee to IBS when at least one biological parent had got IBS relative to the odds of an adoptee to IBS when no biological parents had IBS, and similarly for adoptive parents. We also created a new age-stratified category variable based on an adopted child's age distribution after matching.

We used Falconer's regression, which is based on the liability of the threshold, to obtain heritability in adoptees of the biological parents.[36] Using the prevalence rate of the relatives of the biological probands and the controls from the case-control study, the heritability h^2 (and ±SE) was calculated.[36] We also used the approach described by Frisell *et al* to evaluate heritability.[37] Using the case-control procedure, we calculated tetrachoric correlations and heritability, according to the prevalence in the present cohort study and for a wide range of different population prevalences of IBS.[37] Under the assumption that only additive genetic factors contribute to similarity among relatives without any shared familial environment, the heritability of liability may be estimated as twice the observed tetrachoric correlation among first-degree relatives according to Falconer and Mackay.[38]

Statistical analysis was performed with SAS V.9.3 (SAS Institute) and for calculating heritability, we used R software (V.3.3.2). A level of p<0.05 (two-sided) was considered statistically significant.

RESULTS

Descriptive statistics

During the study period (1951–1995), a total of 2288 individuals were diagnosed with IBS (excluding individuals with a concomitant coeliac disease, IBD and

Table 3 Descriptive statistics of 30 693 adoptees with and without diagnosis of IBS

	No IBS (n=29 917)	IBS (n=776)	p Value
Sex			
Female	14 331 (47.90%)	552 (71.13%)	<0.0001*
High education (12 years or more)	8756 (29.27%)	248 (31.96%)	0.104*
NDI (high socioeconomic status)	403 (1.35%)	4 (0.52%)	0.053†
Occupation‡	5657 (18.91%)	118 (15.21%)	*0.009
Age at end of follow-up (years) (median and IQR)	49 (43–54)	48 (43–54)	0.239§

*X^2 test.
†Fisher's exact test.
‡Chief or occupation with a requirement for in-depth university competence.
§Wilcoxon test.
IBS, irritable bowel syndrome; NDI, Neighbourhood Deprivation Index.

Table 4 OR determined with logistic regression for IBS in adoptees with an affected biological or adoptive parent (cohort design)

		Biological parents		Adoptive parents	
Risk factors	Ref	Model 1*	Model 2†	Model 3*	Model 4†
IBS	0	1.66 (1.17–2.35)	1.63 (1.14–2.32)	0.77 (0.44–1.34)	0.75 (0.43–1.32)
Year of birth		1.01 (1.00–1.02)	1.01 (1.00–1.02)	1.01 (1.00–1.02)	1.01 (1.00–1.02)
Sex	Male	2.68 (2.29–3.14)	2.61 (2.23–3.06)	2.68 (2.29–3.14)	2.61 (2.23–3.06)
County (region)		1.00 (0.99–1.01)	1.00 (0.99–1.01)	1.00 (0.99–1.01)	1.00 (0.99–1.01)
Education		1.25 (1.13–1.39)	1.16 (1.04–1.29)	1.25 (1.13–1.39)	1.16 (1.04–1.29)

*Univariate model.
†Multivariate model.
IBS, irritable bowel syndrome; Ref, reference.

colorectal cancer). Table 1 shows the descriptive statistics for adopted offspring, biological parents and adoptive parents, that is, age, sex, educational attainments, NDI, occupation, IBS and age at IBS diagnosis and age at end of follow-up. Cases of IBS were more often found among females. The prevalence of IBS among biological parents was 1.68% (840/49 912), while among the adoptive parents it was 1.28% (660/51 634). Thus, there was no statistically significant difference between these groups (X^2=1.42, p=0.23). The adoptive parents with median age of 76 years (IQR 63–83 years) were older than biological parents with a median age of 68 years (IQR=60–75 years) at end of follow-up. Table 2 shows that the median birth year of adoptees was 1963 (IQR 1957–1968), for biological parents it was 1939 (IQR 1932–1946), while it was 1928 (IQR 1921–1938) for adoptive parents. The age distribution for Swedish born (1951–1995) adoptees at first time diagnosis of IBS is shown in figure 1. Biological parents also had lower education, lived in more deprived neighbourhoods and less often had an occupation with a requirement for in-depth university competence. In table 3, non-affected adoptees are compared with affected adoptees. Affected adoptees were significantly more often females (p<0.0001) and less often had an occupation with a requirement for in-depth university competence (p=0.009).

Cohort design

The estimated OR with 95% CI in the cohort design is shown in table 4. In the crude model, the OR for IBS in adoptees of biological parents of which at least one had IBS was increased, OR 1.66 (95% CI 1.17 to 2.35). The OR in the adjusted model (model 2) was also significantly increased, OR 1.63 (95% CI 1.14 to 2.32). The estimated OR for IBS in adoptees with an affected adoptive parent was not significantly increased either in the crude model (OR 0.77; 95% CI 0.44 to 1.34) or in the adjusted model (OR 0.75; 95% CI 0.43 to 1.329).

Case-control study

The results of the case-control study are shown in table 5. IBS in the adoptees was significantly associated with IBS in biological parents with an OR of 1.67 (95% CI 1.06 to 2.62) in adoptees with an affected biological parent. IBS in an adoptive parent was not significantly associated with IBS in adoptees (OR 0.88 (95 % CI 0.48 to 1.63)). The age-stratified ORs were not significantly increased.

Heritability

By using Falconer's method, we obtained the estimated heritability (h^2) in biological parents of adoptees with IBS. The heritability h^2 for IBS calculated from the case-control study was 19.5%±8.5%. The heritability was also determined by tetrachoric correlation in the case-control study with different estimates of the population prevalence of IBS (table 6). We did not know the prevalence in the particular source population exactly but based on previous studies we were able to choose a range of likely values and present a corresponding range of heritability estimates. The results are presented in

Table 5 Results for the matched case-control study (1:5)

	All*	Age≤45 years†	Age>45 years‡
ORs for IBS in adoptees with an affected biological parent	1.67 (1.06 to 2.62)	1.70 (0.93 to 3.08)	1.63 (0.82 to 3.25)
ORs for IBS in adoptees with an affected adoptive parent	0.88 (0.48 to 1.63)	1.03 (0.48 to 2.21)	0.69 (0.24 to 1.96)

ORs for IBS among adoptees with an affected biological or adoptive parent. Age-stratified ORs for IBS are also shown. Data are presented as OR (95% CI).
*Cases (n=569) and controls (n=2 845).
†Cases (n=315) and controls (n=1 575).
‡Cases (n=254) and controls (n=1 270).
IBS, irritable bowel syndrome.

Table 6 Heritability of irritable bowel syndrome based on estimated population prevalence and tetrachoric correlation in case-control study according to Frisell *et al*[37]

Exposed cases	Unexposed cases	OR	Prevalence	Tetrachoric correlation	Heritability (%)
26	543	1.67	0.5	0.08	16
26	543	1.67	1.0	0.09	17
26	543	1.67	3.0	0.10	20
26	543	1.67	5.0	0.11	22
26	543	1.67	10.0	0.12	24
26	543	1.67	15.0	0.125	25
26	543	1.67	20.0	0.133	27

table 6. The heritability varied from 16% in a population with 0.5% prevalence to 27% in a population with 20% prevalence. With a prevalence of 1.73% (table 1), as in the present population, the heritability was 18.3%.

DISCUSSION

This is the first study of IBS in adoptees and their biological and adoptive parents. An association was found between IBS disease in adoptees and their biological but not adoptive parents. The OR estimated in the present study is lower than among first-degree relatives that are not adopted according to previous published studies,[5–9] which suggests a contribution of familial environmental factors. However, familial environmental factors on their own are not enough to cause IBS among adoptees. IBS in adoptive parents does not increase the odds of IBS in adoptive children. The heritability h^2 could also be estimated among adoptees in the present study and was determined to be 19.5%±8.5% with Falconer's method and between 16% and 27% tetrachoric correlations depending on the prevalence of IBS in the population. These numbers are close to several published twin studies, although the heritability in published twin studies varies from 19% to 48%.[12–19] The present study adds to increasing evidence for genetic factors being important in IBS.[20–22] Recently genetic variants have been associated with IBS.[21 22]

The present study cannot rule out that shared environmental factors are of importance. Most adoptees who were diagnosed with IBS at first time were adults. We do not know whether any possible effects of familial environmental factors are weakened or not after adoptees become adults and move from their adoptive parents. Previously, an increased risk of IBS has been observed among spouses, which suggests an effect of shared adult familial environment.[9]

Strength of this study is that we used nationwide specialist care registers and a large primary healthcare database containing information on all primary healthcare visits from well-defined areas. This approach minimised any selection bias. A limitation of our present study is that we did not have access to how diagnosis of IBS was determined. However, the prevalence is low and similar to previously published Swedish register-based studies.[9 32] A limitation is that we do not know whether the Rome criteria were followed or not. Moreover, the criteria for IBS have also changed over time. IBS has not been evaluated in the present register but IBS diagnoses have been evaluated in an English primary healthcare register with a positive predictive value of 77%.[39] The sex and age distribution is as expected in an IBS population.[1–3] This may indirectly suggest that the ICD code mostly identifies patients with IBS in the used registers. However, it is possible that those seeking healthcare are the most severely affected cases. This might be an advantage in genetics because there are usually more genetic factors in more severe cases in complex traits, which could be an advantage of the present study.[4] The study population is limited to Swedish-born adoptees and is therefore only valid for Caucasians.

In conclusion, the present study shows that biological (genetic) factors are important in the familial transmission of IBS. We have also, in a novel way, determined the heritability with results that confirm twin studies, which suggests that future studies of genetics of IBS will be fruitful.

Acknowledgements The authors wish to thank the CPF's science editor Patrick Reilly for his useful comments on the text. The registers used in the present study are maintained by Statistics Sweden and the National Board of Health and Welfare.

Contributors RW, BZ, JS, KS and MP were involved in study design and execution, and finalising the paper. RW and BZ drafted the manuscript. All authors critically revised the paper and all authors approved the final draft submitted. All authors had full access to all the data (including statistical reports and tables) and take responsibility for the integrity of the data and the accuracy of their analysis.

Funding This work was supported by grants to BZ and KS and JS from the Swedish Research Council, ALF funding awarded to BZ, KS and JS, and the Swedish Heart-Lung Foundation (BZ).

Competing interests None declared.

Ethics approval Lund University.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The nationwide registers used in the present study are maintained by Statistics Sweden and the National Board of Health and Welfare.

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Supplementary Table 1.

Number of visits registered according to county in the Swedish Primary Healthcare register.

County (abbreviation)	County	Number of visits to Primary Healthcare	Percentage of total number of visits to Swedish Primary Healthcare
LB	LANDSTINGET BLEKINGE	3944618	1.8
LIV	LANDSTINGET I VÄRMLAND	4573075	2.09
LK	LANDSTINGET I KALMAR LÄN	3053602	1.39
LUL	LANDSTINGET I UPPSALA LÄN	1724872	0.79
LVN	LANDSTINGET I VÄSTERNORRLAND	6085525	2.78
NLL	NORRBOTTENS LÄNS LANDSTING	5031623	2.3
RH	REGION HALLAND	1512183	0.69
RK	REGION KRONEBERG	2752631	1.26
RS	REGION SKÅNE	21606265	9.87
RÖ	REGION ÖSTERGÖTLAND	12040082	5.5
SLL	STOCKHOLMS LÄNS LANDSTING	115380000	52.69
VGR	VÄSTRA GÖTALANDSREGIONEN	41274282	18.85

Supplementary Table 2.

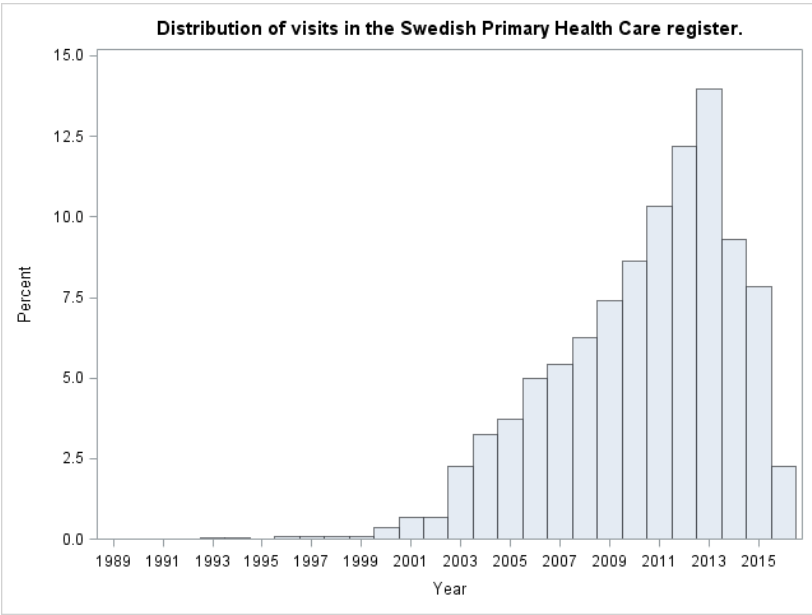
Number of visits registered according to year in the Swedish Primary Health Care register.

year	n	%
1989	143	0
1990	13427	0.01
1991	17664	0.01
1992	23722	0.01
1993	53254	0.02
1994	78909	0.04
1995	45497	0.02
1996	156309	0.07
1997	215761	0.1
1998	196243	0.09
1999	158877	0.07
2000	784658	0.36
2001	1487175	0.68
2002	1485746	0.68
2003	4985848	2.28
2004	7143041	3.26
2005	8186602	3.74
2006	10910794	4.98
2007	11918714	5.44
2008	13699043	6.26
2009	16228411	7.41
2010	18931696	8.65
2011	22618457	10.33
2012	26670863	12.18
2013	30565154	13.96
2014	20337155	9.29
2015	17147817	7.83
2016	4919300	2.25

Supplementary Table 3.

IBS patients with coeliac disease, inflammatory bowel disease, and colorectal cancer were excluded. ICD codes for these differential diagnoses are shown.

	ICD-10	**ICD-9**	**ICD-8**	**ICD-7**
Coeliac disease	K900	579A	269.00	286.00
Inflammatory bowel disease (IBD)	K50, K51	555, 556	563	572
Colorectal cancer.	C18, C19, C20, C21	153, 154	153, 154	153, 154



Supplementary Figure 1

Number of visits registered according to year in the Swedish Primary Healthcare register.

Paper IV

SCANDINAVIAN JOURNAL OF GASTROENTEROLOGY, 2017
https://doi.org/10.1080/00365521.2017.1398345

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ORIGINAL ARTICLE

Perinatal and familial risk factors for irritable bowel syndrome in a Swedish national cohort

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ABSTRACT

Objective: Studies of the importance of perinatal factors for the development of irritable bowel syndrome (IBS) are sparse. We conducted a large national cohort study to examine perinatal and familial risk factors for IBS.

Material and methods: A national cohort of 1,963,685 persons who were born in Sweden in 1973–1992 (identified from the Swedish Birth Registry) were followed up for adult (18 years and older) IBS incidence in the Swedish Patient Register through 2010 (maximum age 38 years). There were 24,633 IBS cases in 46,784,296 person-years of follow-up.

Results: After adjusting for potential confounders, significant risk factors for IBS included caesarean (HR = 1.10, 95% confidence interval [CI] 1.05–1.11, $p < .001$), low birth weight (<2500g) (HR = 1.11, 95%CI 1.01–1.22, $p = .02$), being second in birth order (HR = 1.04, 95%CI 1.01–1.08, $p = .01$), foetal growth ≥1 SD (HR = 1.06, 95%CI 1.00–1.11, $p = .05$), young maternal age (<20 years) (HR= 1.09, 95%CI 1.02–1.17, $p = .02$), maternal marital status (divorced/widowed) (HR = 1.12, 95%CI 1.08–1.17, $p < .001$), maternal education of 10–11 years (HR = 1.04, 95%CI 1.01–1.08, $p = .01$), maternal education of 12–14 years (HR = 1.06, 95%CI 1.01–1.11, $p = .03$), parental history of IBS (HR = 1.54, 95%CI 1.42–1.66, $p < .001$), parental history of anxiety (HR = 1.21, 95%CI 1.17–1.26, $p < .001$) and parental history of depression (HR = 1.09, 95%CI 1.02–1.17, $p = .02$). Protective factors were male sex (HR = 0.36, 95%CI 0.35–0.37, $p < .001$) and old maternal at delivery (≥35 years) (HR = 0.95, 95%CI 0.90–1.00, $p = .03$).

Conclusions: In this large cohort study, several perinatal and familial factors were associated with an increased risk of IBS independently, suggesting that perinatal and familial factors may play an important long-term role in the aetiology of IBS.

ARTICLE HISTORY
Received 14 July 2017
Revised 19 September 2017
Accepted 6 October 2017

KEYWORDS
Irritable bowel syndrome; epidemiology; peripartum period; cohort studies; risk factors

Introduction

Irritable bowel syndrome (IBS) is a common, chronic, relapsing, functional gastrointestinal disorder with a pooled global prevalence of 11% [1]. New diagnostic criteria from Rome IV define IBS as a disease with recurrent abdominal pain at least one day a week within the last 3 months related to defaecation and associated with a change in frequency and/or form of stool; onset beginning at least six months before diagnosis [2]. The economic burden for the society is substantial [3,4] and the health-related quality of life for patients with IBS is lower than in patients with diabetes or end stage renal disease [5].

The pathogenesis of IBS has focused on visceral hypersensitivity, abnormalities in motility, brain–gut interaction, infection in the intestines and psychosocial stress. More recently, altered gut immune activation, the intestinal microbiome and intestinal permeability have emerged as pathogenic factors in some patients with IBS [6,7]. According to Chitkara et al., these environmental exposures may occur during childhood or early adulthood such as the early manifestation of gastrointestinal symptoms, affluent childhood socio-economic status, prenatal, infant and childhood trauma and social learning of illness behaviour may affect adult development of IBS [8].

Perinatal risk factors in humans, such as small size and relative thinness at birth, have been shown to play a role in adult disease such as metabolic syndrome, type-2 diabetes mellitus, coronary heart disease and osteoporosis [9]. Also, in gastrointestinal disease, early adverse life events may play an important role [10]. A maternal mice separation model, that is, separation of the mouse pup from the dam for shorter or longer periods during the postnatal period, has shown to increase visceral hypersensitivity and change motility – two of the cornerstones in the pathophysiology of IBS [10]. In a few studies, perinatal factors have been shown to be associated with risk of developing IBS in adulthood [11–14]. In a twin study, Bengtson et al. found a 2.4-fold increased risk of IBS in adult age in twins with a birth weight below 1500 g, compared with twins with greater birth weights, when adjusted for gestational age [11]. The authors suggested that restricted foetal growth in pregnancy, rather than prematurity, contributed to IBS [11]. Raslau et al. also found that lower birth weight was a risk factor for adult IBS in a population-based nested case–control study [12]. They found no

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difference in risk of IBS in adulthood in delivery method, post-natal feeding, maternal age at delivery and antibiotic exposure [12]. Koloski et al. conducted a study of a random population sample from Sydney [13]. Bedroom sharing and pet exposure was associated with IBS development. Moreover, shorter breast feeding was also associated with IBS. A non-significant trend was observed for higher numbers of caesarean deliveries in IBS. Prematurity was not associated with IBS [13]. In a population-based study Brummond et al. found support for a possible birth cohort phenomenon in IBS, which suggests that early-life risk factors may play a role in the development of IBS [14].

We conducted a national cohort study in Sweden, to examine the association between perinatal and familial factors and IBS. A national cohort of infants born in 1973–1992 was followed through 2010 for adult (18 years and older) IBS. Information on perinatal and family characteristics for IBS were obtained from the Swedish Birth Registry, the Swedish Multi-Generation Register and the Swedish Patient Register. We tested whether birth year, sex, foetal growth, gestational age at birth, birth weight, birth length, multiple birth status, birth order, maternal age at delivery, and certain family characteristics is associated with an increased risk of IBS.

Methods

Study population

We identified individuals in the Swedish Birth Registry [15] who were live-born from 1973 through 1992, and living in Sweden at age 18 years. We excluded 5293 (0.3%) persons who had missing information for birthweight, and 45,542 (2.2%) others who had missing information for gestational age at birth. Individuals with any inpatient or outpatient diagnosis in the Swedish Patient Register of gastrointestinal, neurological and chromosomal anomalies or syndromes were also excluded (codes 740-743, 749-751 and 759 in ICD-8, 740-742, 749–751, 758 and 759.8 in ICD-9, and Q00-Q07, Q35-Q45, Q87 and Q90-Q99 in ICD-10) ($n = 1613$, 0.1%). To remove possible coding errors, we excluded 6598 (0.3%) who had a reported birthweight more than four standard deviations (SD) above or below the mean birthweight for gestational age and sex based on a Swedish reference growth curve. To examine the risk of incident IBS in young adulthood, we excluded 1292 (0.1%) others with a prior diagnosis of IBS before age 18 years (564.19 in ICD-8; 564B in ICD-9; and K58 in ICD-10). A total of 1,963,685 individuals (96% of the original cohort) remained for inclusion in the study.

IBS ascertainment

The study cohort was followed up for the earliest incidence of IBS from age 18 years through 31 December 2010 (maximum attained age was 38 years). IBS was identified using primary and all secondary diagnoses from the International Classification of Diseases (ICD), revisions 9 and 10 (codes ICD-9 564B; and ICD-10 K58) in the Swedish Patient Register (inpatient and outpatients). We also excluded IBS patients with gastrointestinal differential diagnosis, that is, coeliac disease (ICD-9 579A and ICD-10 K900), inflammatory bowel disease (ICD-9 555 and 556, and ICD-10 K50 and K51), and colorectal cancer (ICD-9 153 and 154 and ICD-10 C18, C19, C20, C21) (all primary and secondary diagnosis) [16]. The Swedish Patient Register contains all primary and secondary hospital discharge diagnoses for six populous counties in southern Sweden starting in 1964, and with nationwide coverage since 1987; and the Swedish Patient Register also contains all outpatient specialist clinic diagnoses nationwide starting in 2001 [17]. The Cause of Death Registry includes all deaths nationwide since 1964 for all persons registered in Sweden at the time of death. The Cause of Death Registry was used for censoring individuals in the Cox proportional hazards regression models and also for the exclusion of individuals who died before age 18 years. The validity of the Hospital Discharge Register is generally 85–95% [17].

Perinatal, familial and comorbidity variables

Perinatal and familial characteristics that may be associated with IBS were identified from the Swedish Birth Registry and national census data, which were linked using an anonymous personal identification number [18,19]. The multi-generation register was used to link offspring to parents to define family history of IBS, anxiety and depression based on diagnoses from the Swedish Patient Register. The following variables were examined as predictors of interest or adjustment variables: birth year (modelled as a continuous variable); sex (male or female); gestational age at birth (based primarily on maternal report of last menstrual period in the 1970s, at which time ultrasound estimation was gradually introduced until it was used exclusively starting in the 1990s; modelled as a categorical [$<$37, 37–41, $>$42 weeks]; foetal growth (a standardised variable defined as the number of SD from the mean birthweight for gestational age and sex based on a Swedish reference growth curve [20], modelled as a categorical [< -2; -2 to < -1; -1 to <1; ≥ 1 SD] variable); birthweight (modelled as a categorical [$<$2500, 2500–3999, $\geq$4000 g] variable); birth length (crown-heel length in cm, modelled as a categorical [$<$48, 48–52, $\geq$53 cm] variable); multiple birth (singleton vs. twin or higher order); birth order (1, 2, $\geq$3); maternal age at birth ($<$20, 20–24, 25–29, 30–34, $\geq$35 years); caesarean (yes/no), maternal marital status (married/cohabiting, never married, divorced/widowed); maternal and paternal education level (compulsory high school or less [$<$9 years], practical high school or some theoretical high school [10–11 years], theoretical high school and/or some college [12–14 years], college and/or post-graduate study [$\geq$15 years]; examined separately for mothers and fathers); and parental history of IBS (yes or no; identified from the Swedish Hospital Registry in 1964–2010 and Outpatient Registry in 2001–2010 [codes 573.21 in ICD-7, 564.19 in ICD-8; 564B in ICD-9; K58 in ICD-10]. Parental history of anxiety (codes 310-313 in ICD-7; 300 in ICD-8; 300A-D, 308, 309 in ICD-9; and F40-F43 in ICD-10) and parental history of depression (codes 301.10, 314.99 in ICD-7; 296.00, 298.00 in ICD-8; 296B, 311, in ICD-9; and F32-F33 in ICD-10) were also registered.

Statistical analysis

Cox proportional hazards regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for associations between perinatal and familial variables, and IBS. Individuals were censored at the time of death, or at the time of emigration as determined by the absence of a Swedish residential address in census data. Two different adjusted models were used: The first was adjusted for birth year and sex, and the second was further adjusted for other variables (foetal growth, gestational age at birth, multiple birth status, birth order, caesarean, maternal age at delivery, maternal marital status, maternal and paternal education (separately), parental history of IBS, parental history of anxiety and parental history of depression). Birthweight and birth length were each examined in separate models as alternatives to the standardised foetal growth variable. First-order interactions between sex and other variables were examined using likelihood ratio tests. However, no significant interactions were identified. A Chi-squared trend test was used to compare differences between those who developed IBS and those who did not. All statistical tests were two sided and used an α-level of 0.05.

Study approval

The study was approved by the Ethics Committee of Lund University, Sweden and was performed in compliance with the Declaration of Helsinki. Informed consent was waived as a requirement by the ethics committee.

Results

Descriptive statistics

Among the 1,963,685 persons in this cohort 24,633 (1,25%) from the Swedish Medical Birth Register were affected by specialist treated IBS during follow-up. The sum of follow-up time was 46,784,296 years corresponding to a specialist treated IBS incidence rate of 52.7 (95% CI 52.0–53.3) per 100,000 person years. Sex was strongly associated with specialist treated IBS during follow-up: 28.1% of IBS patients were men and 71.9% of IBS patients were women ($p < .001$) (Table 1). IBS during follow-up was associated with all studied variables in Table 1. For instance, we found a significant trend towards higher foetal growth and risk of IBS in young adulthood per additional one standard deviation, a significant trend towards lower birthweight and risk of IBS per 1000 g, and also a significant trend towards lower birth length per cm (Table 1). There was also a significant trend towards lower maternal age at delivery and risk of IBS and a significant trend towards lower maternal and paternal education and risk of IBS in young adulthood was found. Family history of IBS, anxiety, and depression was also associated with IBS during follow-up.

Risk of IBS

In the model adjusting for birth year and sex, the HR for being a male was 0.36 (95% CI 0.35–0.37; $p < .001$), which remained significant when adjusting for all other factors ($p < .001$) (Table 2). Lower birth year was also associated with lower risk of IBS (HR = .96, 95% CI 0.96–0.96, $p < .001$).

Perinatal factors

Foetal growth < -2 standard deviations (SD) was a significant risk factor for IBS when adjusting for birth year and sex, but non-significant when adjusting for all other factors ($p = .16$). Foetal growth >1 SD above the mean was associated with an increased risk of IBS when adjusting for birth year and sex (HR = 1.07, 95% CI 1.03–1.12, $p < .001$) and remained borderline significant when adjusting for all other factors (HR = 1.06, 95% CI 1.00–1.11, $p = .05$) (Table 2). Birthweight <2500 g was associated with an increased risk of IBS when adjusting for birth year and sex and remained significant when adjusting for all other factors as well (HR = 1.11, 95% CI 1.01–1.22, $p = .02$). Caesarean resulted in an increased risk of adult IBS in both models (HR = 1.12, 95% CI 1.07–1.18, $p < .001$ and 1.10, 95% CI 1.05–1.15, $p < .001$). Being second but not third or more in birth order was associated with IBS in the multivariate model ($p = .01$). Multiple birth status showed no significant association.

Socioeconomic factors

Maternal age at delivery <20 years of age was significantly associated with increased risk of IBS in both the adjusted models ($p = .013$ and .02). A decreased risk of IBS for maternal age ≥ 35 years of age was also significant in both models ($p = .0343$ and .03). Having a divorced/widowed mother resulted in a significantly increased risk of IBS in adult life in both models (HR = 1.15, 95% CI 1.10–1.19, $p < .001$ and HR = 1.12, 95% CI 1.08–1.17, $p < .0001$, respectively). Maternal education 10–11 years was associated with Increased risk of IBS in both models (HR = 1.04; 95% CI: 1.01–1.08 $p = .008$ and .01, respectively). Maternal education 12–14 years were also associated with increased risk, children with mothers with the highest education had no increased risk of IBS. Paternal education had no significant influence on IBS risk during follow-up.

Inherited factors

A parental history of IBS was strongly associated with an increased risk of adult IBS in both models (HR = 1.58, 95% CI 1.46–1.71, $p < .001$ and HR = 1.54; 95% CI 1.42–1.66, $p < .0001$). A parental history of anxiety resulted in an increased risk of adult IBS in both models (HR = 1.25, 95% CI 1.20–1.30, $p < .001$ and HR = 1.21, 95% CI 1.17–1.26, $p < .0001$). A slight increased risk of IBS was also observed in children with parental history of depression (HR = 1.18, 95% CI 1.10–1.27, $p < .001$ and HR = 1.09, 95% CI 1.02–1.17, $p = .02$) (Table 2).

Multiple risk factors

There was no multiplicative interaction between risk factors. The HRs for a combination of risk factors may therefore be calculated by multiplication of the HRs for the individual risk

Table 1. Baseline characteristics of individuals in the Swedish Birth Registry who were alive-born from 1973 through 1992 and living in Sweden at age of 18 years according to incident irritable bowel syndrome (IBS) during follow up from 18 years of age through 2010.

	Population					
	(*N* = 1,963,685)	%	IBS (*N* = 24633)		No IBS (*N* = 1,939,052)	
Sex						
Male	1,010,143	51.4	6923	28.1	1,003,220	51.7
Female	953,542	48.6	17,710	71.9	935,832	48.3
Fetal growth (SD)			<0.001			
<−2	26,725	1.4	211	0.9	26,514	1.4
−2 to <−1	72,844	3.7	496	2.0	72,348	3.7
−1 to <1	1,684,586	85.8	21,597	87.7	1,662,989	85.8
≥1	179,530	9.1	2329	9.5	177,201	9.1
Per additional 1 SD (trend test)			<0.001			
Gestational age at birth (weeks)						
<37	89,300	4.5	1150	4.7	88,150	4.5
37–41	1,687,272	85.9	20,984	85.2	1,666,288	85.9
≥42	187,113	9.5	2499	10.1	184,614	9.5
Per additional 1 week (trend test)			<0.001			
Birthweight (g)						
<2500	59,420	3.0	897	3.6	58,523	3.0
2500–3999	1,561,919	79.5	20,020	81.3	1,541,899	79.5
≥4000	342,346	17.4	3716	15.1	33,8630	17.5
Per 1000 g (trend test)			<0.001			
Birth length (cm)						
<48	175,733	8.9	2552	10.4	173,181	8.9
48–52	1,461,652	74.4	18,591	75.5	1,443,061	74.4
≥53	316,845	16.1	3387	13.7	313,458	16.2
Unknown	9455	0.5	103	0.4	9352	0.5
Per cm (trend test)			<0.001			
Multiple birth status						
Singleton	1,938,594	98.7	24,363	98.9	1,914,231	98.7
Twin or higher order	25,091	1.3	270	1.1	24,821	1.3
Trend test			<0.001			
Birth order						
1	822,291	41.9	10,261	41.7	812,030	41.9
2	721,346	36.7	9289	37.7	712,057	36.7
≥3	420,048	21.4	5083	20.6	414,965	21.4
Per 1 higher birth order (trend test)		0.0	<0.001			
Maternal age at delivery (years)		0.0				
<20	60,737	3.1	934	3.8	59,803	3.1
20–24	465,279	23.7	6224	25.3	459,055	23.7
25–29	738,391	37.6	9300	37.8	729,091	37.6
30–34	487,050	24.8	5833	23.7	481,217	24.8
≥35	212,228	10.8	2342	9.5	209,886	10.8
Per each higher category (trend test)			<0.001			
Maternal marital status						
Married/cohabiting	1,377,314	70.1	17,705	71.9	1,359,609	70.1
Never married	419,262	21.4	4191	17.0	415,071	21.4
Divorced/widowed	167,109	8.5	2737	11.1	164,372	8.5
Trend test			<.000			
Maternal education (years)						
<9	594,773	30.3	7791	31.6	586,982	30.3
11 October	709,863	36.1	8846	35.9	701,017	36.2
14 December	170,224	8.7	2055	8.3	168,169	8.7
≥15	488,825	24.9	5941	24.1	482,884	24.9
Per each higher category (trend test)			<0.001			
Paternal education (years)						
≤9	733,325	37.3	9667	39.2	723,658	37.3
11 October	534,947	27.2	6276	25.5	528,671	27.3
14 December	242,792	12.4	3206	13.0	239,586	12.4
≥15	452,621	23.0	5484	22.3	447,137	23.1
Per each higher category (trend test)			<0.001			
Caesarean						
No	1,799,711	91.6	22,652	92.0	1,777,059	91.6
Yes	163,974	8.4	1981	8.0	161,993	8.4
Per each category (trend test)			<0.001			
Parental history of IBS						
Yes	206,792	10.5	642	2.6	32,417	1.7
No	1,756,893	89.5	23,991	97.4	1,906,635	98.3
Trend test			<0.001			
Parental history of anxiety						
Yes	206,792	10.5	3059	12.4	203,733	10.5
No	1,756,893	89.5	21,574	87.6	1,735,319	89.5
Trend test			<0.001			
Parental history of depression						
Yes	58,217	3.0	831	3.4	57,386	3.0
No	1,905,468	97.0	23,802	96.6	1,881,666	97.0
Trend test			<0.001			

Chi-square trend test was used to compare perinatal and familial factors between those who were affected and not affected by IBS during follow-up.

Table 2. Age- and sex-adjusted and multivariable hazard ratios (HR) with 95% confidence interval (CI) and *p* values for incident irritable bowel syndrome (IBS) during follow-up in a nationwide Swedish birth cohort (1973–1992) from the age of 18 years through until 2010 (ages 18–38 years).

	Adjusted model 1[a]				Adjusted model 2[b]			
	HR	95% CI		*p* value	HR	95% CI		*p* value
Sex								
Male	0.36	0.35	0.37	<.001	0.36	0.35	0.37	<.0001
Female	1.00				1.00			
Birth year	0.96	0.96	0.96	<.001	0.96	0.96	0.96	<.001
Fetal growth (SD)								
< −2	1.20	1.05	1.38	<.001	1.12	0.96	1.32	.16
−2 to < −1	1.03	0.94	1.13	.577	1.01	0.92	1.11	.81
−1 to <1	1.00				1.00			
≥1	1.07	1.03	1.12	<.001	1.06	1.00	1.11	.05
Gestational age at birth (weeks)								
<37	1.10	1.03	1.16	.002	0.96	0.88	1.05	.35
37–41	1.00				1.00			
>42	0.98	0.94	1.02	.383	0.97	0.93	1.02	.20
Birthweight (g)								
<2500	1.18	1.10	1.26	<.001	1.11	1.01	1.22	.02
2500–3999	1.00				1.00			
>4000	0.98	0.95	1.02	.307	0.98	0.94	1.02	.26
Birth length (cm)								
<48	1.08	1.03	1.12	<.001	1.02	0.97	1.07	.43
48–52	1.00				1.00			
≥53	1.01	0.97	1.05	.711	1.03	0.98	1.07	.26
Unknown	1.16	0.95	1.40	.141	1.08	0.88	1.31	.47
Multiple birth status								
Singleton	1.00				1.00			
Twin or higher order	0.92	0.81	1.03	.146	0.91	0.81	1.03	.13
Birth order								
1	1.00				1.00			
2	1.02	1.00	1.05	.095	1.04	1.01	1.08	.01
≥3	0.99	0.96	1.03	.676	1.02	0.98	1.06	.27
Maternal age at delivery (years)								
<20	1.09	1.02	1.17	.013	1.09	1.02	1.17	.02
20–24	1.02	0.98	1.05	.363	1.02	0.98	1.05	.40
25–29	1.00				1.00			
30–34	0.99	0.96	1.02	.5013	0.99	0.96	1.02	.48
≥35	0.95	0.91	1.00	.0343	0.95	0.90	1.00	.03
Maternal marital status								
Married/cohabiting	1.00				1.00			
Never married	1.01	0.98	1.05	0.603	0.99	0.96	1.03	0.67
Divorced/widowed	1.15	1.10	1.19	<0.001	1.12	1.08	1.17	<.0001
Maternal education (years)								
<9	1.00				1.00			
10–11	1.04	1.01	1.08	.008	1.04	1.01	1.08	.01
12–14	1.05	1.00	1.10	.073	1.06	1.01	1.11	.03
>15	1.00	0.97	1.04	.959	1.02	0.98	1.06	.31
Paternal education (years)								
≤9	1.00				1.00			
10–11	1.04	1.01	1.07	.025	1.03	1.00	1.07	.06
12–14	1.02	0.98	1.06	.301	1.03	0.99	1.07	.15
≥15	1.00	0.97	1.04	.802	1.02	0.99	1.06	.22
Caesarean								
No	1.00				1.00			
Yes	1.12	1.07	1.18	<.001	1.10	1.05	1.15	<.001
Parental history of IBS								
No	1.00				1.00			
Yes	1.58	1.46	1.71	<.001	1.54	1.42	1.66	<.0001
Parental history of anxiety								
No	1.00				1.00			
Yes	1.25	1.20	1.30	<.001	1.21	1.17	1.26	<.0001
Parental history of depression								
No	1.00				1.00			
Yes	1.18	1.10	1.27	<.001	1.09	1.02	1.17	.02

[a]Adjusted for birth year and sex.
[b]Adjusted for birth year, sex and all other factors in table.
Birthweight and birth length were each examined in separate models as alternatives to the standardised foetal growth variable. The reference category for all variables is indicated by an HR of 1.00. SD = standard deviation. Birth year was modelled as a continuous variable.

factors. Figure 1 shows the HRs for men (1–5) and women (6–10) with increasing numbers of risk factors compared with men (reference = 1) with no risk factor. Men born with caesarean section, those living alone, those with a family history of anxiety, and those with a family history of IBS had a HR of 2.30 compared with men without these risk factors. Women born with caesarean section, those living alone, those with a family history of anxiety, and those with a family history of

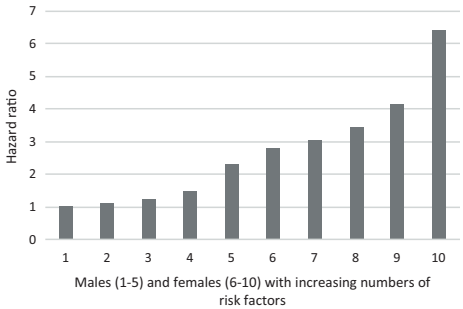

Figure 1. Hazard ratios (HR:s) for men (1–5) and women (6–10) with increasing numbers of risk factors compared with men (reference = 1) without any risk factor. Reference = 1 = men without risk factors, 2 = men born with caesarean, 3 = 2 + living alone, 4 = 3 + family history of anxiety, 5 = 4 + family history of IBS, 6 = women without risk factors, 7 = women born with caesarean, 8 = 7 + living alone, 9 = 8 + family history of anxiety, and 10 = 9 + family history of IBS.

IBS had a HR of 6.38 compared with men without these risk factors.

Discussion

In this large national cohort study, we identified several perinatal and familial factors associated with developing IBS in adulthood. Low birth weight and caesarean were significant risk factors for IBS in young adulthood, when adjusting for birth year, sex and all other factors. Foetal growth $\geq$ 1 SD above the mean was a significant risk factor, when adjusting for birth year and sex and remained borderline significant, when adjusting for all other risk factors. The finding that low birth weight is a risk factor for adult IBS has been shown in two other studies [11,12]. One found increased risk only in newborn with a birth weight $\leq$ 1500 g [11] and the other found lower normal birth weight to be a risk factor but did not have enough subjects meeting the criteria for birth weight = < 2500 grams to be analysed [12]. We examined newborn with a birth weight $\leq$ 2500 g. The finding that caesarean section is a risk factor for IBS in our study has not been confirmed in two other studies where delivery method was found not to be a risk factor [12,13], though a non-significant trend was observed for higher numbers of caesarean deliveries in IBS by Koloski et al. [13]. The difference might be due to lower statistical power in previous studies. For instance, the study by Raslau et al. was powered to detect only large odds ratios [12]. In some studies, the microbiota in individuals with IBS differs from individuals with no IBS [21]. The infants gut microbiota differs according to the mode of delivery. Infants born vaginally are colonised with their mother's bacteria and the gut microbiota shows a greater diversity and abundance compared to newborns delivered by caesarean [22]. A recent review of seven studies has shown that the microbiota in a newborn delivered with caesarean is different from vaginally born infants but that the difference disappears within the first six months of life, though [22]. Our finding of an association between caesarean and future IBS risk is therefore of interest. Reasons for caesarean section are acute conditions like dystocia, placenta praevia or foetal distress, but also because it is a choice of the mother, who wishes not to give birth vaginally. We therefore cannot exclude that IBS is due to any of the conditions associated with caesarean. Thus, the reason for the increased risk of IBS in young adulthood in caesarean born infants is not clear.

We also looked at family risk factors in this study. Parental history of anxiety and depression were also risk factors. Young maternal age was also a risk factor while old maternal age was protecting. Maternal age was not a risk factor in the smaller study by Raslau et al. [12]. We also found that maternal marital status affect the IBS risk. Children with a divorced/widowed mother had higher risk of IBS during follow-up. Family history as a risk factor for IBS has been shown in some studies [16,23,24], which is confirmed in the present follow-up study. The present study also found and association between parental history of depression and anxiety and risk of IBS. Previously, we have reported an association in sibling pairs between IBS and anxiety and depression [16]. Thus, it is likely that there are common familial (genetic or non-genetic) factors predisposing for IBS and anxiety/depression. An affluent childhood, both family income and education, has been shown to play an independent risk for development of IBS in adulthood [8,25]. However, in the present study, no increased risk was observed in offspring to the highest educated parents, though children with mothers with 10–11 and 12–14 years of education had a minimally higher risk of IBS compared with those with the lowest educated parents.

An important strength of the present study was its ability to examine the association between perinatal risk factors and risk of IBS in young adulthood with the use of a nationwide birth cohort there all data were obtained from large nationwide registers. The results were adjusted for other perinatal risk factors as well as other broadly measured potential confounders. Bias that may potentially result from self-reporting was prevented with the use of registry-based data. The Swedish personal ID numbers (replaced by serial numbers) are a valuable tool for linking medical registers, and allow for almost 100% coverage of the Swedish healthcare system [26]. Study limitations include that only specialist treated cases of IBS in Sweden are included, and the diagnosis of IBS is thus more likely to be correct. However, the diagnosed individuals are likely to represent the most severely affected IBS patients. It is possible that other risk factors are more important in the less severe cases. However, previously we have found similar familial inheritance among specialist treated and primary health care–treated IBS patients [16]. The diagnostic criteria have changed over time, which is a limitation of the study [27,28]. Five different sets of diagnostic criteria for IBS have been used: the Manning criteria 1978 [27], the Rome I criteria (1994), the Rome II criteria (1999–2000), the Rome III criteria (2006) and the Rome IV criteria (2016) [28]. The diagnostic criteria may affect the incidence and prevalence of IBS [29,30]. Manning criteria usually gives higher prevalence than Rome criteria [29,30]. Rome positive IBS patients have been suggested to form a

subgroup of Manning positive IBS patients with more severe abdominal symptoms, more psychopathology, and more frequent use of the health care system [30]. The follow up time in the present study (1991–2010) was mainly during the period when the Rome criteria were used, which is a strength of the present study using the stricter Rome criteria. Moreover, the Swedish Patient register has been validated for IBS [31]. IBS diagnosis was judged to be correct in 70% of cases. In further 9.6% of cases, IBS was a probable diagnosis. Thus, in totally, 79.6% IBS cases were correct or a probable diagnosis. Moreover, only 5% of cases had an obvious incorrect IBS diagnosis [31].

In summary, this large national cohort study found that caesarean section and low birth weight was associated with IBS in young adulthood. Higher foetal growth was borderline associated with IBS in young adulthood. A family history of IBS and parental history of anxiety and depression, young maternal age at delivery, marital status (divorced/widowed) were all associated with an increased risk of IBS in young adulthood. The association with caesarean section is of special interest and warrants further investigation in order to delineate the mechanisms involved.

Acknowledgements

The registers used in the present study are maintained by Statistics Sweden and the National Board of Health and Welfare. This work was supported by grants to Bengt Zöller and Kristina Sundquist and Jan Sundquist from the Swedish Research Council, ALF funding awarded to Bengt Zöller, Kristina Sundquist and Jan Sundquist, and the Swedish Heart-Lung Foundation (Bengt Zöller).

Disclosure statement

The authors report no conflicts of interest.

Funding

This work was supported by grants to Bengt Zöller and Kristina Sundquist and Jan Sundquist from the Swedish Research Council, ALF funding awarded to Bengt Zöller, Kristina Sundquist and Jan Sundquist, and the Swedish Heart-Lung Foundation (Bengt Zöller).

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