



Epidemiological study on the prevalence and natural history of functional gastrointestinal disorders in Iceland

Linda Björk Ólafsdóttir

Thesis for the degree of Philosophiae Doctor

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**Faraldsfræðileg rannsókn
á algengi og sjúkdómsgangi starfrænna
meltingarfærakvilla á Íslandi**

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ÁGRIP Á ÍSLENSKU

Inngangur

Langvinn og endurtekin einkenni frá meltingarvegi sem ekki er hægt að finna neinar vefrænar eða lífefnafræðilegar skýringar á eru nefnd starfræn einkenni frá meltingarvegi (SEM). SEM eru algeng og allt að helmingur tíma sérfræðinga í meltingarfærasjúkdómum fer í að sinna þeim. SEM skiptast í þrjá meginflokka: meltuónot (functional dyspepsia), heilkennið iðraólgu (irritable bowel syndrome) og brjóstsviða.

Megin tilgangur rannsóknarinnar var að kanna faraldsfræði SEM hjá Íslendingum og er aðal áhersla lögð á iðraólgu (IBS), meltuónot (dyspepsia) og brjóstsviða og þróun þeirra á tíu ára tímabili. Einungis ein önnur rannsókn hefur skoðað SEM með sambærilegri aðferðafræði og var hún framkvæmd í Olmsted County í Minnesota í Bandaríkunum (OC). Annar tilgangur rannsóknarinnar var i) að bera saman mismunandi greiningaraðferðir (Manning, Rome II, Rome III og self-report) fyrir iðraólgu á 10 ára tímabili, ii) að kanna iðraólgu og tíðaverki hjá konum og breytingar á iðraólgu við tíðahvörf, iii) að kanna þekkingu og notkun lækna á skilmerkjum til að greina iðraólgu og meðferð annars vegar og þekkingu og upplifun einstaklinga með iðraólgu á sjúkdómnum.

Aðferðafræði

Árið 1996 var spurningalisti sendur til 2000 manna slembiúrtaks íslendinga á aldrinum 18-75 ára sem endurspeglaði íslensku þjóðina hvað varðar kyn, búsetu og aldursdreifingu. Spurningalistinn var sendur aftur út tíu árum seinna (2006) til sama úrtaks. Spurningalistinn var byggður á “the Bowel Disease Questionnaire” sem var þýddur og staðfærður yfir á íslensku. Annar spurningalisti var sendur til 191 lækis og innihélt hann spurningar varðandi skilmerki, greiningu og meðferð á iðraólgu. Að auki var hringt í 94 einstaklinga úr fyrri rannsókninni sem uppfylltu skilmerki iðraólgu og þeir spurðir út í þekkingu þeirra á iðraólgu og greiningu og meðferð á iðraólgu.

Niðurstöður:

Lýðfræði: Árið 1996 var svarhlutfallið 1336/2000 (66.8%). Alls var 1180/1336 einstaklingum sendur nýr spurningalisti (156 náðist ekki í eða voru látnir), þar af svöruðu 799 (67.7%) árið 2006. Meðalaldur svarenda var 42 ár 1996 og 53 ár 2006. Fleiri konur svöruðu spurningalistanum árið 2006 (57.8%) heldur en þær sem svöruðu 1996. Svarhlutfallið var hærra hjá eldri einstaklingum en þeim yngri.

Tíðni: Hjá einstaklingum með SEM var tíðni einkenna stöðug milli ára 1996 og 2006: 16.9% og 17.2% á iðraólgu en 4.8% og 6.1% á meltuónotum. Upphaf einkenna í síðari könnuninni var hærri í OC rannsókninni á iðraólgu og tíðum kviðverkjum (frequent abdominal pain). Brotthvarf einkenna var svipað hjá iðraólgu og meltuónotum í báðum rannsóknum. Tíðni umskipta (transition) var mismunandi eftir undirflokkum og milli rannsókna (Ísland/OC). Sama hlutfall einstaklinga var með sömu einkenni í fyrri og síðari rannsókn. Fleiri einstaklingar voru með engin einkenni á Íslandi (52% vs. 39%; $p<0.01$) og voru með önnur einkenni í síðari rannsókninni (38% vs. 23%; $p<0.05$). Algengi iðraólgu var mismunandi eftir skilmerkjum; Manning sýndi hæstu tíðnina (32%) og Rome II þá lægstu (5%). Yngri einstaklingar og konur voru líklegri til að fá greininguna iðraólga. Tíðni var stöðug á tíu ára tímabili samkvæmt öllum skilmerkjum iðraólgu, að undanskildum Rome III skilmerkjunum. Tilfærsla var á öllum undirflokkum iðraólgu og sterk tengsl á milli iðraólgu, meltuónota og brjóstsviða.

Tíðaverkir: Alls voru 254/331 (76.7%) konur með tíðaverki af þeim konum sem ekki voru komnar á tíðahvörf árið 1996 og 74.1% árið 2006. Alls voru 105/254 (41.5%) og 39/152 (25.7%) kvenna með tíðaverki og einnig með iðraólgu samkvæmt skilmerkjum Manning og Rome III árið 2006, og 48.6% og 10.5% 1996. Árið 2006 voru 46/152 (30.3%) kvenna með slæma eða mjög slæma tíðaverki. Fleiri konur 8/31 (26.5%) voru með mjög slæma kviðverki eftir tíðahvörf en fyrir tíðahvörf (10.7%).

Meltuónot: Meltuónot voru greind hjá 13.9% einstaklinga árið 1996 (11.3% karla, 15.8% kvenna; $p=NS$) og 16.7% árið 2006 (12.3% karla, 20.2% kvenna; $p<0.01$). Skilmerki undirflokka meltuónota (UM) sýndu hærri tíðni en hefðbundin skilmerki meltuónota. Tíðni einstaklinga með meltuónot í UM var lág. Það voru marktæk tengsl milli meltuónota og brjóstsviða ($p<0.001$) og iðraólgu ($p<0.05$). Hátt hlutfall þeirra einstaklinga sem nýta sér heilbrigðisþjónustu hafa meltuónot.

Brjóstsviði: Tíðni brjóstsviða (að minnsta kosti einu sinni í mánuði) á síðast liðnu ári var 42.8% (1996) og 44.2% (2006), með sterk tengsl milli þeirra sem höfðu brjóstsviða bæði árin. Brjóstsviði síðast liðna viku (árið 2006) var greindur hjá 20.8 % einstaklinga. Það voru marktæk tengsl á milli brjóstsviða, meltuónota og iðraólgu. Einstaklingar með líkamsþyngdarstuðull sem var lægri eða hærri en meðal líkamsþyngsarstuðul eru líklegri til að hafa brjóstsviða. Einstaklingar tilgreindu brjóstsviða sem þeir telja mjög oft orsakast af fæðu eða drykkjum í 20.0% tilfella. Brjóstsviði hafði mikil áhrif á daglegt líf einstaklinga, svefn og lífsgæði.

Rannsókn meðal lækna og einstaklinga með iðraólgu: Alls svöruðu 80/191 (41.9%) lækna spruningalistanum. Alls reyndust 13 einstaklinga vera greindir mánaðarlega með iðraólgu af sérfræðingum í meltingarsjúkdómum (SM) og 2.5 einstaklinga af sérfræðingum í heilsu-gæslulækningum (SH). Allir SM þekktu mismunandi skilmerki iðraólgu og 46/70 (65.7%)

SH. Einungis 18/80 (22.5%) allra lækna notaði sértæk skilmerki til að greina iðraólgu. Af þeim einstaklingum með iðraólgu (skv. spurningalista) sem undirgengust símakönnunina sögðu 59/94 (62.8%) að þeir höfðu upplifað iðraólgu að eigin mati. Tveir af hverjum fimm einstaklingum voru með þekkingu á iðraólgu og höfðu leitað til læknis vegna einkenna iðraólgu. Helmingur þeirra fékk greininguna iðraólga. Alls voru 13% ánægðir með þá meðferð sem þeir fengu vegna iðraólgu og 43% sögðu að iðraólgan hefði áhrif á daglegt líf.

Umræða og ályktun

Starfræn einkenni í meltingarvegi eru algeng á Íslandi eins og í öðrum löndum. Tíðnin er hærri meðal yngri einstaklinga og algengari meðal kvenna. Mikill munur er á milli greiningaskilmerkja hvað varðar tíðni SEM. Tíðni einkenna SEM var stöðug á tíu ára tímabili en tilfærsla einkenna var mikil. Munur var á milli einkenna og tíðni umskipta milli Íslands og OC rannsóknarinnar. Fleiri einstaklingar höfðu engin einkenni á Íslandi og það voru meiri tilbrigði hjá einstaklingum sem voru með önnur einkenni eftir tíu ár. Niðurstöður rannsóknarinnar draga fram vandamálið við að skilgreina og greina iðraólgu. Ekkert eitt ákveðið skilmerki virðist duga. Niðurstöður rannsóknarinnar benda því til þess að iðraólga sé ekki einn ákveðinn sjúkdómur heldur klasi einkenna sem flýtur í tíma á milli flokka iðraólgu, meltuónota og brjóstsviða.

Lykilorð: Starfræn einkenni í meltingarvegi, iðraólga, meltuónot, brjóstsviði, tíðaverkir, sjúkdómsgangur, faraldsfræði

ABSTRACT

Introduction

Functional gastrointestinal disorders (FGIDs) are common in the community, are of chronic nature and pose a significant health care burden. The causes and pathogenetic mechanisms of FGIDs are not fully known. FGID are classified into three major domains: functional dyspepsia (FD), functional bowel disorders including irritable bowel syndrome (IBS), and heartburn. The primary aim was to study the natural history of FGID in the Icelandic population prospectively over a 10-year period and to focus specifically on the natural history of irritable bowel syndrome, functional dyspepsia and heartburn. Only one other study has been performed on FGIDs using the same methodology, in Olmsted County Minnesota, USA (OC study) and thus providing the possibility of a direct comparison. Secondary objectives of the study were: i) to compare the prevalence and stability of IBS according to the Manning criteria, Rome II, Rome III subtypes, and self-reported IBS over a 10 year period: ii) to study IBS and dysmenorrhea in women and to assess the change in IBS over menopause: iii) To study if and how physicians use the IBS diagnostic criteria and to assess treatment strategies among physicians for IBS patients.

Methods

A questionnaire was mailed to the same age- and gender-stratified random sample of the Icelandic population aged 18-75 in 1996 and again in 2006. A total of 2000 inhabitants aged 18-75 years were studied. The individuals were randomly selected from the National Registry of Iceland. Equal distribution of sex and age was secured in each study group. The questionnaire was based on the Bowel Disease Questionnaire which was translated into Icelandic and modified. Another questionnaire was sent to 191 physicians regarding IBS criteria, diagnostic methods and treatment. Furthermore, 94 subjects from the prior study who met diagnostic criteria for IBS responded to a telephone interview.

Results

Demographics: In 1996 the response rate was 1336/2000 (66.8%). A total of 1180/1336 individuals were traced, of which 799 (67.7%) responded in 2006. The mean age of the individuals in 1996 was 42 against 53 in 2006. A larger proportion of women responded again in 2006 (57.8%) than in 1996. The response rate was higher for older subjects than for younger ones.

Prevalence: For the FGID symptoms the prevalence was stable between 1996 and 2006: 16.9% and 17.2% for IBS, respectively, and 4.8% and 6.1% for FD. Onset of each disorder in the final

survey was higher in the OC study for IBS and frequent abdominal pain. Disappearance rates were similar for IBS and FD in both studies. Transition probabilities varied across the different subgroups and were different between studies. The same proportion of subjects had the same symptoms in the initial and final studies. More subjects had no symptoms in Iceland (52% vs. 39%; $p<0.05$) and had different symptoms at follow-up (38% vs. 23%; $p<0.001$). The prevalence of IBS varied according to criteria; Manning showed the highest (32%) and Rome II the lowest (5%). Younger subjects and females were more likely to have IBS. Prevalence was stable over 10 years for all criteria except Rome III. There was a turnover in all IBS subgroups and a strong correlation between IBS, FD and heartburn.

Dysmenorrhea: A total of 254/331 (76.7%) premenopausal women had dysmenorrhea in 1996 and 74.1% in 2006. Overall 105/254 (41.5%) and 39/152 (25.7%) of women with dysmenorrhea had IBS according to the Manning criteria and Rome III in 2006, respectively and 48.6% and 10.5% in 1996. In 2006 46/152 (30.3%) women had severe or very severe dysmenorrhea. More women 8/31 (26.5%) reported severe abdominal pain after menopause than before menopause (10.7%).

Functional dyspepsia: FD was diagnosed in 13.9% of the subjects in the 1996 sample (11.3% male, 15.8% female; $p=NS$) and 16.7% in 2006 (12.3% male, 20.2% female; $p<0.01$). DS criteria showed a higher prevalence than conventional FD criteria. The proportion of FD subjects in the DS group was low. There was a significant relationship between FD and heartburn ($p<0.001$) and irritable bowel syndrome ($p<0.05$). A high proportion of subjects who seek medical care have FD.

Heartburn: Heartburn (at least once a month) in the preceding year was 42.8% (1996) and 44.2% (2006), with a strong relationship between those who experienced heartburn in both years. Heartburn in the preceding week (in 2006) was diagnosed in 20.8%. There was a significant relationship between heartburn, dyspepsia and IBS. Individuals with a BMI below or higher than normal are more likely to have heartburn. Heartburn caused by food or beverages was reported very often by 20.0%. Heartburn had a great impact on daily activities, sleep and quality of life.

Physicians study: A total of 80/191 (41.9%) of physicians responded to the survey. Overall 13 subjects were diagnosed monthly with IBS by specialists in gastroenterology (SG) and 2.5 subjects by physicians in general practice (GP). All the SGs were aware of criteria to diagnose IBS and 46/70 (65.7%) of the GPs. Only 18/80 (22.5%) of all physicians used specific IBS criteria. Of the subjects diagnosed with IBS that were interviewed, 59/94 (62.8%) indicated that they had experienced IBS. Two out of five subjects had knowledge of IBS and had seen a physician because of IBS symptoms. Half of those received the diagnosis of IBS. A total of 13% were satisfied with treatment and IBS affected daily activities in 43% of cases.

Discussion and conclusion

Functional gastrointestinal disorders are common in Iceland and as in other countries the prevalence is higher in younger than older subjects and more common in females than males. There is a great difference between different diagnostic criteria in terms of the prevalence of these disorders. Prevalence of FGID symptoms was stable over time but the turnover in symptoms was high. There was a difference in prevalence of symptoms and transition probabilities between Iceland and the OC study. A higher number of subjects had no symptoms in Iceland and there was a greater variation in subjects having different symptoms at follow-up. The results of our study highlight the problem of defining IBS as an entity. No single set of criteria seems to hold the answer as yet. The results of our study suggest that IBS is not a single entity but rather a cluster of symptoms that float in time between different IBS categories, functional dyspepsia and heartburn.

Keywords: Functional gastrointestinal diseases, irritable bowel syndrome, functional dyspepsia, heartburn, dysmenorrhea, natural history, epidemiology

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CLARIFICATION OF CONTRIBUTION

Paper I

Olafsdottir, Thjodleifsson and Gudjonsson designed the study. Jonsdottir and Olafsdottir analysed the data. Olafsdottir and Thjodleifsson drafted the paper. Olafsdottir and Jonsdottir take responsibility for the integrity of the data and the accuracy of the data analysis. Olafsdottir and Thjodleifsson critically revised the draft for important intellectual content and gave final approval of the manuscript to be published.

Paper II

Olafsdottir, Thjodleifsson and Gudjonsson designed the study. Jonsdottir and Olafsdottir analysed the data. Olafsdottir and Thjodleifsson drafted the paper. Olafsdottir and Jonsdottir take responsibility for the integrity of the data and the accuracy of the data analysis. Olafsdottir and Thjodleifsson critically revised the draft for important intellectual content and gave final approval of the manuscript to be published.

Paper III

Olafsdottir, Thjodleifsson and Gudjonsson designed the study. Jonsdottir and Olafsdottir analysed the data. Olafsdottir and Thjodleifsson drafted the paper. Olafsdottir and Jonsdottir take responsibility for the integrity of the data and the accuracy of the data analysis. Olafsdottir and Thjodleifsson critically revised the draft for important intellectual content and gave final approval of the manuscript to be published.

Paper IV

Olafsdottir, Thjodleifsson and Gudjonsson designed the study. Jonsdottir and Olafsdottir analysed the data. Olafsdottir, Björnsson and Thjodleifsson drafted the paper. Olafsdottir and Jonsdottir take responsibility for the integrity of the data and the accuracy of the data analysis. Olafsdottir, Thjodleifsson and Björnsson critically revised the draft for important intellectual content and gave final approval of the manuscript to be published.

Paper V

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Paper VI

Olafsdottir, Thjodleifsson and Gudjonsson designed the study. Jonsdottir and Olafsdottir analysed the data. Olafsdottir and Thjodleifsson drafted the paper. Olafsdottir and Jonsdottir take responsibility for the integrity of the data and the accuracy of the data analysis. Olafsdottir, Thjodleifsson and Björnsson critically revised the draft for important intellectual content and gave final approval of the manuscript to be published.

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LIST OF PAPERS

This thesis is based on the following original papers:

- I. Olafsdottir LB, Gudjonsson H, Jonsdottir HH, Thjodleifsson B. **Natural history of functional dyspepsia - A 10-year population-based study.** Digestion, 2010;81:p. 53-61.
- II. Olafsdottir LB, Gudjonsson H, Jonsdottir HH, Thjodleifsson B. **Stability of the irritable bowel syndrome and subgroups as measured by three diagnostic criteria - a 10-year follow-up study.** Aliment Pharmacol Ther. 2010; 32: p. 670-80.
- III. Olafsdottir LB, Gudjonsson H, Jonsdottir HH, Thjodleifsson B. **Natural history of Heartburn. A 10-year population based study.** World J Gastroenterol, 2011; 17: p. 639-45.
- IV. Olafsdottir LB, Gudjonsson H, Jonsdottir HH, Björnsson E, Thjodleifsson B. **Natural history of Functional Gastrointestinal Disorders: Comparison of two longitudinal population-based studies.** Submitted
- V. Olafsdottir LB, Gudjonsson H, Jonsdottir HH, Jonsson JS, Björnsson E, Thjodleifsson B. **Irritable Bowel Syndrome: Physician's awareness and use of diagnostic criteria and management versus IBS subject's experience of diagnosis and treatment.** Submitted
- VI. Olafsdottir LB, Gudjonsson H, Jonsdottir HH, Björnsson E, Thjodleifsson B. **Natural history of irritable bowel syndrome in women and dysmenorrhea: A 10-year follow up study.** Submitted

LIST OF ABBREVIATIONS

5 HT	serotonin (5-hydroxytryptamin)
ANS	autonomic nervous system
BDQ	bowel disease questionnaire
BMI	body mass index
BSS	Bristol stool scale
C	constipation
CNS	central nervous system
CI	confidence interval
D	diarrhea
DIGEST study	the Domestic/International Gastroenterology Surveillance Study
DS	dyspepsia subgroups
COMB	combination
FAP	frequent abdominal pain
Fc	functional constipation
FD	functional dyspepsia
Fd	functional diarrhea
FGID	functional gastrointestinal disorders
FUP	frequent upper pain
GEP	good epidemiology practice
GER	good epidemiology practice
GERD	gastroesophageal reflux disease
GI	gastrointestinal
GP	general practice
HB	heartburn
HPA	hypothalamic-pituitary-adrenal
HRQoL	health related quality of life
MR	meal related

n	number of subjects
N	normal
Neg.	negative
NV	not valid
NV	nausea or vomiting
IBS	irritable bowel syndrome
IBS-D	irritable bowel syndrome – diarrhea predominant
IBS-C	irritable bowel syndrome – constipation predominant
IBS-M	irritable bowel syndrome – both diarrhea and constipation
NPSR1	neuropeptide S receptor
OC	Olmsted County
P	P-value
Pos.	positive
PUD	peptic ulcer disease
UAP	upper abdominal pain
UK	United Kingdom
SD	standard deviation
SG	specialist in gastroenterology
SPSS	statistical package of social science
SSC	somatic symptom checklist
TMD	temporomandibular dysfunction

INTRODUCTION

1.1 A perspective on the functional gastrointestinal disorders

Gut health has throughout recorded history been considered a taboo in the Western world whereas in contrast gut health is a central theme in Asian medicine, which recognises the abdomen as the location of the soul. “Honoured middle” (onaka) and “centre of the spiritual and physical strength” (hara) are how the Japanese describe our largest organ, the intestine, which for many Europeans was barely more than a simple digestive system which had to function (Yu F, 2006; Bischoff, 2011). However, along with structural diseases of the intestinal tract, recorded history has described illnesses that have produced multiple symptoms such as: pain, nausea, vomiting, bloating, diarrhea, constipation, or difficult passage of food or feces (Drossman, 1993; Drossman D, 2006). For too long functional diseases were described by what they are not, rather than as what they are. For the patient they are real enough. Not only does such an exclusive approach fail to provide the patient with the dignity of a diagnosis, but it also generates needless tests and consultations. The endless seeking of an anatomical cause makes functional disorders “diagnoses of exclusion” (Drossman D, 2006). These diagnoses of exclusion are often time consuming and costly, and without credibility for the patient.

Functional gastrointestinal disorders (FGID) are common in the community and pose a significant health care burden (Chang JY, 210; Halder SLS, 2007). FGID are related to an increasing demand on primary health care because of an increased overall comorbidity (Alander T, 2008). The prevalence of any of the FGID symptoms over a 12-year period has been reported with an aggregated rate of 42% (Halder SLS, 2007). Other studies report that more than one third of the general population has one or more FGID (Koloski NA, 2002). There is an increasing interest in the epidemiology of these diseases (Agréus L, 2001; Halder SLS, 2007), but the field has been compounded by rapid introduction of new diagnostic criteria. This has made it very difficult or virtually impossible to compare prevalence rates from different time periods or geographic regions (Gschossmann JM, 2001). With more studies based on the same or similar methodology the understanding of the natural history of FGID will hopefully improve. The main advantage of a population-based epidemiological approach is the possibility of studying the spectrum of symptoms in the whole population (Argéus L, 1995). Patient-based studies from health institutions are inherently biased by figures for health care seeking because only a minority of subjects consult a health care provider regarding their symptoms (Talley NJ, 1992; Agréus, 1993; Drossman DA, 2002).

Irritable bowel syndrome (IBS) patients are often reluctant to consult a physician, paradoxically because they either think their symptoms are not serious enough or are afraid that they have a serious life-threatening illness (Hungin APS, 2003; Hulisz, 2004). In a large population-based cohort study with over 30,999 person-years of follow-up, no significant association was observed between survival and IBS, chronic diarrhea, dyspepsia, or abdominal pain (Chang JY, 2010). No association was found between increase in burden of FGIDs and survival, but subjects with symptoms of chronic constipation were found to be at increased risk of mortality. Several studies have shown diminished quality of life in subjects with FGIDs (Chang JY, 2010).

Three long-term studies have focused on the natural history of FGID (Halder SLS, 2007) (Agréus L, 2001) (Ford AC, 2008), a 12-year longitudinal population-based study from Olmsted County, Minnesota, USA, a 7 year long-term community study from Sweden and 10-year longitudinal follow-up study conducted in Leeds and Bradford, UK. These studies have been carried out in three different countries with different methodologies which make them comparable only to a limited degree. The DIGEST study used the same methods in several populations and registered the three month prevalence of upper GI symptoms (Stanghellini, 1999). That study provided valuable data on the international prevalence of upper GI symptoms and the disparities between the different survey sites.

Comparison of studies from different populations using the same criteria is essential for understanding the natural history of FGID.

1.2 The development of FGID criteria (Rome III definition of FGID)

The development of criteria to diagnose FGID has come a long way. At first the focus was on IBS criteria. However, in 1990 the Rome I criteria were presented, where the Rome classification system for FGIDs was included. This was the first time that diagnostic criteria were proposed for all the functional gut disorders and included the first revision of the 1988 IBS criteria (Drossman D, 2006). (Table 1)

The criteria that have most commonly been used to identify IBS patients are the Manning criteria (Manning AP, 1978), Rome I (Drossman DA, 1994), Rome II (Thompson WG, 1999) and the most recent Rome III criteria (Douglas A. Drossman, 2006; Drossman DA, 2006). The Rome criteria are more refined than the Manning criteria and include the duration of symptoms as part of the definition of IBS (Hungin APS, 2005). Studies have also shown that the Manning criteria are relatively sensitive but lack specificity (Fass R, 2001). Table 1 shows the development of the diagnostic criteria for IBS and FGID.

Table 1: History of the Rome Diagnostic Criteria (Drossman D, 2006)

The Manning Criteria for IBS (1978) (Manning AP, 1978)
The Kruis Criteria for IBS (1984) (Kruis W, 1983)
The Rome Guidelines for IBS (1989) (Thompson WG, 1989) (Rome-2 IBS Criteria)
The Rome Classification System for FGIDs (1990) (Drossman D, 1990) (Rome-1)
The Rome I Criteria for IBS (1992) (Thompson WG, 1992) and the FGIDs (1994) (Drossman D, 1994)
The Rome II Criteria for IBS (1999) (Thompson WG, 1999) and the FGIDs (1999) (Drossman DA, 1999)
The Rome III Criteria (2006) (Drossman D, 2006)

1.3 FGID diagnostic criteria

The Rome committee introduced the Rome III criteria to diagnose FGIDs in 2006. The development had some rationale and limitations, including: rationale for symptom-based diagnostic criteria, site-specific differences, symptom resulting from multiple influencing factors, epidemiologic data, treatment implications, need for diagnostic standards in clinical care and research, qualification for the use of symptom-based criteria, coexistence of other diseases that need to be excluded, symptoms overlapping with other functional GI disorders, requirement that symptoms must have begun 6 months prior to diagnosis and be active for 3 months, diagnostic categories that do not include psychosocial criteria, and determination of criteria by clinical consensus and existing evidence (Drossman D, 2006). According to the Rome III committee FGID are classified into six major domains: esophageal, gastroduodenal, bowel, functional abdominal pain syndrome, biliary and anorectal (Drossman D, 2006), three of which will be addressed in this study: 1) functional dyspepsia and heartburn (FD); 2) functional bowel disorders, including irritable bowel syndrome (IBS), functional constipation (FC) and functional diarrhea (FD); and 3) functional abdominal pain syndrome. Table 2 shows the Rome III diagnostic criteria for the FGID symptoms of the study:

Table 2: Rome III diagnostic criteria for the FGID symptom of the study. (From Drossman et al. The functional gastrointestinal disorders. 3rd edition, Rome III (Drossman D, 2006))

Diagnostic criteria* for functional heartburn

Must include all of the following:

1. Burning retrosternal discomfort or pain
2. Absence of evidence that gastroesophageal acid reflux is the cause of the symptom
3. Absence of histopathology-based esophageal motility disorders

*Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

Diagnostic criteria* for functional dyspepsia

Must include:

1. One or more of the following:
 - a. Bothersome postprandial fullness
 - b. Early satiation
 - c. Epigastric pain
 - d. Epigastric burning

And

2. No evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms

*Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

Diagnostic criteria* for irritable bowel syndrome

Recurrent abdominal pain or discomfort** at least 3 days/month in the last 3 months associated with two or more of the following:

1. Improvement with defecation
2. Onset associated with a change in frequency of stool
3. Onset associated with a change in form (appearance) of stool.

*Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.

***"Discomfort" means an uncomfortable sensation not described as pain.

Diagnostic criteria* for Functional Constipation

1. Must include two or more of the following:
 - a. Straining during at least 25% of defecations
 - b. Lumpy or hard stools in at least 25% of defecations
 - c. Sensation of incomplete evacuation for at least 25% of defecations
 - d. Sensation of anorectal obstruction/blockage for at least 25% of defecations
 - e. Manual maneuvers to facilitate at least 25% of defecations
 - f. Fewer than three defecations per week
2. Loose stools are rarely present without the use of laxatives
3. Insufficient criteria for irritable bowel syndrome

*Criteria fulfilled for the last 3 months with symptom onset at least 6 months with symptom onset at least 6 months prior to diagnosis

Diagnostic criteria* for Functional Diarrhea

Loose or watery stools without pain occurring in at least 75% of stools

*Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

Diagnostic criteria* for functional abdominal pain syndrome

Must include all of the following:

1. Continuous or nearly continuous abdominal pain
2. No or only occasional relationship of pain with physiological events (e.g. eating, defecation, or menses)
3. Some loss of daily functioning
4. The pain is not feigned (e.g. malingering)
5. Insufficient symptoms to meet criteria for another functional gastrointestinal disorder that would explain the pain

*criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

1.4 Pathophysiology of FGID

The causes and pathogenic mechanisms of FGID are not fully known. Figure 1 illustrates the relationship between psychosocial and physiological factors and FGID symptoms and clinical outcome (Drossman D, 2006). More detailed description follows.

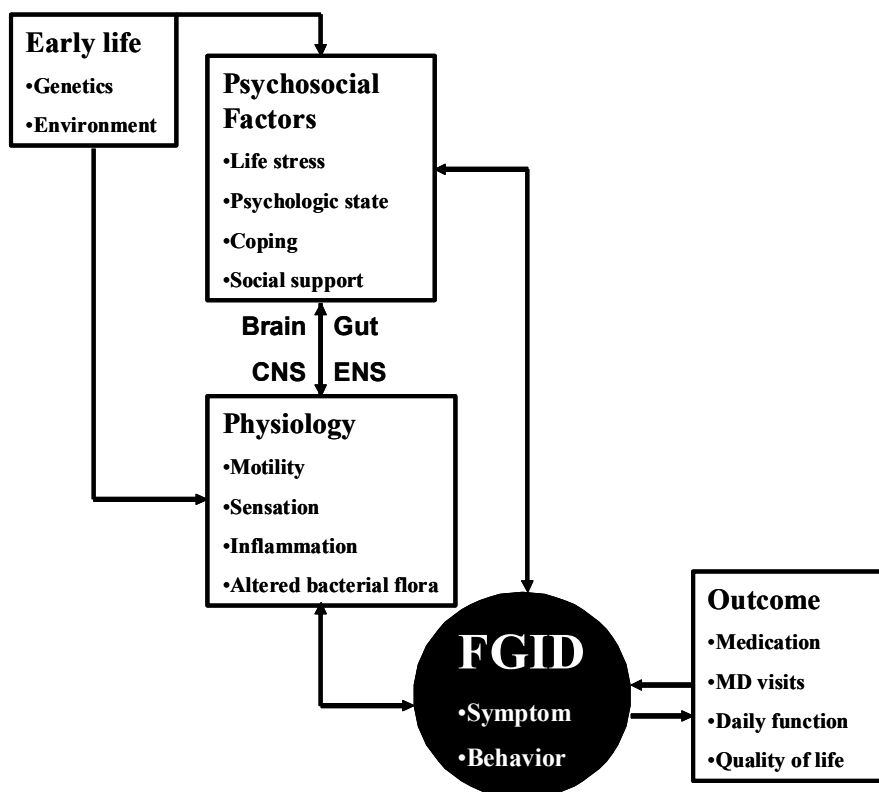


Figure 1: A biopsychosocial conceptualization of the pathogenesis and clinical expression of the functional GI disorders, showing the relationship between psychosocial and physiological factors, functional gastrointestinal symptoms, and clinical outcome. (From Drossman et al. The functional gastrointestinal disorders. 3rd edition, Rome III (Drossman D, 2006)). Permission was granted to use the picture from the Rome foundation.

1.4.1 Genetic Predispositions

Genetic factors may potentially cause some individuals to develop FGID symptoms. It is unlikely, however that a single genetic factor causes FGID. It is rather more likely that a genetic factor (or factors) modulates the risk of developing the abnormalities that are characteristic of FGID after exposure to one or more specific environmental factors (Adam B, 2007). It has been shown that gene polymorphisms associated with pain sensitivity and affective or anxiety disorders are associated with disorders that frequently co-occur with IBS,

such as fibromyalgia and temporomandibular dysfunction (TMD) (Sperber AD, 1999; Aaron LA, 2000; Whitehead WE, 2002; Drossman D, 2006). The pathogenesis of FGID is probably multifactorial, and includes genetic and environmental factors (Adam B, 2007). Polymorphisms of genes that encode cytokines and influence immune function are thought to contribute to the onset of symptoms in at least a subgroup of patients with IBS (Adam B, 2007). A recent study has shown the first evidence of an association of NPSR1 polymorphisms and gastrointestinal motor and sensory functions that are relevant to IBS and FD (Camilleri M, 2010).

1.4.2 Early Family Environment

FGIDs in families may not only be of genetic etiology. Heredity factors probably contribute to development of IBS, but social learning (what an individual learns from those in his or her environment) has an equal or greater influence (Levy RL, 2001). A history of abdominal pain or bowel troubles in first-degree relatives was significantly associated with IBS and FD (Locke GR 3rd, 2000). Familial associations may represent similar exposures in a shared environment, heightened familial awareness of GI symptoms (reporting bias), or genetic factors (Locke GR 3rd, 2000). A history of abdominal pain or bowel troubles in first-degree relatives appears to be independently associated with both persistent and fluctuating IBS (Kalantar JS, 2003).

1.4.3 Psychosocial factors

FGIDs such as IBS are often associated with affective disorders, such as depression, anxiety, panic, and posttraumatic stress disorder (Mayer EA, 2001) and GI symptoms are associated significantly with depression and anxiety in primary care (Mussell M, 2008).

Most people have experienced changes in GI function during stress or emotional arousal, which may lead to symptoms and medical consultation. These feelings and knowledge are reflected in the medical literature as well as in everyday language such as “butterflies in my stomach” and “knot in my bowels” (Van Oudenhove L, 2010). In FGIDs psychological and social influences may affect gut function, the experience of pain, health-related quality of life, work absenteeism, health care use and medical and societal cost (Drossman DA, 1993; Luscombe, 2000; Akehurst RL, 2002; El-Serag HB, 2002; Drossman D, 2006). Psychological illness increases the chance of concomitantly having more severe GI symptoms, which also enhance consultation behavior (Alander T, 2005). A recent study reported that anxiety but not depression is linked to uninvestigated dyspepsia and FD (Aro P, 2009).

Abuse history is common in GI practice and is more prevalent with more severe symptoms or those who are seen in referral academic practice (Drossman, 2011). Patients with FGID diagnoses tend to have a history of more severe abuse. Motivation for psychotherapy in patients with FGIDs is low and is not determined by clinical, but rather, by interpersonal

problems that may exist beyond and independent of GI symptoms (Martens U, 2010). Psychological treatment can be of help to manage the psychological distress which can worsen bowel symptoms and quality of life in these subjects (Prasko J, 2010).

There are relatively few studies that have examined gender differences in psychological symptoms in FGID, and there is no convincing evidence of any major differences between men and women with FGID. Those differences that have been reported most likely reflect the differences between men and women in the general population in relation to the reporting of psychological symptoms rather than any specific gut-related phenomenon (Chang L, 2006).

1.4.4 Abnormal Motility

A person takes in food through the digestive system, where it breaks down and nutrient molecules absorbed into the bloodstream. The indigestible remains are then passed out of from the body. Gastrointestinal motor activity in various parts of the alimentary canal must therefore function properly. Two basic types of movement occur in the gastrointestinal tract; the mixing movement (to keep the intestinal contents mixed) and the propulsive movement (which causes the intestinal contents to move forward). Disorders of GI transit and motility are common, and cause either delayed or accelerated transit through the stomach, small intestine or colon, and affect one or more regions (Rao SS, 2011). Many GI symptoms such as diarrhea, vomiting, acute abdominal pain and others are probably generated by disturbed GI motility (Drossman D, 2006). Tests of gastrointestinal transit are available and can be useful in the evaluation of patients with symptoms suggestive of gastrointestinal dysmotility, since they can provide objective diagnosis and a rational approach to patient management (Rao SS, 2011).

1.4.5 Visceral Hypersensitivity

Visceral hypersensitivity is considered one of the causes of functional gastrointestinal disorders and it is currently the leading hypothesis to explain IBS and other FGIDs (Azpiroz F, 2007). Since James Ritchie in 1973 (Ritchie, 1973), first reported that IBS patients were more sensitive than normal subjects to balloon distension of the colon, numerous reports on increased visceral sensitivity in IBS patients have been confirmed by many researchers (Whitehead WE, 1990; Mertz H, 1995; Azpiroz F, 2007). Like the hypersensitivity of the colon found in IBS patients, intolerance to gastric distension was also documented in patients with FD (Lemann M, 1991; Mearin F, 1991; Bradette M, 2002), as well as in the esophagus (Costantini M, 1993; Trimble KC, 1995), stomach (Zighelboim J, 1995) and the small intestine (Accarino AM, 1995; Holtmann G, 1997; Simrén, 2001).

1.4.6 Inflammation

Inflammation varies widely through the GI tract and appears to alter different sensory modalities at different sites (Azpiroz F, 2007). A few years ago it was recognized that about half of patients with IBS have increased activated mucosal inflammatory cells (Chadwick

VS, 2002; Drossman D, 2006). This is in line with clinical observations that one out of three IBS or dyspepsia patients report that their symptoms started after an acute enteric infection and that up to one out of four of patients presenting with an acute enteric infection will go on to develop IBS-like or dyspeptic symptoms (McKendrick MW, 1994; MW, 1996; Gwee KA, 1999; Mearin F, 2005; Drossman D, 2006).

1.4.7 Bacterial Flora

The bacterial flora of the GI system is thought to have a major physiological and immunological role in gut function (Chang JY, 2010). The bacterial flora are usually divided into two distinct ecosystems: luminal bacteria that are associated with feces or food particles and mucosa-associated bacteria that are bound to the mucus layer adjacent to the intestinal epithelium (Parkes GC, 2008). Changes in fecal microbiota, the use of probiotics, the phenomenon of postinfectious IBS, and the recognition of an unregulated host immune system response suggest that an interaction between the host and GI microbiota may be important in the pathogenesis of IBS (Chang JY, 2010).

1.4.8 Brain-Gut Interactions

The combined functioning of gastrointestinal motor, sensory and CNS activity is termed the brain-gut axis and FGID can be conceptualized as resulting at least in part from dysregulation of the brain-gut axis (Drossman DA, 2002; Jones MP, 2006). Figure 2 demonstrates factors which may potentially play a role at both peripheral and central sites of the brain-gut axis.

Jones et al. have reported that the gut and the brain are highly integrated and communicate in a bi-directional fashion largely through the autonomic nervous system (ANS) and hypothalamic-pituitary-adrenal axis (HPA) (Jones MP, 2006). Furthermore within the central nervous system (CNS) the locus of gut control is chiefly within the limbic system, a region of the mammalian brain responsible for both the internal and external homeostasis of the organism. The limbic system also plays a central role in emotionality, which is a nonverbal system that facilitates survival and threat avoidance, social interaction and learning. The generation of emotion and associated physiological changes is the work of the limbic system and, from a neuroanatomic perspective, the “mind-body interaction” may largely arise in this region. Finally, the limbic system is also involved in the “top-down” modulation of visceral pain transmission as well as visceral perception (Jones MP, 2006).

Patients with IBS seem to have greater engagement of regions associated with emotional arousal and endogenous pain modulation, but similar activation of regions involved in processing of visceral afferent information (Tillisch K, 2011). Controls have greater engagement of cognitive modulatory regions. These results and other studies support a role for central nervous system dysregulation in IBS.

Fukudo and Kanazawa recently reported that gene-by-environment interaction together with brain-gut interactions play crucial roles in IBS (Fukudo S, 2011). Genes regulating brain-gut interactions and environmental factors which mainly affect either the brain or the gut may potentially contribute to the development of IBS (Fukudo S, 2011).

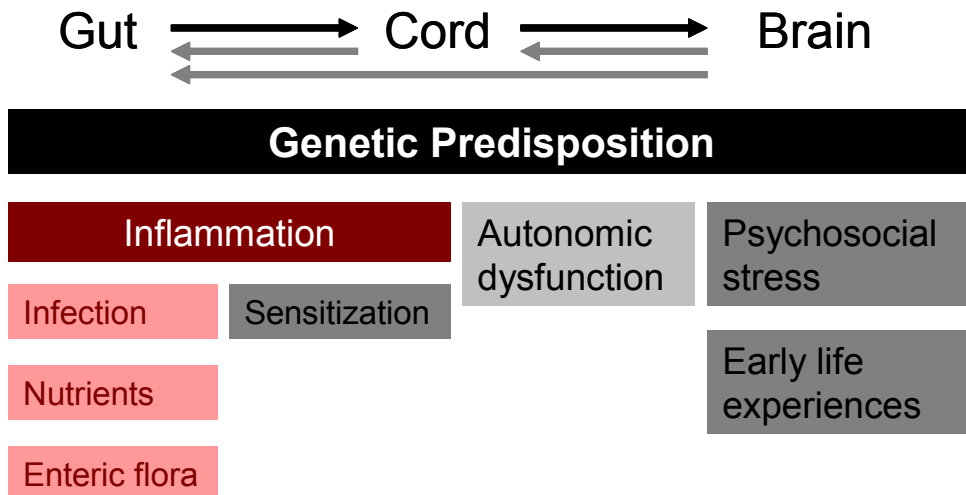


Figure 2: Schematic view of afferent (black arrows) and efferent (grey arrows) signals along the brain-gut axis, and putative factors which may influence these signals (boxes). Afferent signals, particularly consciously perceived ones, are relayed from the gut to the dorsal horn of the spinal cord. Secondary afferents carry these stimuli to the brain. Processing in the brain occurs in several regions, culminating in perception, interpretation, and response. CNS inputs such as psychosocial stress modulate sensory processing and efferent signals to the gut. Efferent signals are generally carried by spinal and vagal/sacral autonomic pathways to the gut. These signals alter motility and secretion in the target organ. From Drossman et.al. The functional gastrointestinal disorders. 3rd edition, Rome III (Drossman D, 2006). Permission was granted to use the picture from the Rome foundation.

1.5 Functional gastrointestinal disorders in the study

1.5.1 IBS

Irritable bowel syndrome (IBS) is a functional bowel disorder in which abdominal pain or discomfort is associated with defecation or a change in bowel habits and with features of disordered defecation (Douglas A. Drossman, 2006). Patients often experience additional symptoms such as bloating, sensation of incomplete evacuation, straining (constipation) and urgency (diarrhea) (Hungin APS, 2005). Previous studies report that IBS is one of the most common disorders observed in the general population (Drossman DA, 1993; Talley, 1999; Hungin APS, 2003) with a major effect on quality of life and health care (Hahn BA, 1999; Hungin APS, 2003; Paré P, 2006). IBS is one of the leading causes of gastroenterology and

primary care consultations (Everhart JE, 1991; Thompson, 2002). Subjects reporting recurrent abdominal pain in childhood are especially at risk for IBS (Gulewitsch MD, 2011). IBS patients who have moderate to severe symptoms have impaired quality of life compared with the general population (Talley, 2008).

IBS prevalence is estimated to range from 3% to 28% (Drossman DA, 1993; Talley, 1999; Lau EM, 2002; Saito YA, 2002; Hungin APS, 2003; KA, 2005; Akhter AJ, 2006) depending on the country and the diagnostic criteria. The criteria available to identify IBS are the Manning criteria (Manning AP, 1978), Rome I (Drossman DA, 1994), Rome II (Thompson WG, 1999) and Rome III (Douglas A. Drossman, 2006; Drossman DA, 2006). The Rome criteria are more refined than the Manning criteria and include symptom duration (Hungin APS, 2005). No consistent differences in sensitivity or specificity between Manning, Rome I and Rome II have been reported (Whitehead WE, 2010) and the stability over time has not been examined. The prevalence of IBS in the Western countries is estimated to be 10-15% (Hungin APS, 2003; Quigley EMM, 2006). Recent studies from around the world where the Rome II criteria were used have reported a lower frequency of IBS, namely 5% (Bommelaer G, 2004; Sperber AD, 2005). Sperber et al. (Sperber AD, 2005, 2007) reported lower frequencies using the Rome II criteria than the Rome III criteria, and lower frequencies than 3% have been reported (Bommelaer G, 2004). A recent study by Bond et al. has shown that more than bowel habits and abdominal pain drive IBS symptom severity (Bond B, 2009). The severity of symptom burden was related more to all symptoms recorded, not just pain or to specific changes in bowel habits.

A multivariable analysis showed that health examinees with physician-diagnosed IBS studies have reported rates of cholecystectomy three times the rate of examinees without IBS, twice the rate of appendectomies and hysterectomies, and 50% more often back surgery (Longstreth GF, 2004). IBS is independently associated with these surgical procedures in physician-diagnosed IBS (Longstreth GF, 2004). Sadik et al. have reported that GI transit is of relevance for the symptom pattern in patients with IBS and that high BMI is associated with fast regional bowel transit and may influence some stool-related symptoms IBS (Sadik R, 2010).

Although altered rectal perception has been proposed as a marker of IBS (Mertz H, 1995; Bouin M, 2002) no clinically useful or reliable biomarkers have been identified. The diagnosis therefore relies upon diagnostic criteria and normal findings on routine clinical investigations (Longstreth GF, 2006). The subtypes of IBS are of crucial importance for defining drug targets since the 5-HT drugs act predominantly on diarrhea (Camilleri M, 2001) or constipation (Müller-Lissner SA, 2001).

Population-based studies are essential for studying IBS since only a minority of IBS patients seek medical care, self-medication is common (Penston JG, 1996) and differences have been

noted in IBS patients and non-patients (not seeking medical care) from the community (Jones R, 1992; El-Serag HB, 2004). The great majority of IBS studies are patient based.

The IBS diagnostic criteria have not been tested over time and population-based follow-up epidemiological studies on IBS are rare. A recent 12-year longitudinal study suggests that many episodes of symptom disappearance were due to changed symptoms in subjects rather than total symptom resolution (Halder SLS, 2007). A patient-based study by Garrigues et al. shows that changes in IBS subtypes over time are common, but changes between constipation and diarrhea are rare (Garrigues V, 2007), at least over a one year period. Symptom reporting is one of several issues that are unresolved regarding prognosis and classification of IBS. Another large population-based study on the natural history of symptoms and factors that influence consultation behaviour of IBS has shown that the prevalence of IBS increased over the 10 years of the study, with an annual incidence of 1.5% (Ford AC, 2007).

1.5.2 Functional dyspepsia

Functional dyspepsia (FD) is a syndrome characterized by central upper abdominal pain or discomfort in the absence of any organic disease that can explain the symptoms. The syndrome is heterogeneous, and the symptoms reported include epigastric pain, postprandial fullness, bloating, early satiety or discomfort, belching, nausea, vomiting, and epigastric burning. FD has been defined as the presence of one or more dyspepsia symptoms that are considered to originate from the gastroduodenal region in the absence of any organic, systemic, or metabolic disease that is likely to explain the symptoms (Douglas A. Drossman, 2006).

The natural history of FD is largely unknown. Although FD can be positively diagnosed it is predominantly a diagnosis of exclusion and most patients with FD do not seek medical care (Drossman DA, 1982). Population-based surveys are therefore necessary for assessing the epidemiology of these conditions in the community and they are mainly conducted by postal surveys. Population-based studies have to rely on symptom criteria for diagnosis of FD, like the Rome II and III criteria (Douglas A. Drossman, 2006).

Dyspepsia is a common condition which seems to fluctuate in the general population in the general population (Talley NJ, 1998; Talley NJ, 1999; Agréus, 2002). With the absence of predominant heartburn in dyspepsia, 20% to 40% of individuals report chronic or recurrent dyspeptic symptoms (R H Jones, 1990; Talley NJ, 1992; Agréus L, 1995; Douglas A. Drossman, 2006; Tack J, 2006; Ford AC, 2007). The variations in prevalence are due both to different ethnic populations and the methods used to diagnose dyspepsia (Stanghellini, 1999). Agréus et al. studied the long-term natural history of symptomatic gastroesophageal reflux disease (GERD), dyspepsia and IBS in a general population in Sweden over a seven year period (Agréus L, 2001). The prevalence of GERD appeared to be stable over time, whereas dyspepsia decreased with advancing age and IBS increased over time. These findings support the hypothesis that in distinction to GERD, dyspepsia and IBS are different

manifestations of one (or more) common pathophysiological aberrations (Agréus L, 1995; Agréus L, 2001).

It has been estimated that approximately 50% of subjects seek health care for their dyspeptic symptoms at some time in their life (Talley NJ, 1992; Talley NJ, 1998; Koloski NA, 2001; Drossman D, 2006). Agréus et al. have shown that most primary care visits for dyspepsia are followed by improvement (Agréus L, 2008). Pain severity and anxiety (including fear of serious disease) appear to be factors associated with consulting behavior (Lydeard S, 1989; Talley NJ, 1998; Koloski NA, 2001; Hu WH, 2002; Drossman D, 2006). The economic cost of dyspepsia is considerable (Agréus, 2002; Agréus L, 2002).

FD impacts on all main domains describing physical, mental and social aspects of health-related quality of life in the general population. Overlap between functional dyspepsia and irritable bowel syndrome or reflux symptoms impacts on the domain related to bodily pain (Aro P, 2011).

A Bowel Disease Questionnaire (BDQ) which can be used in epidemiological studies has been developed and shown to have adequate validity to diagnose GI functional disorders, including FD (Talley NJ, 1989; O'Keefe EA, 1992) (Locke GR III, 2005) and has been used in a recent publication (Halder SLS, 2007).

The Rome II criteria attempted furthermore to classify FD into subgroups according to the most predominant or most bothersome single dyspeptic symptom reported by the subject. However, the heterogeneity and instability of the proposed dyspepsia subgroups and lack of agreement on what predominant means made this attempt unsuccessful (Talley NJ, 1993; Agréus L, 1995; Boeckxtaens GE, 2001; Fischler B, 2003; Pallotta N, 2004).

A recent population-based study of outpatients, using factor analysis, suggests that distinct subgroups of uninvestigated dyspepsia do exist in the general population. Three subgroups were found: 1) an epigastric pain factor, 2) an early satiety factor, and 3) a nausea/vomiting factor (Choung RS, 2007).

1.5.3 Heartburn

Gastroesophageal reflux disease (GERD) is one of the most prevalent diseases worldwide (David Armstrong, 2004). GERD is a chronic condition which usually manifests symptomatically, is a great burden for patients, and has significant socioeconomic implications (Kulig M, 2004). The prevalence of predominant gastroesophageal reflux symptoms appears to be relatively stable over time (Agréus L, 2001). Heartburn is the typical GERD symptom and may be induced by various physiological and pathophysiological mechanisms (Lee KJ, 2009). Heartburn, coupled with acid regurgitation and odynophagia, are considered to be highly specific for GERD (David Armstrong, 2004).

Functional heartburn is defined as episodic retrosternal burning in the absence of GERD, histopathology-based motility disorders or structural explanations (Douglas A. Drossman, 2006). When defined as at least weekly heartburn and/or acid regurgitation, the prevalence in the Western world generally ranges between 10% and 20% whereas in Asia the prevalence is reported to be less than 5% (Dent J, 2005; Drossman D, 2006). The age- and sex-adjusted prevalence rate for any episode of heartburn in the past year was 42%, and the prevalence of either heartburn or acid regurgitation in the past year was 59% (Locke GR 3rd, 1997; Kulig M, 2004)

The prevalence of upper gastrointestinal symptoms in the general population is high and symptoms are associated with significant health-care utilization and diminished quality of life (Frank, 2000). GERD places a significant burden on primary care and is associated with increased work absenteeism and disturbance in daily life (Gisbert JP, 2009). In contrast, the natural history of heartburn has received limited attention and few epidemiological studies have focused on heartburn. Subjects meeting criteria for ulcer or GERD are more likely to use prescription medication and were more likely to see a physician about symptoms than those with heartburn (Frank, 2000). There has been more focus on GERD but less focus on heartburn itself. Individuals experiencing daily and weekly reflux symptoms are likely to have a clinically significant reduction in most aspects of HRQoL (Ronkainen J, 2006). According to a European observational study, GERD was associated with a substantial impact on the daily lives of affected individuals managed in the primary care setting (Gisbert JP, 2009).

1.6 Effect of age on FGID

Subjects of all ages are affected by FGIDs. Some FGIDs increase with age whereas others decrease (Drossman D, 2006). The challenge is that these studies do not include diagnostic tests. Thus, they measure symptom reporting rather than being true estimates of the prevalence of the FGIDs. Extensive epidemiological data exist for IBS, dyspepsia, heartburn, constipation and fecal incontinence (Drossman D, 2006). Some studies have shown that the prevalence of dyspepsia decreases with age (Agr us L, 1994; Kay L, 1994; Chang L, 2006). The prevalence of IBS gradually decreases with age according to most studies (Talley NJ, 1995; Bennett G, 2002; Drossman D, 2006). IBS is a common disorder in the elderly, but may be less common than in middle-aged subjects (Bennett G, 2002). However, there are hints that IBS in older subjects differs significantly from the condition in younger subjects (Bennett G, 2002). There is a connection between aging and an increasing prevalence of many chronic neurological difficulties, cardiovascular diseases and mental disabilities (Sasaki D, 2006); therefore the management of the IBS needs to take the age-related issues into account in the elderly. In a Japanese study adolescent IBS had almost the same prevalence as adult IBS, though the rate of IBS subtypes was different (Endo Y, 2011): IBS-C was dominant in females and IBS-D is dominant in males in adult IBS, there was no significant difference in adolescent IBS in dominant subtype between boys and girls, although the tendency was seen. Sexual maturation may play some role in developing into adult IBS (Endo Y, 2011).

1.7 Health care seeking

Patients with FGID often experience emotional distress, a perceived lack of validation and an unsatisfactory experience with health care providers (Chang L, 2006). It has been shown that some IBS patients experience dissatisfaction and negative attitudes in GP interactions in primary care (Dhaliwal SK, 2004). Patients and physicians have different experiences and expectations with regards to IBS and its treatment (Bijkerk CJ, 2003). IBS patients may seek GPs as the first health care provider to vent their frustration: therefore appropriate education programs for optimal management of patients with IBS are needed in primary care (Dhaliwal SK, 2004). Counseling and reassurance, as well as dietary advice and medication, seem to be the first choices of treatment by GPs (Thompson WG, 1997; Paterson WG, 1999; Janssen HA, 2000; Bijkerk CJ, 2003). GPs however aim at global symptom improvement, while patients consider improvement of their most bothersome symptoms as the main target (Bijkerk CJ, 2003).

Diagnostic criteria like the Rome criteria are largely unknown among GPs (Franke A, 2009). A recent study showed that knowledge and use of the Rome criteria or their positive predictive values for IBS did not correlate with reduced use of diagnostic tests (Charapata C, 2006). It has been questioned whether the Rome criteria are sensitive enough to diagnose patients in general practice. The current lack of interest in these criteria, especially among GPs, is unlikely to change unless they can be considerably improved. Therefore an improved understanding of the recommended diagnostic and therapeutic approaches for IBS will lead to greater patient satisfaction, as well as reduced health care costs (Lea R, 2004; Khan S, 2010). The challenges and uncertainties for diagnosis of IBS have been suggested to be the following (Spiegel, 2007; Spiegel BM, 2010):

1. There is currently no consistent biological marker of IBS, leaving clinicians to rely on patient symptoms alone to make the diagnosis
2. The symptoms of IBS are often difficult to quantify objectively
3. Symptoms can vary among individuals with IBS
4. Many organic conditions can masquerade as IBS

With these uncertainties many physicians approach IBS as a diagnosis of exclusion (Spiegel BM, 2010). A recent study concluded that: (i) the best practise diagnostic guidelines have not been uniformly adopted in IBS, particularly among primary care providers; (ii) most community providers believe IBS is a diagnosis of exclusion (this belief is associated with increased diagnostic resource use); and (iii) despite the dissemination of guidelines regarding diagnostic testing in IBS, there remains extreme variation in beliefs among both experts and non-experts (Spiegel BM, 2010).

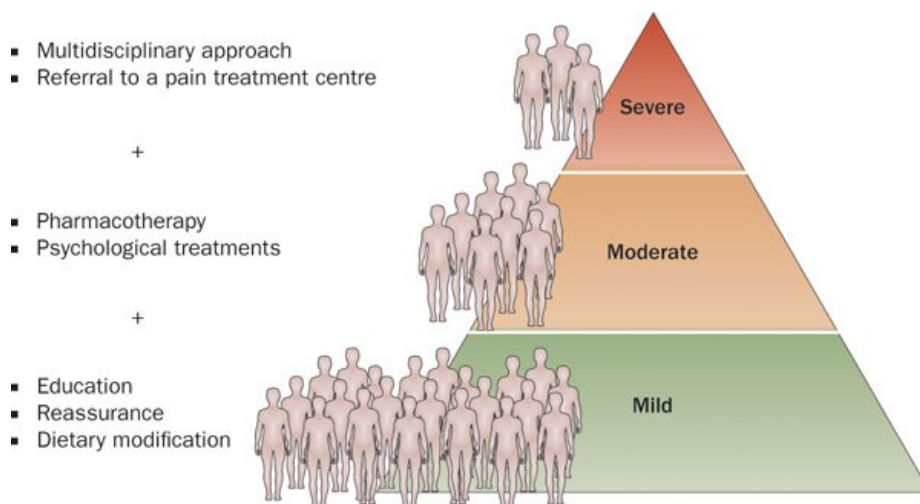


Figure 3: Graduated treatment approach for IBS. From Khan, S. & Chang, L. (2010) Diagnosis and management of IBS. Nat. Rev. Gastroenterol. Hepatol. (Khan S, 2010).

Patients diagnosed with IBS exhibit a higher use of outpatient visits, inpatient stays, outpatient prescriptions and number of hospitalizations than those not diagnosed with IBS (Eisen GM, 2000; Ganguly R, 2001; Longstreth GF, 2003). A recent study showed that knowledge and use of the Rome criteria or their positive predictive values for IBS did not correlate with reduced use of diagnostic tests (Charapata C, 2006). The cost for outpatient visits, drugs and diagnostic testing has been shown to be 50% higher for IBS patients than for others (Eisen GM, 2000; Ganguly R, 2001; Longstreth GF, 2003). IBS subjects have been shown to lose time from work more often than others and are less productive while at work (Hulisz, 2004). This may reflect the morbidity in this relatively benign disorder, although up to 70% of IBS patients in the United States do not consult a health care provider regarding their symptoms (Drossman DA, 2002). US family practitioners have attitudes about IBS patients which include difficulties in satisfying patients and difficulties in making a strategy decision and finding the time required, and their lack of knowledge could interfere with patient care (Longstreth GF, 2003). The management of IBS is multifaceted and often driven by illness severity, predominant symptoms, and patient and practitioner preferences (Figure 3) (Khan S, 2010). Multiple treatment options are available for IBS but none specific. Most do not effectively improve symptoms in all patients even within a particular subtype. Predominant symptoms, severity of the IBS, and patient and practitioner preferences usually guide management. Given the complex and multifactorial nature of IBS, the optimal treatment is often individualized and patient-centered (Khan S, 2010). In clinical practice the treatment strategies are up to the discretion of the physician (Hulisz, 2004). There is accumulating and compelling evidence that hypnotherapy is an effective treatment for irritable bowel syndrome (Gonsalkorale WM, 2005). Peter Whorwell has pointed out that

hypnotherapy is best provided as part of an integrated approach to treating IBS (Whorwell, 2006) rather than being regarded as a 'stand-alone' treatment. It also has to be remembered that it only helps a finite number of individuals (approximately 70%), and those who do not respond to it become very despondent as they often view hypnotherapy as their last chance to gain some improvement in the quality of their lives (Whorwell, 2008).

1.8 Gender differences

In the Western countries more women than men seek health care services for IBS (Chial HJ, 2002; Heitkemper M, 2008). This can possibly be explained by factors involving physiological gender differences in gonadal hormones, stress reactivity, and inflammatory responses, as well as sociocultural differences in response to pain and/or bowel pattern changes (Heitkemper M, 2008). In a recent study of men and women with IBS, the gender differences found were more complicated than a simple ratio of men:women (Herman J, 2010). Women with IBS report more constipation, nausea, bloating and extraintestinal and psychological symptoms than men with IBS (Chang L, 2002). Gender-related differences in gastrointestinal and somatic symptoms are apparent in persons with IBS but are most prominent in postmenopausal women (Cain KC, 2009). Abdominal pain has been shown to be the most disruptive symptom in IBS (Lembo T, 1999; Cain KC, 2006) and impacts on the quality of life in women with IBS. The differences between genders in the occurrence of IBS could furthermore be the result of cultural, psychosocial, or healthcare access issues instead of purely physiological differences (Heitkemper MM, 2008).

Women with chronic FGID in many cases have a history of physical, emotional or sexual abuse in childhood or adulthood, which is associated with a poor HRQL and increased health care seeking (Alander T, 2008).

Population-based studies are essential for studying IBS since only a minority of IBS patients seek medical care, self-medication is common (Penston JG, 1996) and differences have been noted in IBS patients and non-patients from the community (Jones R, 1992; El-Serag HB, 2004). A recent meta-analysis summarized gender variance in IBS (Adeyemo MA, 2010). In the general population, women were more likely to report abdominal pain and pain-related IBS diagnostic symptoms (Smith RC, 1991; Talley NJ, 1991; Taub E, 1995; Thompson, 1997; Talley NJ, 1998; Si JM, 2004; Kim YJ, 2005; Zuckerman MJ, 2006; Shen L, 2009; Adeyemo MA, 2010). The great majority of IBS studies are patient or healthcare based. Women overall have a greater prevalence of IBS symptoms than men, particularly those associated with constipation (Adeyemo MA, 2010). Studies suggest that female sex hormones influence the severity of IBS symptoms (Adeyemo MA, 2010). A recent study suggests that an increase in gastrointestinal symptoms around the time of menses and early menopause occurs at times of declining or low ovarian hormones, suggesting that estrogen and progesterone withdrawal may contribute either directly or indirectly (Heitkemper MM, 2009). Women with dysmenorrhea report more gastrointestinal symptoms prior to or concurrent with uterine cramping pain at menses than women who are nondysmenorrheic (Kane SV, 1998).

Gastrointestinal symptoms tend to be elevated across all cycle phases in women with IBS compared to healthy women, but both groups demonstrated a similar increase in severity immediately prior to or at the onset of menses (Heitkemper MM, 2003). Women report increased GI symptoms at time of menses compared with other phases (Simmons L, 1988; Hinds JP, 1989; Whitehead WE, 1990; Jackson NA, 1994; Heitkemper MM, 1995; Kane SV, 1998; Chang L, 2001; Houghton LA, 2002; Heitkemper MM, 2003; Adeyemo MA, 2010; Lee OY, 2001).

1.9 Summary

In the last decade numerous studies on FGIDs have been published and results are still conflicting concerning prevalence and outcomes. Few longitudinal studies have been performed on the natural history of FGID. Comparison of studies using the same methods and criteria is essential for understanding the natural history of FGID. The Rome III criteria were introduced in 2006 and provide an important tool to use in future epidemiological studies.

The range of prevalence of FGID symptoms is broad and differs between studies and country sites. The rapid change in criteria has made it difficult to compare studies. Recent studies have suggested that there is a stability of FGID symptoms but a flow between symptom groups.

Different factors can affect FGID. Psychosocial factors and social influences are known to affect the severity of FGID symptoms and differences in prevalence of gender are known in IBS. The effect of dysmenorrhea in women with IBS and the changes in IBS severity caused by menopause are interesting factors in gender differences. Patients with FGID often experience FGID as a chronic condition and physicians make FGID as a diagnosis of exclusion. This makes patients often experience FGID as a diagnosis of uncertainty and without the dignity of a diagnosis of a disease that can be managed.

With more information on the natural history and prevalence of FGID, we will be able to provide more knowledge and understanding for physicians and patients and therefore give FGID more weight in the field of medicine.

1.10 Primary aim of this study

The primary objective of this study was to document the natural history of FGID in the Icelandic population.

Specific aims of the thesis were:

- To study the natural history and the prevalence of FGID and compare it with the Olmsted County study (paper I). Both studies used the same methodology, i.e. the Bowel Disease Questionnaire (BDQ), thereby ensuring a reasonable degree of comparability for the Rome II data. Another objective for the study was to assess the birth cohort effect on the prevalence (%) of FGID (paper IV)

- To compare the prevalence and stability of IBS according to the Manning criteria, Rome II, Rome III subtypes, and self-reported IBS over a 10 year period. Another objective of the study was to assess the birth cohort effect on the prevalence (%) of IBS (paper II).
- To study the natural history of IBS and dysmenorrhea in women over a 10 year period. The secondary objective was to assess the change in IBS over menopause and the birth cohort effect on dysmenorrhea (paper VI)
- To analyze IBS from the physician's and the IBS patient's point of view. The specific aims of this study were the following (paper V):
 - The physician study: to assess if and how physicians (general practitioners - GPs, specialists in gastroenterology - SGs): (i) use the diagnostic criteria to identify IBS; (ii) diagnose patients with IBS, and which symptoms of IBS they identify; and (iii) which treatment they recommended
 - The patient study: to assess how subjects with IBS based on criteria are diagnosed and treated by physicians and which treatment they received, as well as studying the ideas the subjects have of IBS
- To evaluate the natural history of FD as defined by the Bowel Disease Questionnaire (modified), in the Icelandic population prospectively over a 10-year period and furthermore to evaluate the natural history over a 10-year period of dyspepsia subgroups with symptoms compared to the FD criteria (paper I)
- To study the natural history of heartburn in the Icelandic population prospectively over a 10-year period, as well as to evaluate different factors which are affected by heartburn, both physically and sociodemographically (paper III)

2 MATERIALS AND METHODS

2.1 Study Design

In 1996 an epidemiological study of gastrointestinal diseases was performed in Iceland (Ólafsdóttir LB, 2005). A total of 2000 inhabitants aged 18-75 years were studied. The individuals were randomly selected from the National Registry of Iceland. Equal distribution of sex and age was secured in each age group. In 2006 we attempted to contact all the individuals from the 1996 study as well as adding 300 new individuals in the age group 18-27, who were also randomly selected from the National Registry.

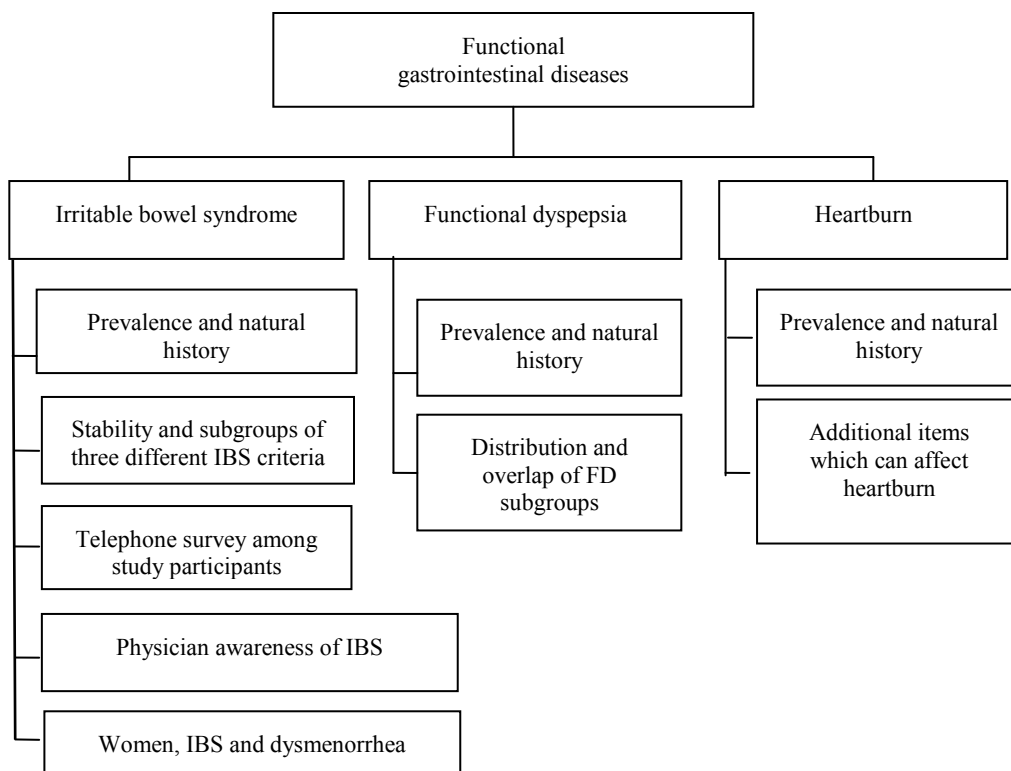


Figure 4 Study design and symptom categories

A questionnaire was mailed to individuals at baseline and the study questionnaire and an explanatory letter mailed to all eligible individuals. Reminder letters were mailed at 2, 4, and 7 weeks, using the Total Method of Dillman (Dillman, 1978). Individuals who indicated at any point that they did not want to participate in the study were not contacted further. The study was conducted in compliance with the guidelines for Good Epidemiology Practice (GEP).

Study design and symptom categories can be seen in figure 4.

2.2 Study population. Age and sex distribution

Figure 5 is a flow chart of the participation and follow-up in the study.

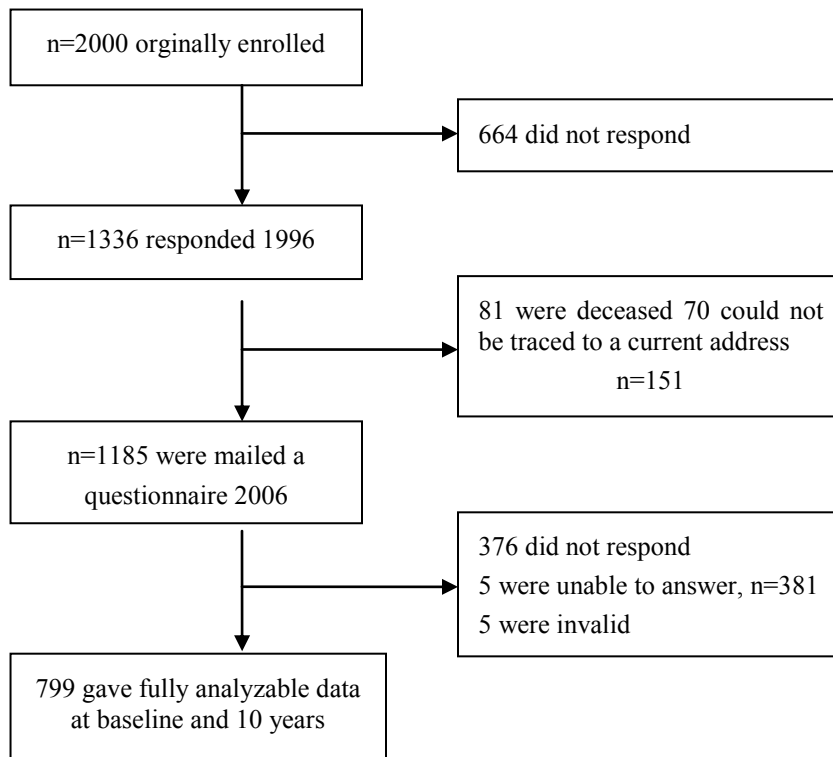


Figure 5: Flow chart of participation and follow-up in the study (Paper IV)

2.3 Mortality data

For the 2006 survey we identified all deceased individuals with the assistance of the National Registry of Iceland (Thjodskra).

2.4 The questionnaire

The Bowel Disease Questionnaire (BDQ) (Talley NJ, 1989; Nicholas J. Talley, 1990) was translated from English into Icelandic and modified for this study (see appendix 1). The questionnaire was translated by two gastroenterologists and a pharmacist. A specialist in the Icelandic language at the University of Iceland made linguistic modifications. The questionnaire was piloted within a small group of IBS patients diagnosed by a gastroenterologist.

The questionnaire was designed as a self-report instrument to measure symptoms experienced over the previous year and to collect the participant's past medical history (Halder SLS, 2007). The Icelandic version of the BDQ questionnaire addresses 47 gastrointestinal symptoms and 32

items that measure past illness, health care use, and sociodemographic and psychosomatic symptoms items, together with a valid measure of non-GI somatic complaints, the Somatic Symptom Checklist (SSC) (Attanasio V, 1984). The SSC consists of 12 non-GI and 5 GI symptoms or illnesses. Individuals are instructed to indicate, on a 5-point scale, how often each symptom appears and how bothersome it is. There were a few changes in the latter questionnaire when used in 2006, which addressed 51 gastrointestinal symptoms and 33 items that measure past illness, health care use, and sociodemographic and psychosomatic symptoms items. The 2006 questionnaire furthermore addressed 17 items to identify heartburn and items related to heartburn and Rome criteria to identify IBS.

2.5 Diagnostic criteria

We used different approaches for FGID symptom categories. Different criteria were used both to compare prevalence between criterias and to be able to compare our results to published papers.

2.5.1 Symptom Categories

Subjects were classified according to the methodology used by Halder et al. (Halder SLS, 2007) into a priori symptom groups, based on their responses to each of the questionnaires, which recorded their symptoms over the previous year. A subject could have more than one disorder. The same modification of Rome II was used to categorize subjects as in the study by Halder et al. (Halder SLS, 2007).

2.5.2 IBS

Criteria to identify IBS

The criteria for identification of IBS are presented in table 3.

Diagnosis of IBS according to the Manning criteria (Manning AP, 1978) required two or more of the six symptoms listed in table I and abdominal pain six or more times during the previous year (Drossman, 1989; Talley NJ, 1991).

Rome II: the 2006 questionnaire included Rome II criteria (Thompson WG, 1999) to identify IBS. The 1996 questionnaire made it possible with minor modification to create surrogate Rome II criteria.

Rome III: a close approximation of the Rome III criteria was used. The data were re-evaluated retrospectively to conform to Rome III criteria.

Self-report IBS, subjects were asked whether or not they had IBS. Two commonly used Icelandic translations were given (ristilkrampar and idraolga). No further explanation of the disease was provided.

Table 3: Criteria to identify IBS

Manning
Pain eased after BM
Looser stools at onset of pain
More frequent BM at onset of pain
Abdominal distension
Mucus per rectum
Feeling of incomplete emptying
Rome II criteria
At least 12 weeks (which need not be consecutive) in the preceding 12 months, of abdominal discomfort or pain that has two out of three features: Relieved with defecation; and/or Onset associated with a change in frequency of stool, and/or Onset associated with a change in form (appearance) of stool
Rome III criteria
Recurrent abdominal pain or discomfort at least 3 days/month in the last 3 months association with two or more of the following: Improvement with defecation Onset associated with a change in frequency of stool Onset associated with a change in form (appearance) of stool
BMs, bowel movements.
<i>Subgroups of Rome III:</i>
Subjects fulfilling the Rome III criteria were divided into 4 subgroups according to their bowel habits: (1) diarrhea-predominant (IBS-D), IBS-D is determined by predominantly loose or watery stools $\geq 25\%$ of the time; (2) constipation- predominant (IBS-C), IBS-C is determined by predominantly hard or lumpy stools $\geq 25\%$ of the time; (3) diarrhea and constipation (IBS-M), categories for mixed [mixed irritable bowel syndrome (IBS-M): meeting criteria for IBS-D and IBS-C $\geq 25\%$ of time], and (4) no diarrhea or constipation, un-subtyped [un-subtyped irritable bowel syndrome (IBS-U): not meeting criteria for of IBS-C nor IBS-D, i.e. both are $< 25\%$ of the time].

2.5.3 Symptom Categories (Halder SLS, 2007)

Subjects were classified according to the methodology used by Halder et al. (Halder SLS, 2007) into a priori symptom groups based on their responses to each of the questionnaires, which recorded their symptoms over the previous year. A subject could have more than one disorder. The same modification of Rome II was used to categorize subjects as in the study by Halder et al. (Halder SLS, 2007). See table 4.

Table 4: Diagnostic criteria used by Halder et al. (Halder SLS, 2007)

IBS
<p>The criteria for identification of IBS were a slight modification of Rome II criteria.</p> <p>IBS was defined as a combination of frequent (more than 6 times per year) abdominal pain and an altered bowel habit.</p> <p>The abdominal pain had to have 2 of the following 3 characteristics:</p> <ol style="list-style-type: none">1. relieved by defecation2. associated with a change in stool frequency3. associated with a change in stool form. <p>Rome II: the 2006 questionnaire included Rome II criteria [25] to identify IBS.</p>
IBS-constipation predominant
<p>IBS-constipation predominant (IBS-C) fulfils the criteria of IBS and reports 2 or more of the following symptoms:</p> <ol style="list-style-type: none">1. less than 3 bowel movements per week2. straining to have a bowel movement3. often passing hard stools4. incomplete evacuation.
IBS-diarrhea predominant (IBS-D)
<p>IBS-diarrhea predominant (IBS-D) fulfils the definition of IBS and reports often passing loose or watery stools.</p>
IBS-both
<p>IBS-both meets the definitions for both IBS-C and IBS-D.</p>
IBS neither C nor D
<p>IBS-neither meets the definitions for IBS with the exclusion of IBS-C and IBS-D.</p>
Functional constipation
<p>Functional constipation (C) in the absence of frequent abdominal pain is defined as having 2 or more of the following symptoms:</p> <ol style="list-style-type: none">1. less than 3 bowel movements per week2. straining to have a bowel movement3. often passing hard stools4. incomplete evacuation.
Functional diarrhea
<p>Functional diarrhea (D) in the absence of frequent abdominal pain has 1 or more of the following symptoms:</p> <ol style="list-style-type: none">1. reporting diarrhea as the usual bowel pattern2. more than 3 bowel movements per day3. having loose or watery stools4. urgency to have a bowel movement.
Both C and D
<p>Both C and D meet the definition for both constipation and diarrhea with no abdominal pain.</p>
FD
<p>FD was defined as when 2 or more of the following are present</p> <ol style="list-style-type: none">1. frequent upper pain (>6 times per year)2. nausea (at least weekly >3)3. vomiting (at least weekly >3)4. early satiety5. loss of appetite
Abdominal pain
<p>Subjects who reported having had more than 6 episodes of abdominal pain in the prior year were considered to have frequent abdominal pain; those who reported fewer episodes were not included to remove those experiencing only gastroenteritis or other acute illness.</p> <p>This is not functional abdominal pain as defined by Rome II (Drossman D, 2006).</p>

2.5.4 Heartburn

Subjects were classified with heartburn if they reported heartburn according to the following definition: Heartburn is a burning sensation in the retrosternal area (behind the breastbone). The pain often rises in the upper abdomen and may radiate to the chest.

2.5.5 Dyspepsia

1. Functional Dyspepsia Score List (Table 5). Subjects were classified with dyspepsia if they reported symptoms from the Functional Dyspepsia Score List (Nicholas J. Talley, 1990): Pain from the upper abdomen more than six times in the preceding year and 19 dyspepsia-related symptoms (in our study we combined two symptoms, nausea and vomiting, into one question and therefore had 18 dyspepsia-related symptoms). Each set of questions in Table 5 was ranked according to the method by Talley et al. (Talley NJ, 1990). These calculations provided an average rank for each subject and were divided into 3 categories: mild, moderate and severe. Subjects with significant functional dyspepsia were classified as having moderate to severe symptoms but a report of ulcer disease was an exclusion criterion.

Table 5: Subjects were classified with dyspepsia if they reported symptoms from the Functional Dyspepsia Score List

Functional dyspepsia score (FD)
Abdominal pain score above the navel >6 times in the past year
Severity of ache or pain
Ache or pain awakens subject from sleep at night
Pain comes and goes periodically
Ache or pain occurs before meals or when hungry
Ache or pain occurs immediately after meals
Ache or pain occurs 30 minutes to 2 hours after meals
Pain relieved by burping
Pain relieved by eating
Pain relieved by antacids
Pain intensified by consumption of food or milk
Pain intensified by drinking of beer, wine, or other alcoholic beverages
Number of times subject had pain in the last year
Radiation of pain
Initial occurrence of pain
Nausea or vomiting in the past year
Change in weight in the past year
Change in appetite in the past year

2. Dyspepsia subgroups: Subjects were categorized into 4 groups: (1) frequent upper pain (FUP), more than 6 times per year; (2) meal-related (MR) (discomfort related to eating), (3) nausea or vomiting (NV) once a week or more, (4) combination (COMB), more than one of the above 3 symptom complexes.

2.6 Women, IBS and dysmenorrhea

Women were asked if they experienced dysmenorrhea in the beginning of their menstruation. Those who had dysmenorrhea were asked to state the magnitude of the pain; minor pain, medium pain, severe pain, very severe pain and no pain. Those who did not have menstruations were excluded.

2.7 Telephone survey among study participants

In the questionnaire subjects were asked to write down their telephone number and give their permission to participate in a telephone survey. Subjects who were diagnosed with IBS based on the Manning criteria and/or the Rome III criteria and had written down their telephone number were called and interviewed.

2.8 Physician study

In Iceland (population ca. 330,000) there are 177 physicians working in general practice (GP) and 17 specialists in gastroenterology (SG) (3 physicians who were involved in carrying out this study were excluded). A questionnaire was sent to these 191 physicians regarding awareness and application of the 3 sets of criteria used to diagnose IBS (Table 3) as well as diagnostic methods and treatment of this disorder. We assessed the knowledge of validated symptom-based criteria for IBS.

2.9 Ethics

The National Bioethics Committee of Iceland and The Icelandic Data Protection Authority (Personuvernd) gave their permission for the research.

2.10 Statistical Methods

Tables were constructed for frequency and percentage. Categorical data were analyzed using the χ^2 test (Chi square test) and independent samples using the T-test. The type I error protection rate was set at 0.05. The exact p is listed in the tables and text. All the research data were imported into SPSS (Statistical Package of Social Science) software.

2.11 Transition between disorders from the initial to the final survey

A transition model used by Halder et al. was modified and applied for this study (Halder SLS, 2007) (Figure 6). The responses from the initial (1996) and final (2006) surveys were

matched for each subject to examine the changes between disorders (for example A-D in Figure 4) at an individual level for the various categories depending on the subject (papers I, II, III, IV, V). An XxX table was used to model these multiple changes and collapsed into 6 groups, as illustrated in Figure 7. Those with the most symptoms were prioritized higher. Those who developed more symptoms and those who reported fewer symptoms could be categorized into groups. There were six patterns of symptoms, identified as follows: (1) symptom stability, (2) symptom increase, (3) symptom decrease, (4) symptom onset, (5) becoming asymptomatic, and (6) none of these symptoms.

Disorder in 1996	Proportion of disorder in 2006 based on primary survey disorder				
	A %	B %	C %	D %	No symptoms (%?)
A					
B					
C					
D					
No symptoms					
	Remaining asymptomatic			Developed symptoms	
	Became asymptomatic			Decreased symptoms	
	Stable			Increased symptoms	

Figure 6: A transition model (Halder SLS, 2007)

3 RESULTS

3.1 Study participants

3.1.1 Demographic Data of Involved Individuals

In 1996 the response rate was 66.8% (1336/2000). Of the 1336 individuals who participated in 1996, 81 were deceased by 2006, five subjects were unable to answer, mainly because of old age, 70 could not be traced to a current address, and 5 were invalids. This left 1180 individuals, out of which 799 (40.0%) responded in 2006 (Figure 5). Therefore the response rate in 2006 was 67.7% (799/1180).

The mean age of the individuals in 1996 was 42 and in 2006 was 53 ($p=NS$). Women were more apt to respond than men in both years. A larger proportion of women responded again in 2006 (57.8%) than those who responded in 1996. The response rate was higher for older subjects than younger ones. There was no significant difference between those who responded or those who did not respond in 2006, whether or not they were diagnosed with IBS in 1996. Age distribution and demographic details of the study cohort are presented in table 6.

Table 6: Study population. Age and sex distribution

		Population 2006 (%)	Respondents 2006 (%)
Gender			
	Men	50.3	42.2
	Women	49.7	57.8
Age			
	28-35	19.5	14.52
	36-45	24.9	20.40
	46-55	22.8	22.15
	56-65	15.6	19.52
	66-75	10.4	15.14
	76-85	6.8	8.26
Total		N=173859	n=799

3.2 Prevalence of FGID (IV)

3.2.1 Natural history of FGID

The prevalence of any of the FGID in Iceland over the 10 year period was 36.8% in 1996 and 35.7% in 2006. In paper IV the natural history of FGID was studied and compared to the Olmsted County study (Halder SLS, 2007).

3.2.2 Comparison of two longitudinal population-based studies

Demographic Data of Involved Individuals

Comparison of the demographics of Olmsted County and Icelandic studies can be seen in table 7. The major difference between these two studies was the mean age as the Icelandic study population was younger. The time points of the initial and final surveys of the studies were also different.

Table 7: Study population, comparison with the Olmsted County study

	Iceland*	Olmsted County*			
Number of subjects in initial survey	2000	4816			
Response rate	67%	79%			
Mean age (years)	42	47			
Women responding	55%	55%			
Number of subjects in final survey	1.180	2914			
Subjects who responded to both initial and final surveys	40% (779/2000)	28% (1365/4816)			
Mean age (years)	53	57			
Women responding	58%	52%			
Mean (\pm SD) time between completion of the initial and final surveys	10 years	12 years (\pm 2)			
Study period	1996/2006	1988/2003	t-test	df	p-test
IBS initial	16.9%	8.3%	6.476	794	<0.001
IBS final	17.2%	11.4%	4.325	754	<0.001
IBS-D initial	6.8%	3.3%	3.83	761	0.035
IBS-D final	9.1%	4.9%	3.912	730	<0.001
IBS-C initial	9.7%	2.7%	6.615	784	0.07
IBS-C final	6.8%	2.4%	4.762	749	<0.001
IBS-M initial	2.8%	1.3%	2.446	760	0.015
IBS-M final	3.6%	1.2%	3.279	730	0.001
IBS at both initial and final (stable)	20%	24%			
Developed IBS symptoms at final	11%	16.20%	-4.215	667	<0.001
Lost IBS symptoms at final	56%	55.10%	0.102	125	0.919

*Age- and sex adjusted in order to represent sex- and age distribution in the population

Prevalence of each disorder and comparison with the Olmsted County study

The prevalence rates for each FGID studied can be seen in table 8. In the Olmstead County study there was a higher prevalence of any of the FGID over the 12 year period, with an aggregated rate of 42.3%.

IBS and subgroups. In our survey the age- and sex-adjusted rate of any IBS in the initial study was 16.9% (95% CI: 14.3-19.6) and 17.2% (95% CI: 14.4-19.9) in the final study (Table 8). The prevalence of IBS in women was much higher than in men. There was an increase among the females (20.5%, 22.7%) and a decrease among the males (13.4%, 11.6%) between the two studies. Among the IBS subgroups, there was a decrease in IBS-C (9.7%, 6.8%), an increase in both IBS-D (6.8%, 9.1%) and IBS-M (2.8%, 3.6%). In comparison to the Olmsted County study the IBS numbers in Iceland were significantly much higher in all IBS categories except for IBS-C initial. IBS (any) in the Olmsted County study had the initial prevalence of 8.3% and 11.4% in the final survey (Figure 7).

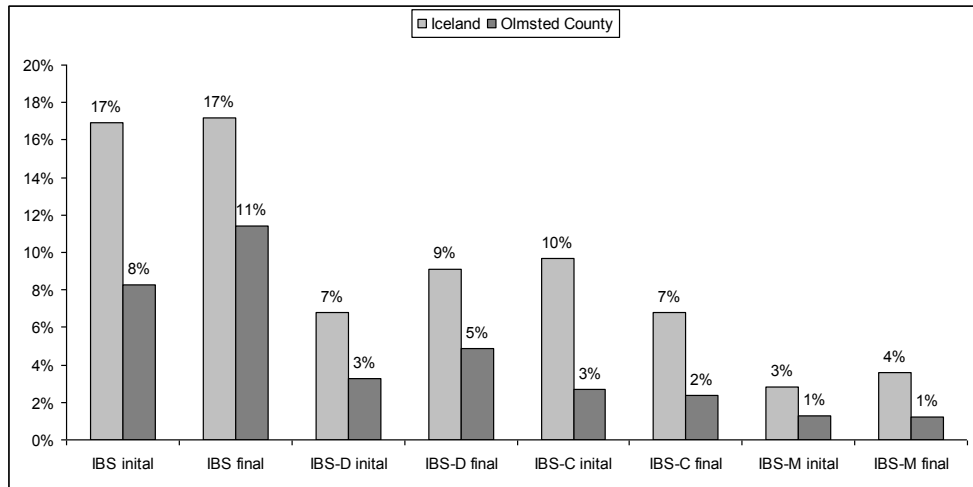


Figure 7: Comparison of IBS and subgroups in Iceland and Olmsted County

Table 8: Prevalence (%) of functional GI disorders in Iceland

FGID	Initial (baseline - 1996)			Final (follow up - 2006)		
	Female (95% CI)	Male (95% CI)	All (95% CI)	Female (95% CI)	Male (95% CI)	All (95% CI)
IBS (any)	20.5 (16.5-24.5) <i>(9.7)</i>	13.4 (10.0-16.7) <i>(7.0)</i>	16.9 (14.3-19.6) <i>(8.3)</i>	22.7 (18.3-27.2) <i>(13.0)</i>	11.6 (8.4-14.8) <i>(9.5)</i>	17.2 (14.4-19.9) <i>(11.4)</i>
IBS-C	12.2 (9.0-15.5) <i>(3.0)</i>	7.2 (4.6-9.7) <i>(2.4)</i>	9.7 (7.6-11.8) <i>(2.7)</i>	9.4 (6.4-12.4) <i>(3.1)</i>	4.2 (2.2-6.2) <i>(1.6)</i>	6.8 (5.0-8.6) <i>(2.4)</i>
IBS-D	8.0 (5.2-10.7) <i>(3.9)</i>	5.6 (3.3-8.0) <i>(3.2)</i>	6.8 (5.0-8.6) <i>(3.6)</i>	10.6 (7.4-13.8) <i>(5.7)</i>	7.7 (5.0-10.5) <i>(4.0)</i>	9.1 (7.0-11.3) <i>(4.9)</i>
IBS-both	2.5 (0.9-4.1) <i>(1.6)</i>	3.0 (1.3-4.7) <i>(1.0)</i>	2.8 (1.6-3.9) <i>(1.3)</i>	4.3 (2.2-6.4) <i>(1.2)</i>	2.9 (1.2-4.6) <i>(1.0)</i>	3.6 (2.2-4.9) <i>(1.2)</i>
C	3.2 (1.4-4.9) <i>(4.5)</i>	2.5 (0.9-4.0) <i>(4.1)</i>	2.8 (1.7-4.0) <i>(4.3)</i>	2.5 (0.9-4.1) <i>(5.3)</i>	1.7 (0.4-3.0) <i>(3.1)</i>	2.1 (1.1-3.1) <i>(4.1)</i>
D	5.1 (3.0-7.3) <i>(5.0)</i>	3.3 (1.5-5.0) <i>(6.2)</i>	4.2 (2.8-5.6) <i>(5.6)</i>	3.9 (1.9-5.9) <i>(5.4)</i>	3.4 (1.6-5.3) <i>(6.2)</i>	3.7 (2.3-5.0) <i>(5.7)</i>
Both C and D	1.6 (0.4-2.9) <i>(1.0)</i>	1.0 (0.0-2.0) <i>(0.8)</i>	1.3 (0.5-2.1) <i>(0.9)</i>	1.7 (0.4-3.0) <i>(0.8)</i>	0.4 (0.0-1.0) <i>(1.0)</i>	1.0 (0.3-1.8) <i>(0.9)</i>
Functional dyspepsia	6.4 (3.9-8.8) <i>(2.0)</i>	3.3 (1.5-5.0) <i>(1.8)</i>	4.8 (3.3-6.3) <i>(1.9)</i>	9.8 (6.7-13.0) <i>(4.2)</i>	2.5 (1.0-4.1) <i>(2.3)</i>	6.1 (4.4-7.9) <i>(3.3)</i>
Frequent abdominal pain	39.4 (34.5-44.2) <i>(21.9)</i>	24.0 (19.8-28.1) <i>(18.2)</i>	31.6 (28.2-35.0) <i>(20.1)</i>	40.1 (34.6-45.7) <i>(22.3)</i>	26.6 (22.1-31.1) <i>(17.8)</i>	33.3 (29.8-36.9) <i>(20.2)</i>

FGID, functional gastrointestinal disorders; IBS, irritable bowel syndrome; C, constipation; D, diarrhea.
Numbers in *italic* = from the Olmsted County study

Constipation and diarrhea. The functional constipation rates were 2.8% (95% CI: 1.7-4.0) in 1996 and 2.1% (95% CI: 1.1-3.1) in 2006, respectively, and the functional diarrhea rates were 4.2 (95% CI: 2.8-5.6) in 1996 and 3.7% (95% CI: 3.7-5.0) in 2006 (Table 8). Subjects reported both constipation and diarrhea as 1.3% (95% CI: 0.5-2.1) in 1996 and 1.0 (95% CI: 0.3-1.8) in 2006. The prevalence of both functional diarrhea and functional constipation was higher in women than in men. The prevalence of functional diarrhea and constipation was higher in the Olmsted County study than in the Icelandic study (Figure 8).

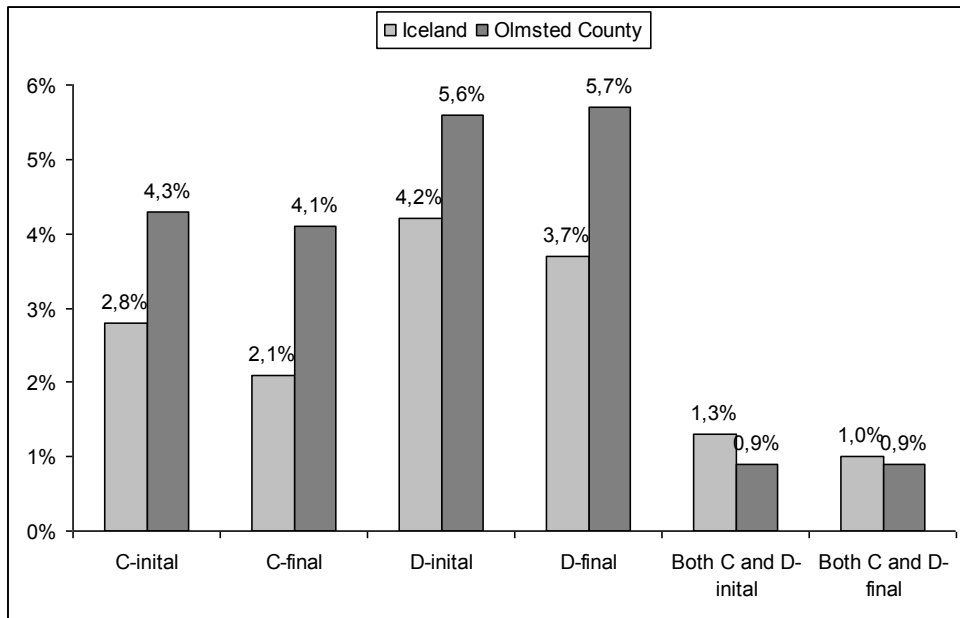


Figure 8: Comparison of constipation and diarrhea in Iceland and Olmsted County

Functional dyspepsia. The functional dyspepsia rates were 4.8% (95% CI: 3.3-6.3) in 1996 and 6.1% (95% CI: 4.4-7.9) in 2006 (Figure 9). The prevalence of functional dyspepsia was higher in women than in men in both years. There was an increase among the females (6.4% 1996 and 9.8% 2006) and there was a decrease among the males (3.3% 1996 and 2.5% 2006). The prevalence of functional dyspepsia was much higher in the Icelandic study (1996: 4.8%/2006: 6.1%) than in the Olmsted County study (initial: 1.9%/final: 3.3%).

Frequent abdominal pain (FAP). The rates of FAP were 31.6 (95% CI: 28.2-35.0) in 1996 and 33.3% (95% CI: 29.8-36.9) in 2006 (Figure 9). The prevalence was higher in women (1996: 39.4%/2006: 40.1%) than in men (1996: 24.0%/2006: 26.6%) The prevalence of abdominal pain was much higher in the Icelandic study (1996: 31.6%/2006: 33.3%) than in the Olmsted County study (initial: 20.1%/final: 20.2%).

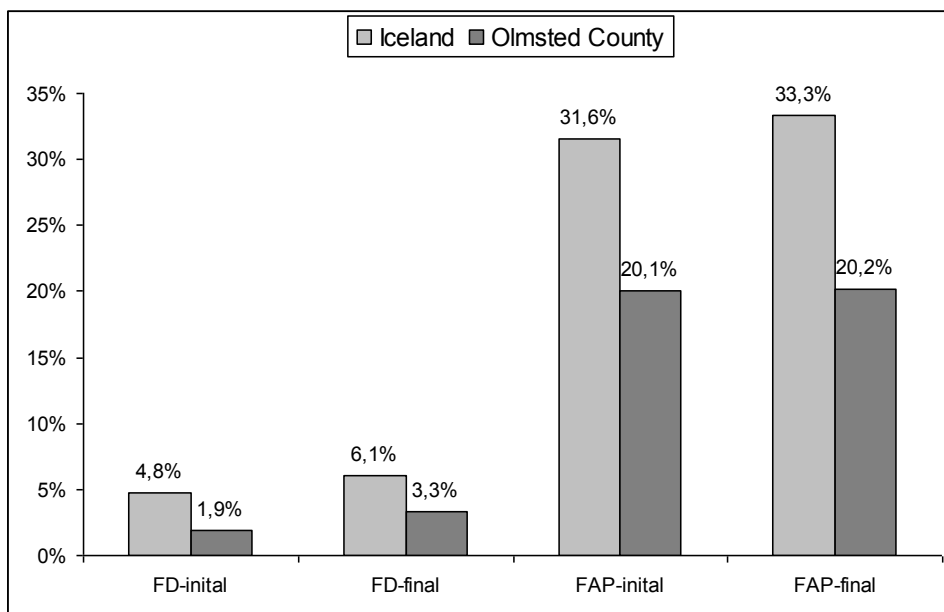


Figure 9: Comparison of FD and FAP in Iceland and Olmsted County

Onset and disappearance rates between the initial and final surveys

Table 9 Onset (%) of different functional GI disorders in 2006 in comparison to 1996.

FGID	Number at baseline	n	Iceland Onset (95% CI)	n	Olmsted County Onset (95% CI)
IBS-any	668	74	11.1 (8.7-13.5)	195	16.2 (14.1-18.4)
IBS neither C nor D	764	26	3.4 (2.1-4.7)	100	7.8 (6.4-9.4)
IBS-C	719	34	4.7 (3.2-6.3)	22	1.6 (1.0-2.5)
IBS-D	721	43	6.0 (4.2-7.7)	56	4.2 (3.2-5.5)
IBS-both	752	18	2.4 (1.3-3.5)	17	1.3 (0.7-2.0)
Constipation	770	15	1.9 (1.0-2.9)	51	3.9 (2.9-5.1)
Diarrhea	763	25	3.3 (2.0-4.5)	90	7.0 (5.7-8.6)
Both C and D	780	9	1.2 (0.4-1.9)	23	1.7 (1.1-2.5)
Functional dyspepsia	748	39	5.2 (3.6-6.8)	67	5.1 (4.0-6.4)
Frequent abdominal pain	545	97	17.8 (14.6-21.0)	235	24.0 (21.4-26.8)

NOTE. For each condition, the left column shows the number of people without the condition at baseline. The right column shows the number and percentage (with 95% CI) of those people who did report the condition at follow-up.

FGID, functional gastrointestinal disorders; IBS, irritable bowel syndrome; C, constipation; D, diarrhea.

Numbers in italics = from the Olmsted County study

Table 9 shows the onset of different functional GI disorders in 2006 as compared to 1996. Subjects could be categorized into more than one FGID group. Onset rates were based on those who were free of symptoms of a specified disorder at the time point of the first survey

and were then identified with symptoms of that specific disorder in the latter survey. Subjects could have had that specific disorder during more than one year prior to the initial survey. Subjects who did not report any form of IBS in 1996 (11.1%, n=74) reported IBS symptoms in 2006. There was an onset of IBS neither C nor D (IBS not fulfilling the criteria for IBS with constipation or diarrhea) in 3.4% of the subjects. The onset of IBS-C was 4.7%, of IBS-D was 6.0% and of IBS-M 2.4%. Compared to the Olmsted County study the numbers in Iceland were lower for the IBS-any (11.1% vs. 16.2%). The rates were also lower for the IBS neither C nor D. However, the rates were higher for subjects in Iceland in the IBS-C, IBS-D and IBS-both. The frequency of onset of constipation, diarrhea, functional dyspepsia and frequent abdominal pain was lower in the Icelandic study (see table 9).

In table 10 the disappearance of different functional GI disorders can be seen. Of those reporting any IBS symptoms in 1996, 55.6% reported disappearance of symptoms in 2006; 86.4% reported disappearance of IBS neither C nor D, 67.6% disappearance of IBS-C, 54.2% disappearance of IBS-D, and 62.5% disappearance of IBS-both. These rates were similar in the Olmsted County study for IBS-any (55.6%/55.1%). The disappearance rates were somewhat higher in the Icelandic study for IBS neither C nor D, IBS-C and IBS-both, and somewhat lower for IBS-D.

The high disappearance rates for constipation and diarrhea (85.0% and 96.9%) were higher than in the Olmsted County study (77.8% and 71.3%). There was also a high disappearance rate for functional dyspepsia, 62.9%, which was similar to the Olmsted County study (66.7%). The disappearance rate for frequent abdominal pain was lower in this study (35.3%) than in the Olmsted County study (42.6%).

We could not directly compare the onset and disappearance of FGID symptoms because of different denominators used. But when we looked at the absolute numbers, we saw that there was not a great difference between the number of subjects with onset and disappearance of symptoms. The only difference was in subjects reporting functional dyspepsia and frequent abdominal pain, with more subjects in the onset group. In comparison, a greater number of subjects had onset of different functional GI disorders than disappearance in most cases in the Olmsted County study compared with our study.

Transition between disorders from the 1996 and 2006 surveys

As described in the methods section, the groups in this analysis were defined as mutually exclusive, using the symptom hierarchy so that each subject appears in only one category for both the 1996 and 2006 surveys. There was a “no symptoms” category for those who did not meet any of the criteria applied for FGID. Due to the hierarchical classification only a few participants occurred in some categories.

Table 10: Disappearance (%) of different functional GI disorders in 2006 in comparison to 1996

FGID	Number at baseline	n	Iceland Disappearance (95% CI)	nOC	Olmsted County Disappearance (95% CI)OC
IBS-any	126	70	55.6 (46.9-64.2)	87	55.1 (47.0-63.0)
IBS neither C nor D	22	19	86.4 (72.0-100.0)	40	52.6 (40.8-64.2)
IBS-C	68	46	67.6 (56.5-78.8)	15	60.0 (38.7-78.9)
IBS-D	48	26	54.2 (40.1-68.3)	24	60.0 (43.3-75.1)
IBS-both	16	10	62.5 (38.8-86.2)	8	47.1 (23.0-72.2)
Constipation	20	17	85.0 (69.4-100.0)	35	77.8 (62.9-88.8)
Diarrhea	32	31	96.9 (90.8-100.0)	62	71.3 (60.6-80.5)
Both C and D	10	10	100.0 (100.0-100.0)	7	87.5 (47.4-99.7)
Functional dyspepsia	35	22	62.9 (46.8-78.9)	28	66.7 (50.5-80.4)
Frequent abdominal pain	252	89	35.3 (29.4-41.2)	165	42.6 (37.7-47.7)

NOTE. For each condition, the left column shows the number of people with the condition at baseline. The right column shows the number and percentage (with 95% CI) of those people who did not report the condition at follow-up.

FGID, functional gastrointestinal disorders; IBS, irritable bowel syndrome; C, constipation; D, diarrhea.

Numbers in *italic* = from the Olmsted County (OC) study

Transition between disorders from the 1996 and 2006 surveys

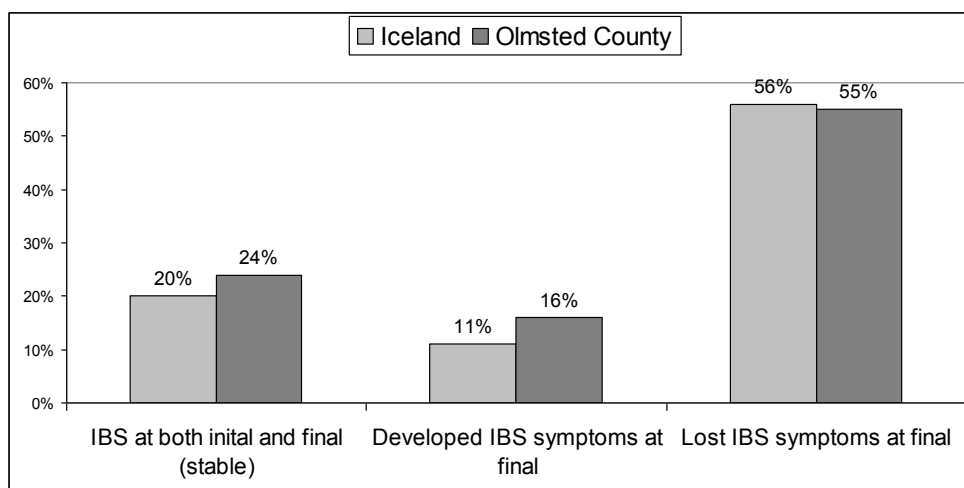


Figure 10: Changes in IBS symptoms at initial and final surveys

There was a substantial change in numbers in all the categories between the two surveys. The group “no symptoms” was the most common. Of the IBS groups the IBS-D was the most stable with 34.4%, and one third reported no symptoms at follow up. IBS-both and IBS –C were similar with almost one fifth in those categories, but more of the IBS-C moved into the no symptoms category. A few of the IBS-C moved into the IBS-D over the 10 year period and vice versa. That did not happen in the Olmsted County study where IBS-C did not transition into the IBS-D nor

FGID in 1996	Proportion of FGID in 2006 based on primary survey disorder									
	IBS-both%	IBS-C%	IBS-D%	IBS-no C or D%	Both C and D%	C%	D%	FD%	Frequent Abd. Pain%	No symptoms
IBS-both (n=16)	18.8 (23.5)	0.0 / (0.0)	12.5 / (29.4)	12.5 / (0.0)	6.3 / (0.0)	0.0 / (0.0)	0.0 / (5.9)	0.0 / (0.0)	31.3 / (11.8)	18.8 / (29.4)
IBS-C (n=52)	11.5 / (12.0)	17.3 / (12.0)	3.8 / (0.0)	5.8 / (16.0)	3.8 / (0.0)	1.9 / (8.0)	0.0 / (8.0)	7.7 / (0.0)	21.2 / (24.0)	26.9 / (20.0)
IBS-D (n=32)	3.1 / (2.5)	3.1 / (0.0)	34.4 / (20.0)	6.3 / (17.5)	0.0 / (0.0)	0.0 / (0.0)	3.1 / (15.0)	6.3 / (5.0)	9.4 / (5.0)	34.4 / (35.0)
IBS-no C or D (n=22)	0.0 / (1.3)	0.0 / (7.9)	18.2 / (7.9)	9.1 / (30.3)	0.0 / (2.6)	0.0 / (5.3)	0.0 / (2.6)	9.1 / (0.0)	36.4 / (11.8)	27.3 / (30.3)
Both C and D (n=10)	10.0 / (0.0)	40.0 / (0.0)	10.0 / (12.5)	10.0 / (0.0)	0.0 / (12.5)	10.0 / (0.0)	0.0 / (0.0)	0.0 / (0.0)	20.0 / (12.5)	0.0 / -62.5
C (n=10)	0.0 / (0.0)	10.0 / (6.7)	10.0 / (0.0)	0.0 / (4.4)	0.0 / (4.4)	0.0 / (22.2)	0.0 / (0.0)	10.0 / (6.7)	0.0 / (8.9)	70.0 / (46.7)
D (n=22)	0.0 / (3.5)	0.0 / (1.1)	4.5 / (5.8)	9.1 / (4.6)	0.0 / (2.3)	0.0 / (4.6)	4.5 / (28.7)	9.1 / (0.0)	31.8 / (6.9)	40.9 / (42.5)
FD (n=19)	0.0 / (0.0)	0.0 / (0.0)	10.5 / (0.0)	5.3 / (25.0)	0.0 / (0.0)	0.0 / (0.0)	15.8 / (0.0)	15.8 / (0.0)	15.8 / (25.0)	36.8 / (50.0)
Frequent Abdominal Pain (n=111)	5.4 / (2.5)	9.9 / (4.6)	6.3 / (10.6)	3.6 / (9.1)	1.8 / (0.5)	1.8 / (3.5)	1.8 / (6.6)	7.2 / (0.0)	22.5 / (22.2)	39.6 / (40.4)
No symptoms (n=505)	1.2 / (1.0)	0.6 / (1.0)	2.0 / (3.4)	2.6 / (8.7)	0.8 / (1.9)	0.6 / (3.9)	2.0 / (7.6)	0.6 / (0.2)	7.9 / (9.9)	81.8 / (62.3)

Remaining asymptomatic

Became asymptomatic

Stable

Developed symptoms

Decreased symptoms

Increased symptoms

FGID - Functional Gastrointestinal Disorders

FD - Functional Dyspepsia

D - Diarrhea

C - Constipation

Numbers in italics = Olmsted County Study

Figure 11: Transitions among symptom subgroups between the initial and final surveys and comparison with the Olmsted County study

did the IBS-D subjects move into the IBS-C. None of the IBS-C transitioned into the diarrhea group and none of the IBS-D moved into the constipation group. No one of those having IBS- neither C nor D was stable over the 10 year period. (Fig. 11)

A total of 15.8% had a stable FD in both years but 31.6% developed FD (increased symptoms) in 2006 and 36.8% had moved into the “no symptoms” group.

The category “frequent abdominal pain” was stable in 22.5% of cases, whereas 34.2% moved into the “increased symptoms” category and 39.6% into the “no symptoms” category.

IBS-any was more stable in the Olmsted County study (24%) than in Iceland (20%) (Figure 10). There was a significant difference between those two studies in developed IBS symptoms at final survey ($p<0.001$) but not for the IBS symptoms which were lost at final survey (NS).

The distribution of the 6 transition groups is illustrated in figure 12. The distribution for Iceland was 7% symptom stability, 9% symptom increase, 8% symptom decrease, 11% development of symptoms, 13% becoming asymptomatic, and 52% having no symptoms in either 1996 or 2006. When comparing these numbers with Olmsted County there was a significant difference ($p<0.001$) mainly caused by difference in the symptom onset which was 12% for this study and 24% for the Olmsted County study, and for the subjects who had no symptoms in both the initial and final surveys 52% in this study and 39% in the Olmsted County study.

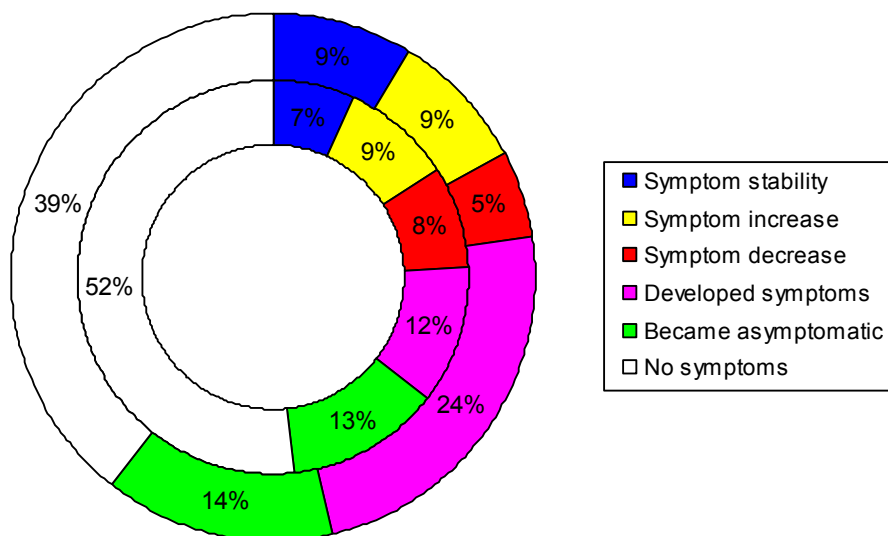


Figure 12: Six-group transition model, change from initial to the final survey. Iceland (n=799) in the inner circle and Olmsted County (n=1365) in the outer circle ($p<0.001$).

Birth cohort effect of functional gastrointestinal disorders

Data in table 11 suggest a birth cohort effect in IBS subjects, diarrhea subjects and subjects in the no symptom category. Other symptoms were not as prevalent and did not show a strong birth cohort relationship, as can be seen in figure 13.

Table 11: Birth cohort effect on the prevalence (%) of functional gastrointestinal disorders

	IBS (any)		Constipation		Diarrhea		Both C and D		FD		Abdominal pain		No symptoms	
	1996	2006	1996	2006	1996	2006	1996	2006	1996	2006	1996	2006	1996	2006
Born 1971-78	26.7	27.6	0.0	1.7	2.6	0.9	3.4	1.7	0.9	4.3	15.5	9.5	50.9	54.3
Born 1961-70	13.5	15.3	0.6	0.6	1.8	3.1	1.2	2.5	3.1	4.3	11.0	11.7	68.7	62.6
Born 1951-60	16.9	16.4	3.4	1.1	5.1	3.4	1.1	0.6	1.7	3.4	14.1	16.9	57.6	58.2
Born 1941-50	10.9	9.0	0.6	1.3	2.6	2.6	0.6	0.6	3.2	1.3	14.1	17.3	67.9	67.9
Born 1931-40	8.3	11.6	0.8	0.0	0.8	0.8	0.8	0.0	1.7	3.3	15.7	7.4	71.9	76.9
Born 1921-30	18.2	13.6	1.5	0.0	3.0	0.0	0.0	1.5	4.5	1.5	13.6	12.1	59.1	71.2

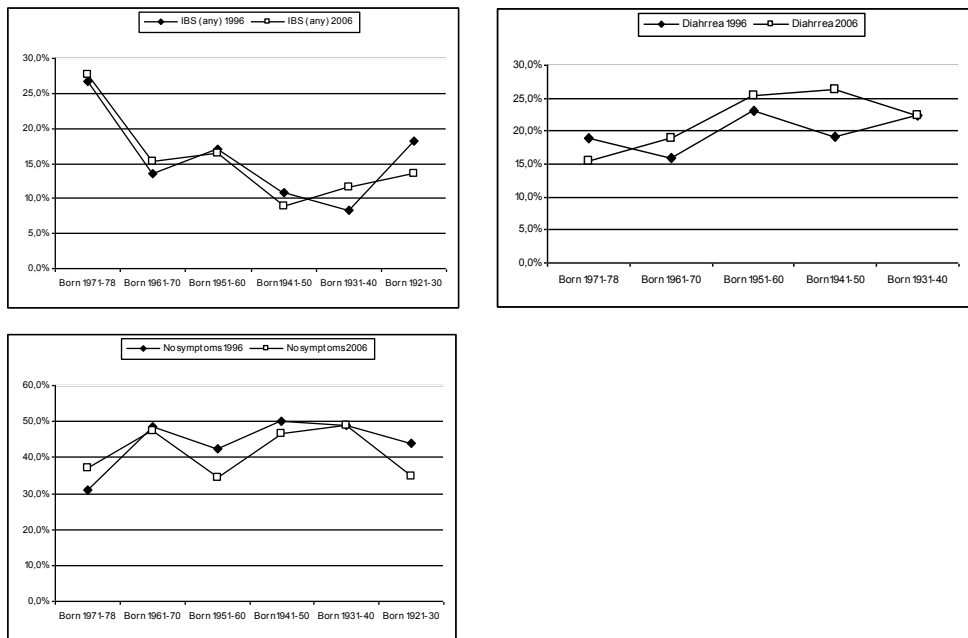


Figure 13: Birth cohort effect on the prevalence (%) in 10 years.

3.3 IBS

3.3.1 Prevalence and natural history (II)

The prevalence and natural history of IBS through three criteria were studied. The prevalence of IBS according to the Manning criteria showed similar results in 1996/2006 or

31%/32%, respectively (Fig.14). According to the Rome II criteria the prevalence of IBS in 2006 was significantly lower than for the Manning criteria or 5.0%. The Rome II criteria were not part of the questionnaire in 1996. The Rome III criteria showed a prevalence of IBS in 1996/2006 as 10%/13%, respectively. Self-reported IBS showed the same prevalence in 1996/2006 or 16% /16%. The yield from the different criteria can be seen in Fig. 14. Females were significantly more likely to report IBS than males when diagnosed with Manning, self-report IBS, Rome II or Rome III. There was no significant relationship between gender and Rome III for IBS in 1996 but there was a significant increase in prevalence of IBS (Rome III) for women between 1996 and 2006 (10% and 17%, respectively). This increase can only be seen in younger groups of females (age 26-55). The mean age was significantly lower for Manning, self-report, Rome II and Rome III criteria for IBS (2006) but this had not been a significant factor in Rome III in 1996 (Tables 13-14). Comparison of age group prevalence in each IBS category showed that the Manning and self-report criteria did not change significantly over the 10 year period. As can be seen in fig. 15 the prevalence of each birth cohort stayed pretty much the same during the 10 years (the 26-35 age group in the 2006 Manning group had a prevalence of 46.5% in 2006 and 41.8% in 1996, the 36-45 age group a prevalence of 31.4% in 2006 and 28.9% in 1996 etc.) The prevalence within age groups therefore remained fairly constant in most cases (Fig. 15). In the IBS Rome III group there were some changes in the 46-75 age groups (Fig. 15).

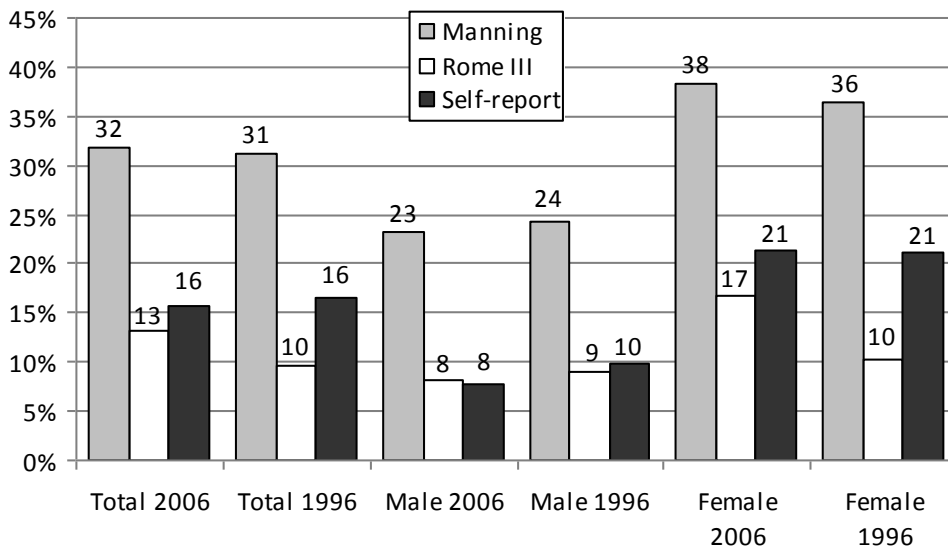


Figure 14: Prevalence of IBS for three IBS criteria and gender.

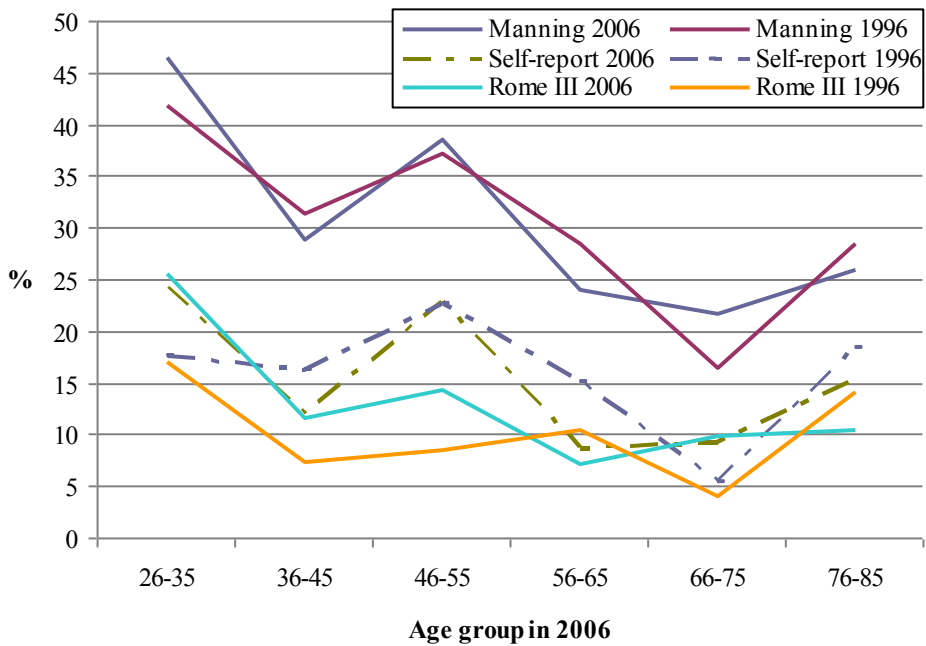


Figure 15: Birth cohort of IBS for three IBS criteria by age.

Data in Fig. 15 suggest a birth cohort effect on the prevalence of IBS, particularly with regard to the Manning criteria for subjects born 1971-78, but the difference was not significant.

Table 12: Birth cohort effect on the prevalence (%) of IBS according to three criteria

	Self-report		Rome III		Manning	
	1996	2006	1996	2006	1996	2006
Born 1971-78	17,7	24,1	17	25,7	41,8	46,5
Born 1961-70	16,3	12,1	7,4	11,5	31,4	28,9
Born 1951-60	22,7	22,9	8,6	14,4	37,2	38,6
Born 1941-50	15,1	8,6	10,5	7,2	28,6	24
Born 1931-40	5,5	9,4	4,1	9,9	16,5	21,8
Born 1921-30	18,4	15,4	14,1	10,5	28,6	26

Table 13: Sociodemographic factors and comorbidity in subjects fulfilling the Manning criteria, 1996 and 2006

	1996			2006		
	IBS-neg.	IBS-pos.	<i>P</i>	IBS-neg.	IBS-pos.	<i>P</i>
Gender (% Female)	52.9	66.8	<0.001	52.1	69.2	<0.001
Mean age (years)	43.9	39.8	<0.001	53.7	49.1	<0.001
Employment status (% employed)	85.5	77.5	0.008	76.2	76.2	0.980
Sick leave from work			<0.001			<0.001
≥6 times a year	4.1	13.8		4.6	12.8	
1-5 times a year	51.7	57.3		50.5	56.6	
Never	44.2	28.9		44.9	30.6	
Smoking			0.091			0.017
Smokers >15 cigarettes per day	19.8	26.4		7.5	11.1	
Smokers ≤15 cigarettes per day	32.5	36.4		15.4	22.6	
No smokers	48.6	37.2		77.2	66.3	
Gastrointestinal pain as a child	14.1	27.4	<0.001	16.8	30.2	<0.001
Appenectomy	19.4	31.9	<0.001	22.9	29.1	0.077
Cholecystectomy	2.5	7.8	<0.001	4.7	8.6	0.043
Gastroduodenal ulcer	7.6	13.9	0.008	8.8	14.9	0.016
Abdominal operation	18.3	28.3	0.002	22.4	28.3	0.095
Seeking physician in last 12 months			<0.001			<0.001
Never	23.7	12.6		22.9	10.8	
1-5 times	69.0	64.5		67.5	68.5	
>6 times	7.3	22.9		9.6	20.7	
Seeking physician because of gastro-pain	4.3	34.6	<0.001	4.5	26.0	<0.001
Heartburn	34.1	60.5	<0.001	35.4	60.8	<0.001
Functional dyspepsia	4.9	34.5	<0.001	6.9	41.1	<0.001

Table 14: Sociodemographic factors and comorbidity in subjects fulfilling the Rome criteria, 1996 and 2006

	Rome III 1996			Rome II 2006			Rome III 2006		
	IBS-neg.	IBS-pos.	<i>P</i>	IBS-neg.	IBS-pos.	<i>P</i>	IBS-neg.	IBS-pos.	<i>P</i>
Gender (% Female)	57.0	60.5	0.559	56.4	78.1	0.015	55.2	73.5	<0.001
Mean age (years)	43.4	40.8	0.142	53.6	47.7	0.028	53.4	48.0	<0.001
Level of education			0.731			0.042			0.529
> 4 years' further education	16.8	12.0		26.6	45.2		29.4	33.0	
3-4 years' further education	41.8	44.0		38.3	25.8		37.6	29.9	
< 3 years' further education	18.7	21.3		12.5	19.4		12.6	13.4	
No further education	22.8	22.7		22.5	9.7		20.4	23.7	
Employment status (% employed)	83.7	71.1	0.006	73.6	81.3	0.335	74.9	75.3	0.937
Sick leave from work			0.019			<0.001			<0.001
≥6 times a year	5.9	14.3		6.1	23.2		6.1	16.3	
1-5 times a year	53.5	54.3		52.0	56.7		51.2	57.0	
Never	40.6	31.4		41.9	20.0		42.6	26.7	
Gastrointestinal pain as a child	17.7	24.3	0.161	20.9	29.0	0.278	19.4	36.5	<0.001
Cholecystectomy	3.3	12.2	NV	6.1	21.9	NV	5.2	14.3	<0.001
Gastroduodenal ulcer	8.8	18.7	0.006	10.2	16.7	NV	10.3	17.7	0.034
Abdominal operation	21.7	28.4	0.193	24.2	43.8	0.013	23.6	31.9	0.081
Seeking physician in last 12 months			<0.001			0.025			0.002
Never	21.7	5.3		19.0	9.4		20.1	8.2	
1-5 times	67.6	69.7		68.7	62.5		68.2	70.1	
>6 times	10.7	25.0		12.4	28.1		11.7	21.6	
Seeking physician because of gastro-pain	10.9	46.1	<0.001	6.9	46.9	NV	7.9	38.1	<0.001
Heartburn	40.6	59.2	0.003	39.1	71.9	<0.001	41.0	61.9	<0.001
Functional dyspepsia	10.6	43.4	<0.001	11.1	65.6	NV	11.5	57.1	<0.001

Education and employment status

There was a significant relationship between level of education and the Rome II IBS criteria with higher proportion with higher education among IBS subjects (Table 14); other criteria showed no relationship. Employment status was associated with IBS in 1996 using both Manning and Rome III IBS criteria (Tables 13 and 14).

Smoking and alcohol

Smoking was associated with IBS for only one set of criteria (Table 13). There was no significant association with IBS and alcohol consumption for any of the criteria.

Gastrointestinal pain and operations

For all criteria the frequency of pain was greater for subjects with IBS than for subjects without IBS. The intensity of gastrointestinal pain was significantly greater than for others in the Rome II and III subjects in 2006. In the Manning IBS and Rome III criteria (2006) subjects there was a significant relationship between gastrointestinal pain as a child and IBS (Table 13-14).

For the Manning criteria subjects there was a significant relationship with having had an appendectomy and IBS subjects in 1996 but not in 2006. There was a significant relationship between cholecystectomy and the Manning and Rome III (2006) criteria in IBS subjects. There was also a significant relationship between abdominal surgery and the Manning criteria for IBS in 1996 and Rome II. There was a relationship with gastroduodenal ulcer and subjects diagnosed with IBS for the Manning criteria and Rome III. Subjects with Rome III IBS indicated no relationship between operations such as appendectomy and other abdominal surgery (Table 13-14).

Medical care

Subjects with IBS according to Manning and Rome II/III criteria sought physicians more often than subjects without IBS. Subjects who sought a physician because of abdominal-pain significantly more often had IBS as diagnosed by Manning and Rome III criteria than did others (Table 13-14).

Heartburn and functional dyspepsia

There was a significant relationship between subjects with heartburn and IBS subjects according to all the criteria. There was also a significant relationship between subjects reporting functional dyspepsia and Manning and Rome III criteria for IBS (Tables 13-14).

3.3.2 Stability and subgroups of three different IBS criteria (II)

Development of IBS in 10 years

The development of IBS symptoms over the ten year period showed a similar proportion of IBS subjects who developed and lost IBS in the Manning and self-report groups, whereas many more subjects developed IBS in the Rome III group than became free of the symptoms (Table 15). A much higher proportion of IBS subjects retained IBS (18.7%) in the Manning group than in the self-report (8.2%) and the Rome III (4.4%) groups.

Table 15: Development of IBS, retained, lost and developed in 10 years

	n	Never IBS (%)	Lost IBS (%)	Retained IBS (%)	Developed IBS (%)
Manning	663	56.7	12.2	18.7	12.4
Self-report	610	75.2	8.0	8.2	8.5
Rome III	735	81.4	5.6	4.4	8.7

NOTE. For each condition, the left column shows the number of people without the condition at baseline.

Transitions among symptom subgroups between the initial and final surveys

As described in the methods section, the groups in this analysis were defined as mutually exclusive, using the symptom hierarchy so that each subject appears in only one category for both the 1996 and 2006 surveys. There was a “no symptoms” category for those who did not meet any of the criteria applied for FGIDs. Due to the hierarchical classification only a few participants occurred in some categories.

	Rome III	Manning	Self report	FD	Frequent Abd. Pain	No symptoms
Rome III (n=71)	39%	23%	10%	4%	6%	18%
Manning (n=165)	17%	37%	6%	8%	6%	26%
Self report (n=33)	15%	21%	12%	3%	6%	42%
FD (n=28)	14%	36%	0%	21%	21%	7%
Frequent Abdominal Pain (n=77)	8%	21%	1%	4%	18%	48%
No symptoms (n=425)	3%	9%	2%	2%	9%	75%



Remaining
Became asymptomatic
Stable



Developed symptoms
Increased symptoms

FGID - Functional Gastrointestinal Disorder

FD - Functional Dyspepsia

D - Diarrhea

C - Constipation

N - Normal

Figure 16: Transitions among symptom subgroups between the initial and final surveys

There was a substantial change in numbers in all the categories. The group with “no symptoms” was the most common. Of the Rome III group 39% were stable. Most of the subjects were in the Manning group and 37% were stable over the 10 year period; 26% reported “no symptoms” in 2006 and 17% showed an increase in symptoms over the ten years. Of the self-report subjects 12% were stable, 42% reported “no symptoms”, and 34% had increased symptoms in 2006 (Figure 16).

One out of five had a stable FD in both years, but 50.0% developed FD (increased symptoms) in 2006 and 7% had moved into the “no symptoms” group.

The category “frequent abdominal pain” (FAP) was stable in 18% cases, whereas 34% moved into the “increased symptoms” category and 48% into the “no symptoms” category.

The distribution of the 6 transition groups was 12 % symptom stability, 11% symptom increase, 10% symptom decrease, 14% developed symptoms, 14% became asymptomatic, and 40% had no symptoms in either 1996 or 2006.

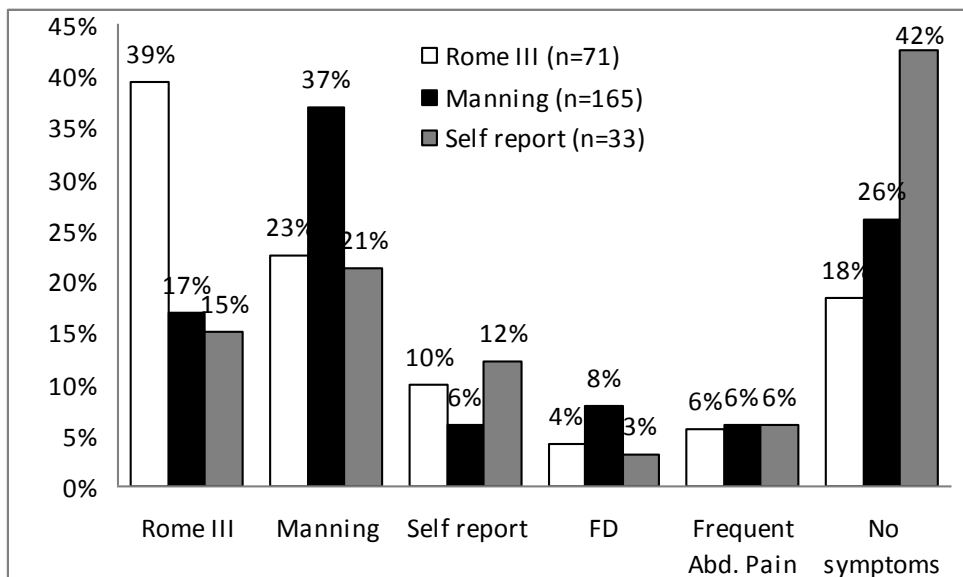


Figure 17: Distribution of subjects in 2006 who were diagnosed with Rome III, Manning and Self-report in 1996.

Subjects who were diagnosed with IBS in 1996 moved into other IBS groups, FD, FAP and the no symptom group can be seen in figure 17. Only 39% of subjects diagnosed with IBS by the Rome III criteria remained in the same IBS group, 23% moved into the Manning criteria group and 18% into the no symptom group. Only 37% of the Manning group (1996) remained in the same group, 26% were in the no symptom group and 17% in the Rome III. Of the self-report group from 1996 42% moved into the no symptom group and 21% into the Manning group and 15% into the Rome III group. Only 12% remained in the same self-report group.

Subgroups of Rome III

Subjects fulfilling the Rome III criteria were divided into 4 subgroups: (1) diarrhea-predominant (IBS-D), which is determined by predominantly loose or watery stools $\geq 25\%$ of the time, (2) constipation- predominant (IBS-C) determined by predominantly hard or lumpy stools $\geq 25\%$ of the time, (3) diarrhea and constipation (IBS-M), meeting criteria for IBS-D and IBS-C $\geq 25\%$ of time, and (4) no diarrhea or constipation, un-subtyped (IBS-U): not meeting criteria for of IBS-C nor IBS-D, i.e., both $< 25\%$ of the time. The IBS-D was the most prevalent group in both 1996 and 2006. There was a significant increase in prevalence of IBS-D in the year 2006. There was a significant decrease in the IBS-C group and an increase in the IBS-U group. (Fig. 18)

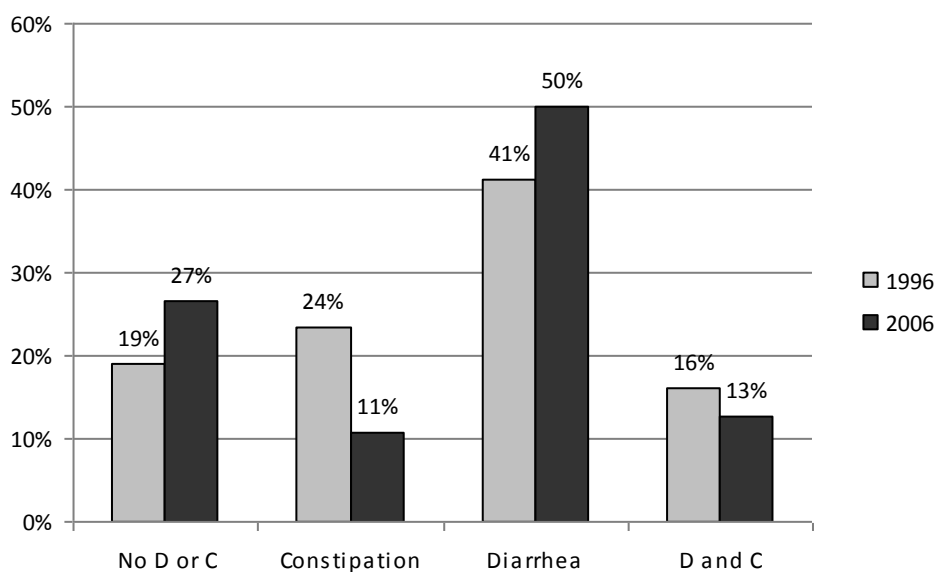


Figure 18. Subgroups of Rome III

3.3.3 Telephone survey among study participants (V)

A total of 94 subjects were interviewed by telephone (29.8% male, 70.2% female) with a mean age of 47 years. Of these, all subjects had IBS according to the Manning criteria and 56.0% according to the Rome III criteria (the Rome III criteria being more refined and stricter than Manning criteria). When subjects were asked if they had experienced IBS (self-assessed), 62.8% admitted and 21.3% confirmed that they had received an IBS diagnosis from a physician, 60% of these had a Rome III-based diagnosis, and 100% had a Manning-based diagnosis.

Table 16 shows the awareness of IBS. Two out of five subjects had knowledge of IBS and the same proportion had seen a physician because of IBS symptoms, but only half of those

had received a diagnosis of IBS. Only 12/94 (12.8%) of IBS subjects were satisfied with the treatment they had been given. IBS did affect daily activities in approximately 43% of the cases. One third of the IBS subjects thought they would be cured of IBS, whereas a similar proportion thought they would always suffer from IBS. IBS subjects used more untraditional medication than prescribed drugs. More than half of subjects believed that dietary modification is important for the treatment of IBS (Table 16).

Three out of five IBS subjects were diagnosed by a gastroenterologist and two out of five by general practitioners. Most IBS subjects reported abdominal pain (73.7%), bloating (21.1%), constipation (5.3%) and diarrhea (10.5%) as the symptom that led to the diagnosis. More than half (57.9%) of the IBS subjects who received management for their IBS symptoms were satisfied.

Table 16: Interviewer-diagnosed subjects; awareness of the disorder, the diagnoses and treatment

	All subjects n=94 % (n)
Diagnosed with IBS	22.2 (20)
Knowledge of IBS	39.4 (37)
Seen a physician because of IBS symptoms	39.4 (37)
Satisfied with treatment for IBS	12.8 (12)
IBS affects daily activities	42.6 (40)
Think they will be cured of IBS	30.9 (29)
Think they will always suffer from IBS	28.7 (27)
Takes medication for IBS	11.7 (11)
Uses untraditional medication	16.0 (15)
Thinks dietary modification is important for the treatment of IBS	55.3 (52)

3.3.4 Physician awareness of IBS (V)

An anonymous questionnaire was sent to a total of 191 physicians in Iceland in the fields of primary care or SG (excluding 3 physicians involved in carrying out this study). A total of 80 physicians replied (83% male, 17% female) and completed the questionnaire. Of those who answered, 70 of 175 were GPs and 9 of 15 were SGs.

On average 13 subjects were estimated to be diagnosed with IBS monthly by SGs and 2.5 subjects by GPs.

Physicians reported how they diagnosed subjects with IBS in table 17.

Table 17: Diagnoses of subjects with IBS

	All subjects (%) n=80*	SG (%) n=9	GP (%) n=70
Patients history	79%	78%	80%
Physical examination	38%	22%	41
Exclusion of other diseases	38%	44%	35%
IBS criteria	22%	33%	19%
GI endoscopy	7%	22%	6%

* One physician did not list his profession

All subjects (%)

SG (%)

GP (%)

Two thirds of all the physicians knew that special diagnostic criteria exist for defining and diagnosing IBS (Figure 19).

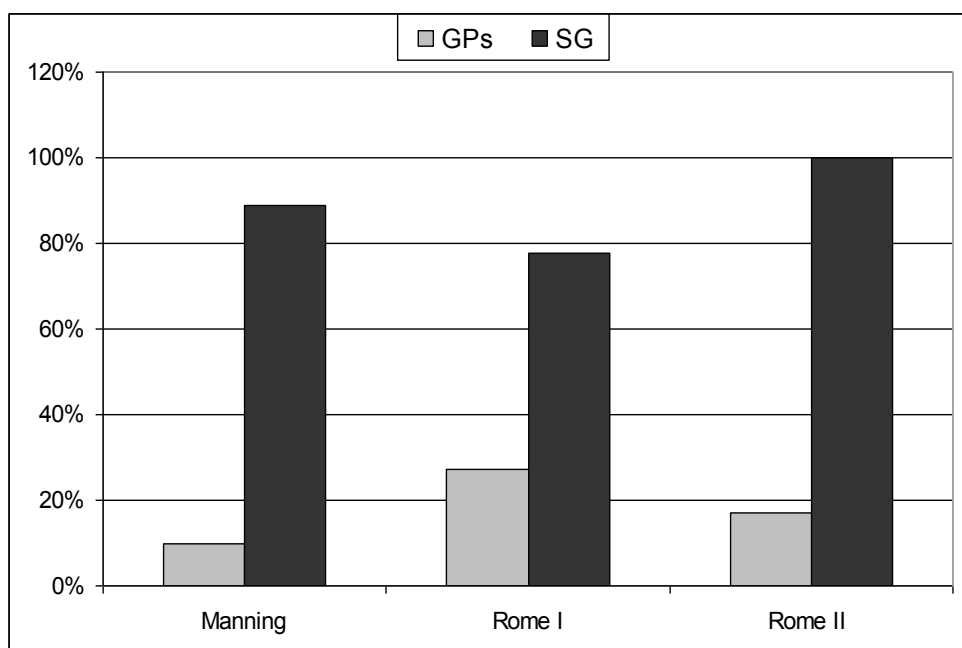


Figure 19: Number of physicians knowing about each set of diagnostic criteria (%)

When physicians were asked if they had awareness of the IBS diagnostic criteria, 71% said yes (64% of GPs, 100% of SGs). Despite the fact that 64% of GPs claimed they knew that diagnostic criteria existed, only 10% had heard of the Manning criteria, 27% of Rome I, and 17% of Rome II (Figure 19).

Physicians stated that abnormal bowel movements such as diarrhea and constipation, abdominal pain and bloating as the most commonly reported symptoms of IBS (Table 18).

Table 18: The most common IBS symptoms reported

	GPs	SG
Abnormal bowel movements	61%	100%
Abdominal pain	86%	67%
Bloating	20%	56%
Gas	9%	11%
Passage of mucus	5%	0%
Incomplete evacuation with defecation	5%	11%

Physicians reported in most cases that they would give advice on diet and education about IBS as a treatment for IBS symptoms. Both GPs and SGs gave their patients mebeverinum in most cases. Psyllium was frequently used by SGs and chlordiazepoxide, and clidinium was in some cases used by both GPs and SGs (Table 19).

Table 19: Treatment of IBS.

	GPs	SG
Medication		
Mebeverinum	89%	86%
Psyllium husk	31%	43%
Chlordiazepoxide and clidinium	29%	14%
Antidepressants	7%	14%
Other medicines	9%	14%
Lifestyle		
Food	98%	86%
Relaxation	14%	14%
Exercise	16%	14%
Education about IBS	90%	86%
Do not know/something else	27%	14%

3.3.5 Women, IBS and dysmenorrhea (VI)

Dysmenorrhea (painful menstruation)

Of the women who responded 331 reported menstruation in 1996 and 205 in 2006. Of these, three out of four reported dysmenorrhea (Table 20). Half of these reported medium severity

of dysmenorrhea. Slightly more reported minor dysmenorrhea in 1996 than in 2006. Slightly more reported severe or very severe dysmenorrhea (Figure 20).

Table 20. Women with menstruation and dysmenorrhea

	1996		2006	
Total women	446		444	
Women without menstruation	115	25,80%	239	53,80%
Women with menstruation	331	74,20%	205	46,20%
Women with dysmenorrhea	254	76,70%	152	74,10%

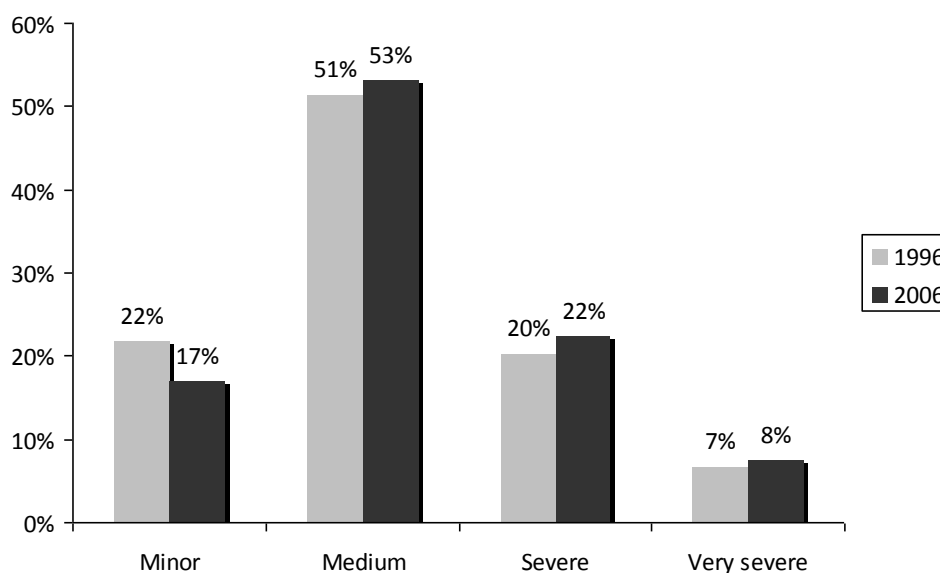


Figure 20: Distribution of dysmenorrhea severity.

Dysmenorrhea and irritable bowel syndrome

One out of ten women with dysmenorrhea had IBS according to Rome III criteria in 1996 and 5.3% of women without dysmenorrhea had IBS ($p=0.17$) (Table 22). One out of four women with dysmenorrhea had IBS according to Rome III in 2006 and 9.4% of women without dysmenorrhea had IBS, with a statistical difference of $p=0.013$ (Table 21).

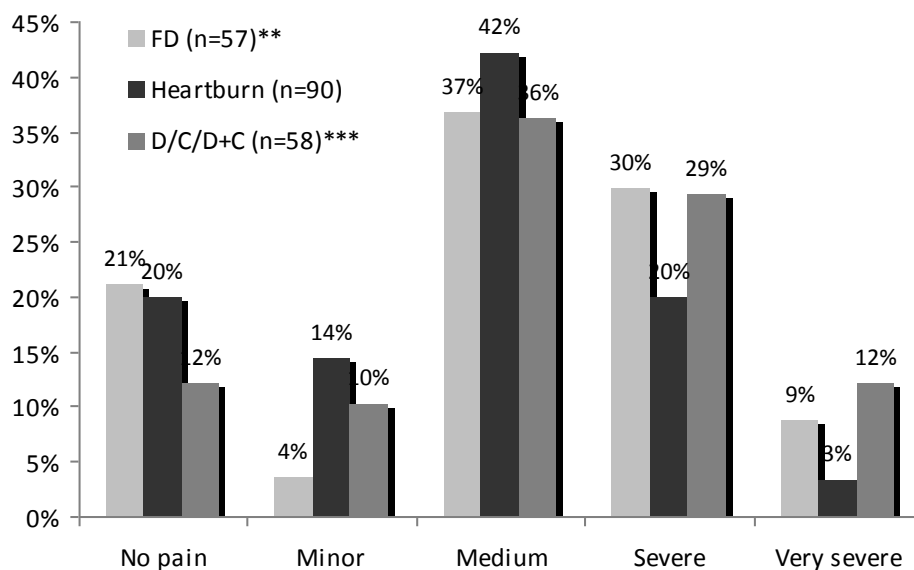
Two out of five of women with dysmenorrhea had IBS according to the Manning criteria in 1996 and one out of four without dysmenorrhea had IBS, with a statistical difference of $p=0.014$. Half of the women in 2006 with dysmenorrhea had IBS according to Manning and a third of the women without dysmenorrhea had IBS in 2006 ($p=0.063$).

Table 21. Women with IBS according to Rome III and Manning and dysmenorrhea

		1996	2006
Rome III	Dysmenorrhea	10,50%	25,70%
	Without dysmenorrhea	5,30%	9,40%
Manning	Dysmenorrhea	41,50%	48,60%
	Without dysmenorrhea	25,30%	33,30%

Dysmenorrhea and other functional gastrointestinal disorders

Four out of five of those who had functional dyspepsia (FD) and heartburn had dysmenorrhea and 88% of those who had diarrhea and or constipation also had dysmenorrhea (Figure 21). A total of 22/57 (39%) of those who had FD and 24/58 (41%) of those who had diarrhea and/or constipation had severe or very severe dysmenorrhea. FD patients more commonly had dysmenorrhea than those without FD. Those with diarrhea and or constipation also had more often dysmenorrhea more often than those who did not.

**Figure 21: Functional gastrointestinal disorders and dysmenorrhea severity (2006).**

Women with dysmenorrhea in 1996 and after menopause 2006, IBS and abdominal pain severity

In 1996 overall 64 women experienced dysmenorrhea but did not menstruate in 2006. In 1996 38.0% of those who had IBS according to the Manning criteria had dysmenorrhea against 40.7% in 2006. A total of 6.2% experienced IBS according to the Rome III criteria in

1996 and 13.2% in 2006. Figure 22 shows the changes in abdominal pain severity in women with dysmenorrhea in 1996 and after menopause in 2006.

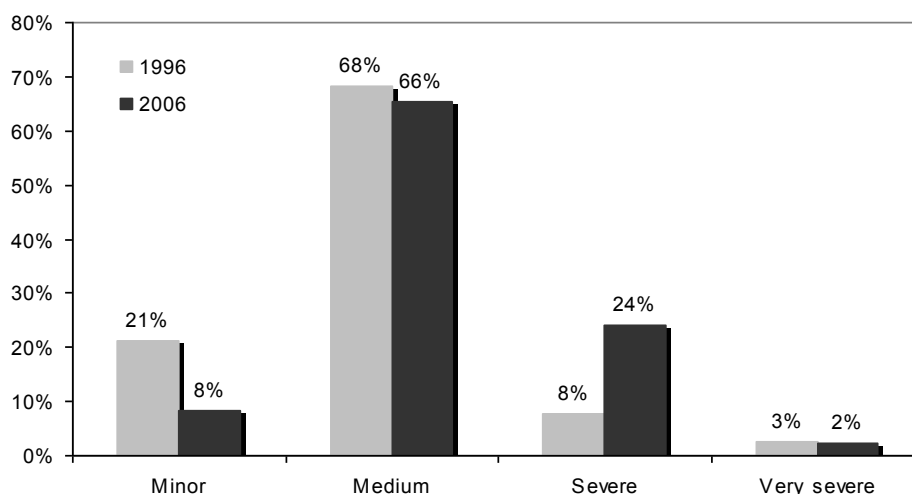


Figure 22: Abdominal pain in women with dysmenorrhea 1996 and after menopause 2006.

Transition between disorders from the 1996 and 2006 surveys

As described in the methods section, the groups in this analysis were defined as mutually exclusive, using the symptom hierarchy so that each subject appears in only one category for both the 1996 and 2006 surveys. There was a “no symptoms” category for those who did not meet any of the criteria applied for FGID. Due to the hierarchical classification only a few participants occurred in some categories.

Transitions between disorders were explored in two ways; for women with dysmenorrhea (Figure 23) and for women without dysmenorrhea (Figure 24). There was a substantial change in numbers in all the categories between the two surveys. The group “no symptoms” was the most common in both transition models. For the women with dysmenorrhea the FD was the most stable one. Overall 17.2% moved into the IBS group and 13.8% into the no symptom group. IBS was stable in 29.7% cases and the same proportion moved into the FD group. One fourth moved into the no symptom group. There were only 4 women in the heartburn group of women with dysmenorrhea. In women without dysmenorrhea the stability of symptoms was greater than for the women with dysmenorrhea. Overall 44.4% of the FD group was stable between the initial and final surveys. One out of four moved into the IBS group. The stability for the IBS group was 37.9%. Overall 17.2% moved into the IBS group and 20.7% into the no symptom group. The highest stability (42.3%) was in the heartburn group.

The transitions were collapsed into six groups. Comparison of the differences between women with and without dysmenorrhea in those transition groups (Figure 25) showed that the greatest difference was between the two groups of women who remained asymptomatic. The women

without dysmenorrhea were twice as likely to remain asymptomatic than the women with dysmenorrhea. The women with dysmenorrhea were also more likely to have stable symptoms at follow-up than women without dysmenorrhea. Furthermore, the women with dysmenorrhea were twice as likely to have increased symptoms as women without symptoms. There was a significant difference between women with and without dysmenorrhea ($p=0.01$).

	Rome III	Manning	Self report	FD	Frequent Abd. Pain	No symptoms
Rome III (n=71)	39%	23%	10%	4%	6%	18%
Manning (n=165)	17%	37%	6%	8%	6%	26%
Self report (n=33)	15%	21%	12%	3%	6%	42%
FD (n=28)	14%	36%	0%	21%	21%	7%
Frequent Abdominal Pain (n=77)	8%	21%	1%	4%	18%	48%
No symptoms (n=425)	3%	9%	2%	2%	9%	75%



Remaining asymptomatic
Became asymptomatic
Stable



Developed symptoms
Decreased symptoms
Increased symptoms

FGID - Functional Gastrointestinal Disorder

FD - Functional Dyspepsia

D - Diarrhea

C - Constipation

N - Normal

Figure 23: Transitions among symptom subgroups between the initial and final surveys: Women with dysmenorrhea

	Rome III	Manning	Self report	FD	Frequent Abd. Pain	No symptoms
Rome III (n=71)	39%	23%	10%	4%	6%	18%
Manning (n=165)	17%	37%	6%	8%	6%	26%
Self report (n=33)	15%	21%	12%	3%	6%	42%
FD (n=28)	14%	36%	0%	21%	21%	7%
Frequent Abdominal Pain (n=77)	8%	21%	1%	4%	18%	48%
No symptoms (n=425)	3%	9%	2%	2%	9%	75%



Remaining asymptomatic
Became asymptomatic
Stable



Developed symptoms
Decreased symptoms
Increased symptoms

FGID - Functional Gastrointestinal Disorder

FD - Functional Dyspepsia

D - Diarrhea

C - Constipation

N - Normal

Figure 24: Transitions among symptom subgroups between the initial and final surveys: Women without dysmenorrhea.

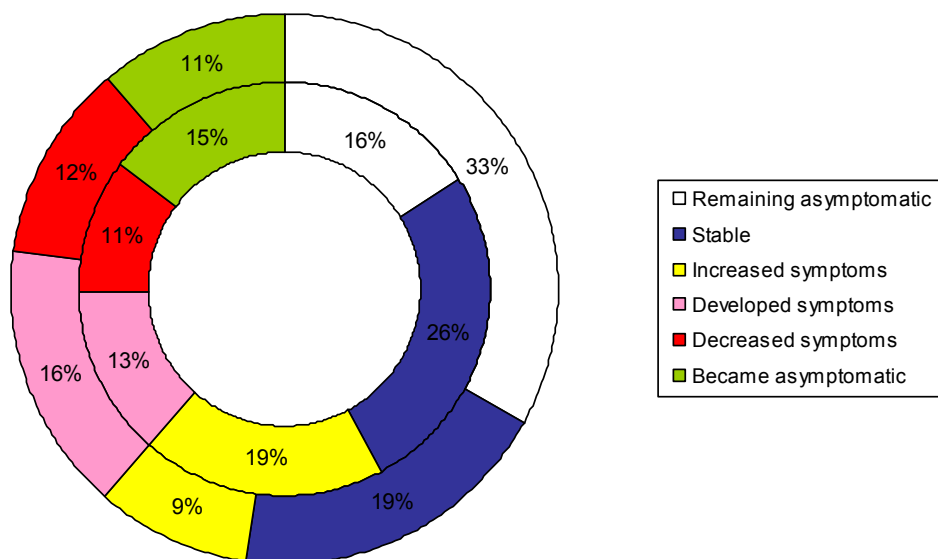


Figure 25: Six-group transition model, change from initial to the final survey. Women with dysmenorrhea (n=130) in the inner circle and Women without dysmenorrhea (n=163) in the outer circle (p=0.01)

Birth cohort effect of dysmenorrhea

Data in figure 26 demonstrate that there is no significant difference in prevalence between birth cohorts in women with dysmenorrhea nor in women without dysmenorrhea.

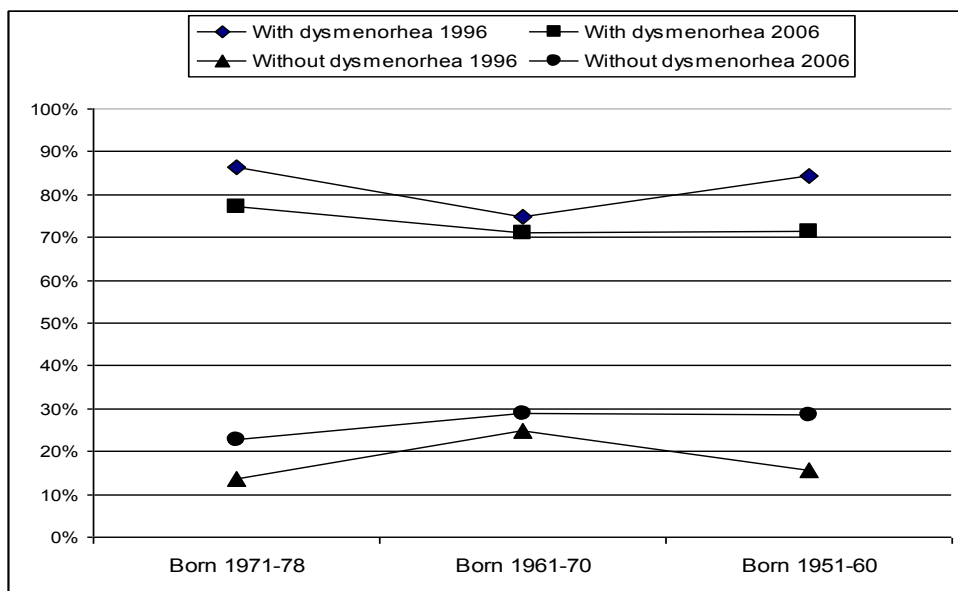


Figure 26: Birth cohort effect on the prevalence (%) in 10-years.

3.4 Functional dyspepsia (I)

3.4.1 Prevalence and natural history

Functional dyspepsia 1996-2006

Of those who answered the questionnaire in both 1996 and 2006, functional dyspepsia (FD) was diagnosed in 13.9% in 1996 (11.3% male, 15.8% female; $p=NS$) and 16.7% in 2006 (12.3% male, 20.2% female; $p<0.01$). Females were more likely to develop FD over the 10 year period than were males. More females developed FD than overcame the symptoms.

Younger subjects were significantly more likely to experience FD than older subjects (Table 22). Employment status was not associated with FD. Those who used sick leaves from work were more likely to have developed FD during the 10 year time period, (Table 23).

Table 22: Sociodemographic characteristics and the development and disappearance of FD

	N	Never FD (%)	Lost FD (%)	Retained FD (%)	Developed FD (%)	χ^2	p-value
Gender						10.427	<0.05*
Male	341	81.8	5.9	5.3	7.0		
Female	465	72.3	7.5	8.6	11.6		
Age group						25.615	<0.001***
66-85 years	188	86.7	4.8	4.3	4.3		
36-65 years	502	75.7	7.2	6.8	10.4		
28-35 years	119	63.0	8.4	13.4	15.1		
BMI						8.861	0.182
>30	161	68.9	8.1	10.6	12.4		
>25<30	330	78.5	5.2	7.0	9.4		
<25	300	77.7	8.0	5.7	8.7		
Level of education						5.840	0.756
>4 years' further education	232	74.57	7.76	7.76	9.91		
3-4 years' further education	288	76.04	6.94	8.33	8.68		
<3 years' further education	100	73.00	9.00	5.00	13.00		
No further education	173	80.35	4.62	6.36	8.67		
Employment status						3.842	0.279
Employed	594	75.59	7.7	6.57	10.77		
No employment	208	78.37	6.25	8.65	6.73		
Alcohol						8.246	0.221
>7 drinks per week	44	88.64	2.27	4.55	4.55		
1-6 drinks per week	422	74.17	6.64	7.11	12.9		
no alcohol	328	77.44	7.32	7.62	7.62		
Smoking						100.834	<0.05*
Smokers	182	70.3	9.9	11.0	8.8		
Non smokers	516	79.1	5.6	5.8	9.5		

* $p<0.05$, ** $p<0.01$. *** $p<0.001$

NV: Not valid due to low expected count

BMI and weight

Body Mass Index (BMI) was not associated with the development of FD over the 10 year period (Table 22). Those who lost weight without dieting were more likely to have FD. Those who had a lower or greater than normal appetite were also more likely to have FD.

Smoking and alcohol

Smoking was associated with the development of FD from 1996 to 2006 (Table 22), but there was no association between FD and the number of cigarettes smoked. There was no significant association with the development of FD and alcohol consumption.

Gastrointestinal pain

Those who reported a greater frequency of pain were significantly more likely to fulfill FD criteria. The same applied to those who had experienced gastrointestinal pain as children or were relieved of pain by burping or eating. The more intense the gastrointestinal pain, the higher the odds of having FD (significant at the 0.05 level for 2006; significant at the 0.05 level for 1996 when combining the alternatives intense and very intense). Administration of H2 blockers and proton pump inhibitors did not seem to relieve the pain (Table 23).

Medical care

Those who consulted a doctor were more likely to have FD and also more frequently because of gastrointestinal pain (Table 23). There was an association between FD and abdominal operations as well as FD and an appendectomy in 1996. There was also an association between FD and a cholecystectomy in 2006.

The relationship of FD, heartburn and irritable bowel syndrome

There was a strong relationship between heartburn and FD. There was also a significant relationship between IBS and FD. In 2006, 43.5% of IBS subjects were identified with FD when applying the Manning criteria and 61.9% using the Rome II criteria.

3.4.2 Distribution and overlap of FD subgroups

Dyspepsia subgroups

According to the dyspepsia subgroup (DS) criteria, subjects having one or more DS, the prevalence of dyspepsia was 24.1% in 1996 and 24.3% in 2006. There were 162 subjects who answered all questions in 2006 and fell into the dyspepsia subgroup. Of these the proportions reporting each dyspeptic subgroup were as follows: 47% had frequent upper abdominal pain, 23% had nausea/vomiting, and 56% had meal-related discomfort (Figure 27).

Because of overlap among these groups the percentage adds up to more than 100%; of the total, 25% fell into the combination group. Table 24 shows the proportion of gender and age and FD subjects in each subgroup of dyspepsia.

Table 23: Symptom characteristics and medical history.

Variables	1996				2006			
	n	% with FD	χ^2	p-value (FD)	n	% with FD	χ^2	p-value (FD)
Gastrointestinal pain			6,654	<0.05*			10,552	<0.01**
Very intense/intense	70	34,3			70	47,1		
Medium	199	37,2			204	43,6		
Little/small	69	20,3			56	21,4		
Frequency of pain			11,533	<0.01**			15,207	<0.001***
Once a month or less	183	25,1			169	30,8		
Once or more weekly	135	41,5			135	50,4		
Daily	21	47,6			24	58,3		
Pain relieve by medication								
Antacids			11,391	<0.001***			6,089	<0.05*
Yes	93	48,4			73	56,2		
No	132	26,5			33	30,3		
H₂ blockers			N.V.	N.V.			0,909	0,340
Yes	62	45,2			52	51,9		
No	11	27,3			18	38,9		
PPI blockers			-	-			1,496	0,221
Yes	-	-			67	49,3		
No	-	-			13	30,8		
Pain relieve by burping			5,441	<0.05*			5,578	<0.05*
Yes	108	41,7			90	52,2		
No	219	28,8			228	37,7		
Pain relieve by eating			15,334	<0.001***			22,864	<0.001***
Yes	76	52,6			84	63,1		
No	241	28,2			235	33,2		
Lost weight without dieting			40,141	<0.001***			5,654	0,059
No	691	11,0			676	15,8		
<3.5 kg	59	33,9			72	22,2		
≥3.5 kg	51	33,3			43	27,9		
Appetite in last year			52,420	<0.001***			7,776	<0.05*
Less	43	44,2			37	29,7		
Same	724	11,0			741	15,7		
More	40	35,0			24	29,2		
Gastrointestinal pain as a child			23,489	<0.001***			18,458	<0.001***
Yes	153	26,1			166	28,3		
No	643	11,0			615	14,1		
Appendectomy			3,943	<0.05*			3,476	0,062
Yes	198	18,2			209	21,1		
No	613	12,6			596	15,4		
Cholecystectomy			N.V.	N.V.			10,886	<0.001***
Yes	33	21,2			50	34,0		
No	773	13,7			749	15,9		
Stomach operation			N.V.	N.V.			N.V.	N.V.
Yes	20	20,0			28	10,7		
No	775	13,5			754	17,5		
Abdominal operation			8,731	<0.01**			2,294	0,130
Yes	181	20,4			194	20,6		
No	617	11,8			585	15,9		
Seeking physician in last 12 months			25,358	<0.001***			9,001	<0.05*
Never	161	5,0			145	10,3		
1-5 times	544	14,3			539	17,4		
≥6 times	99	27,3			110	24,5		
Seeking physician because of gastro-pain			44,782	<0.001***			40,721	<0.001***
Yes	119	33,6			95	40,0		
No	682	10,6			689	13,8		
Heartburn			50,623	<0.001***			46,44	<0.001***
Yes	347	23,9			356	27,0		
No	456	6,4			436	8,7		

*p<0.05, **p<0.01, ***p<0.001

N.V.: Not valid due to low expected coun

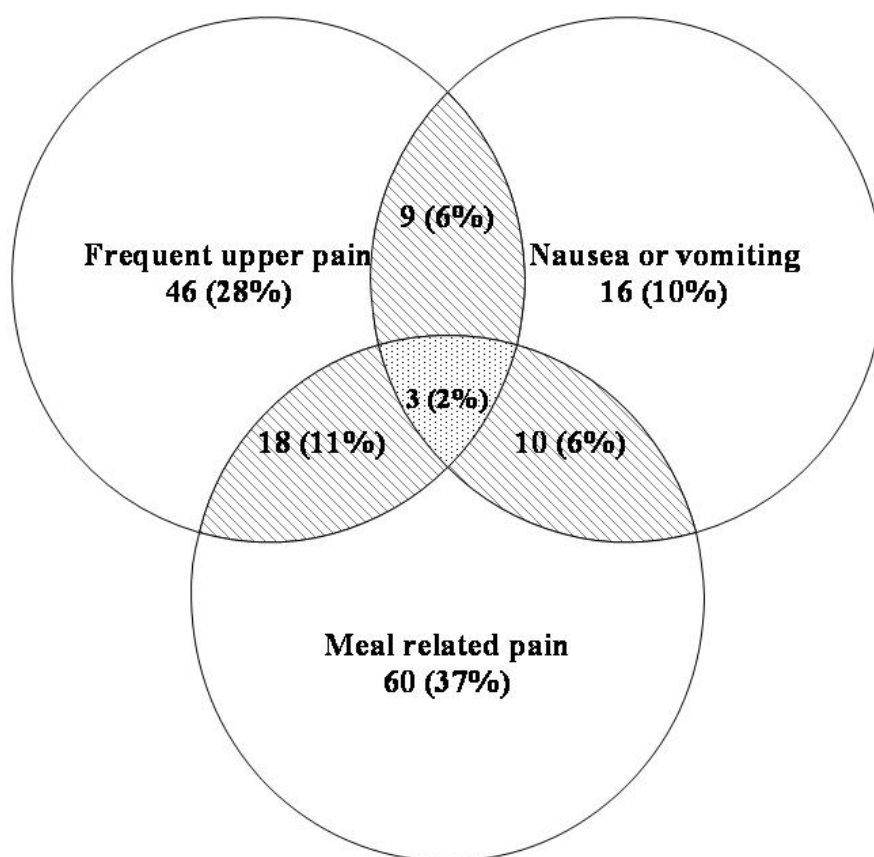


Figure 27: Distribution and overlap of dyspepsia subgroups

Table 24. Non-overlapping dyspepsia subgroups by gender, age and FD

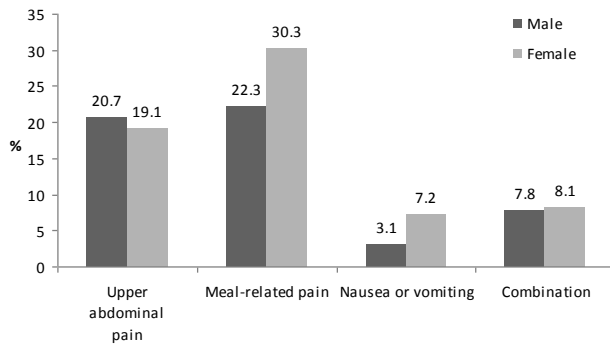
Dyspepsia Subgroups	(%)	FD (%)	Age (%)			Female (%)	Male (%)
			28-35	36-65	66-85		
Frequent upper pain (FUP)	25.8	38.5 ^a	16.4	28.2	26.9	24.2	28.8
Meal related pain (MR)	30.9	39.4 ^b	47.5§	24.6§	35.3§	33.8	24.6
Nausea or vomiting (NV)	6.8	18.0 ^c	11.9	6.1	5.1	9.4†	3.2†
Combination	13.3	22.1 ^d	17.5	12.0	13.5	15.3	9.8

^aFUP – FD: $\chi^2=19.59$, $p<0.001$.
^bMR – FD: $\chi^2=7.52$, $p=0.006$.
^cNV – FD: $\chi^2=32.26$, $p<0.001$.
^dCombination – FD: $\chi^2=15.54$, $p<0.001$.

§ MR - Age: $\chi^2=12.21$, $p=0.002$.
 † NV - Female/Male: $\chi^2=11.12$, $p<0.001$.

Of those who did not report any DS symptoms in 1996, 12.9% reported symptoms ten years later.

1996



2006

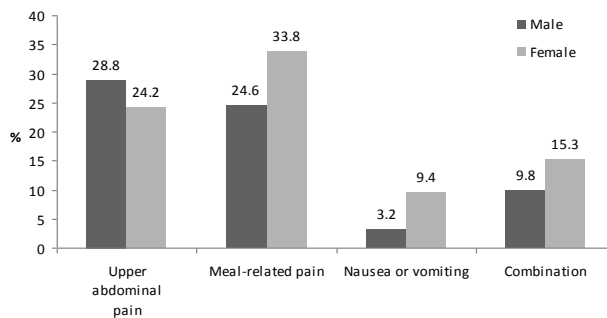


Figure 28: Change in dyspepsia subgroups during the ten year period

Figure 28 shows the changes in the dyspepsia subgroups over the 10 year period. There was an increase in all cases during the 10 years. MR and NV were more prevalent in females than males, as well as in combination in 2006. In contrast, UAP was more prevalent in males than females.

Table 25. Proportion of DS and FD in each group

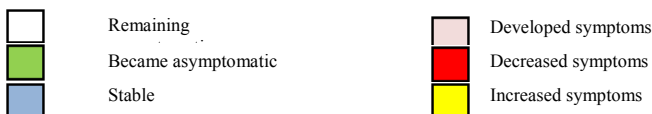
	1996	2006
Proportion of DS subjects in the FD group	55.8%	70.6%
Proportion of FD subjects in the DS group	36.8%	51.3%

In table 25 the proportion of DS and FD subjects is demonstrated for each group, showing that the proportion of DS subjects in the FD group was significantly higher than vice versa.

3.4.3 Transitions among symptom subgroups between the initial and final surveys

As described in the methods section, the groups in this analysis were defined as mutually exclusive using the symptom hierarchy, so that each subject appears in only one category for both the 1996 and 2006 surveys. There was a “no symptoms” category for those who did not meet any of the criteria applied for FGIDs. Due to the hierarchical classification few numbers occurred in some categories.

	Rome III	Manning	Self report	FD	Frequent Abd. Pain	No symptoms
Rome III (n=71)	39%	23%	10%	4%	6%	18%
Manning (n=165)	17%	37%	6%	8%	6%	26%
Self report (n=33)	15%	21%	12%	3%	6%	42%
FD (n=28)	14%	36%	0%	21%	21%	7%
Frequent Abdominal Pain (n=77)	8%	21%	1%	4%	18%	48%
No symptoms (n=425)	3%	9%	2%	2%	9%	75%



FGID - Functional Gastrointestinal Disorder

FD - Functional Dyspepsia

D - Diarrhea

C - Constipation

N - Normal

Figure 29: Transitions among symptom subgroups between the initial and final surveys

There was a substantial change in the proportion in all the categories. The group “no symptoms” was the most common. More than half of FD subjects remained FD for the ten years and 9.7% reported “no symptoms” in 2006. Of all the dyspepsia subgroups only MR remained stable (18.2%), whereas the majority of the DS showed an increase in symptoms over the ten years (Figure 29).

Almost one third had a stable IBS in both years but 24.8% developed FD (increased symptoms) in 2006 and 19.7% had moved into the “no symptoms” group.

Of the heartburn group, 38.6% remained stable whereas 11.1% had moved into the FD group and 11.8% into the IBS group. The category “frequent abdominal pain” was stable in one out of ten cases, whereas 31.0% had moved into the IBS category, 10.3% into NV, 6.9% into FD, and 27.6% into the “no symptoms” category.

The distribution of the 6 transition groups was 21.0% symptom stability, 14.1% symptom increase, 11.4% symptom decrease, 15.3% developed symptoms, 13.5% became asymptomatic and 24.5% had no symptoms in either 1996 or 2006.

3.5 Heartburn (III)

3.5.1 Prevalence and natural history

At the 10-year follow-up, individuals were asked if they had experienced heartburn in the preceding year and 42.8% in 1996 and 44.2% in 2006 reported heartburn. There was a strong relationship between those who experienced heartburn in 2006 and those who reported heartburn in 1996. Two thirds of those who reported heartburn in 1996 also experienced

heartburn in 2006. However, one third of those who reported heartburn in 2006 were not experiencing it ten years earlier (Table 26).

Individuals reported acid reflux once a month or more in 11% of cases 1996 and 10% of cases in 2006. Almost all who were on medication for heartburn reported relief from the medication.

There was a significant relationship between heartburn and dyspepsia with heartburn and IBS, both in 1996 and in 2006.

Individuals of normal weight (BMI 18.5-24.9) were less likely to experience heartburn than individuals with a BMI below or higher than normal weight.

Individuals who smoked were not more likely to have heartburn than those who did not smoke. Individual alcohol consumption within the study group changed during the ten year period of 1996 to 2006. Alcohol consumption was not associated with heartburn.

Table 26: Sociodemographic characteristics and the development and disappearance of heartburn

	n	Never HB (%)	Lost HB (%)	Retained HB (%)	Develope d HB (%)	χ^2	p-value
Gender						1,687	0,640
Male	330	40,3	14,5	30,3	14,8		
Female	441	41,5	14,7	26,5	17,2		
Age group						15,542	<0.05*
66-85 years	170	54,8	10,6	27,1	10,6		
36-65 years	488	37,3	16,4	29,3	17,0		
28-35 years	113	40,7	13,3	24,8	21,2		
BMI						21.685	<0.01**
>30	154	31,8	14,3	37,0	16,9		
>25≤30	314	37,3	14,3	31,5	16,9		
≤25	286	49,3	15,0	19,9	15,7		
Level of education						6.456	0.724
>4 years' further education	225	39,6	12,9	28,9	18,7		
3-4 years' further education	279	41,9	17,6	25,1	15,4		
<3 years' further education	92	39,1	13,0	33,7	14,1		
No further education	161	41,6	13,0	29,8	15,5		
Employment status						6.276	0.099
Employed	574	39,7	15,5	27,0	17,8		
No employment	189	44,4	12,2	31,7	11,6		
Alcohol						4.503	0.609
≥7 drinks per week	43	37,2	9,3	34,9	18,6		
1-6 drinks per week	404	39,1	14,6	28,2	18,1		
no alcohol	309	43,0	15,5	27,5	13,9		
Smoking						8.773	0.187
Smokers, >15 cigarettes per day	63	34,9	20,6	25,4	19,0		
Smokers, <15 cigarettes per day	113	31,9	17,7	34,5	15,9		
No smokers	496	43,5	13,7	26,2	16,5		

*p<0.05, **p<0.01, ***p<0.001

Transitions among symptom subgroups between the initial and final surveys

As described in the methods section, the groups in this analysis were defined as mutually exclusive using a symptom hierarchy so that each subject appears in only one category for both the 1996 and 2006 surveys. There was a “no symptoms” category for those who did not meet any of the criteria applied for FGIDs. Due to the hierarchical classification only a few participants occurred in some categories.

There was a substantial change in numbers in all the categories. The group with “no symptoms” was the most common (63.3%). Of the heartburn group 39.3% were stable and 31.8% reported “no symptoms”; 24.2% reported increased symptoms and 4.6% decreased symptoms. Of the FD group 52.3% remained stable and 9.9% reported “no symptoms” in 2006. Most of the subjects who were in the IBS group, or 30.3% of the total, were stable over the 10 year period; 20.4% reported “no symptoms” in 2006 and 25.0% showed an increase in symptoms over the ten years. In 2006 15.4% of the subjects reported stable frequent abdominal pain, 30.8% reported “no symptoms” and 53.8% reported increased symptoms (Figure 30)

The distribution of the 6 transition groups was: 22.3% symptom stability, 12.6% symptom increase, 10.9% symptom decrease, 14.9% developed symptoms, 13.6% became asymptomatic, and 25.7% had no symptoms in either 1996 or 2006.

FGID in 1996	Proportion of FGID in 2006 based on primary survey disorder				
	FD %	IBS%	Heartburn%	Frequent Abd. Pain %	No symptoms
FD (n=111)	52.3%	21.6%	14.4%	1.8%	9.9%
IBS (n=152)	25.0%	30.3%	19.7%	4.6%	20.4%
Heartburn (n=173)	12.1%	12.1%	39.3%	4.6%	31.8%
Frequent Abdominal Pain (n=39)	12.8%	23.1%	17.9%	15.4%	30.8%
No symptoms (n=324)	3.4%	9.9%	17.3%	6.2%	63.3%



FGID - Functional Gastrointestinal Disorder

FD - Functional Dyspepsia

IBS - Irritable Bowel Syndrome

Figure 30: Transition among symptom subgroups between the initial and final surveys.

3.5.2 Additional items which can affect heartburn (III)

Heartburn in subjects in 2006:

In the 2006 questionnaire individuals were asked additional questions regarding heartburn during the preceding week. Heartburn during the preceding week was reported by 20.8% of the subjects

(19.0% male, 22.1% female). Of these, 60.5% reported taking medicine for heartburn. Increasing age was not a significant factor in prevalence of heartburn/reflux disease. Age, however, was a significant factor associated with the use of medication for heartburn (Figure 31). Most subjects took ranitidine or esomeprazole for their symptoms (Figure 32).

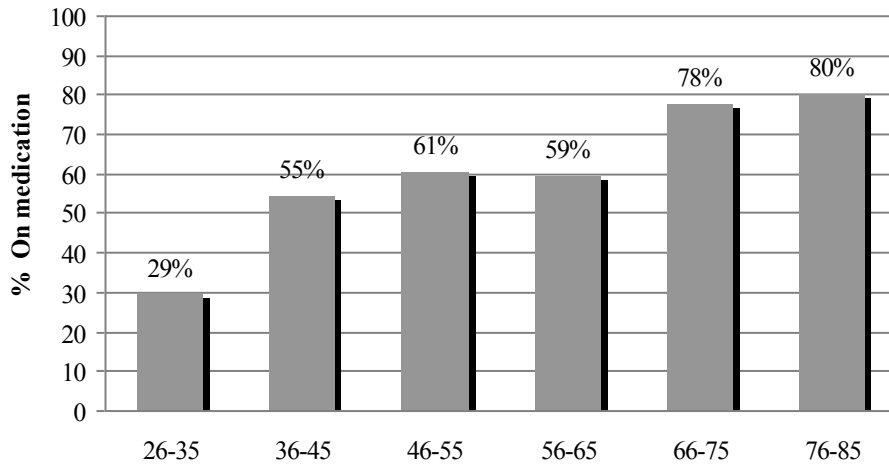


Figure 31: Age and use of medication

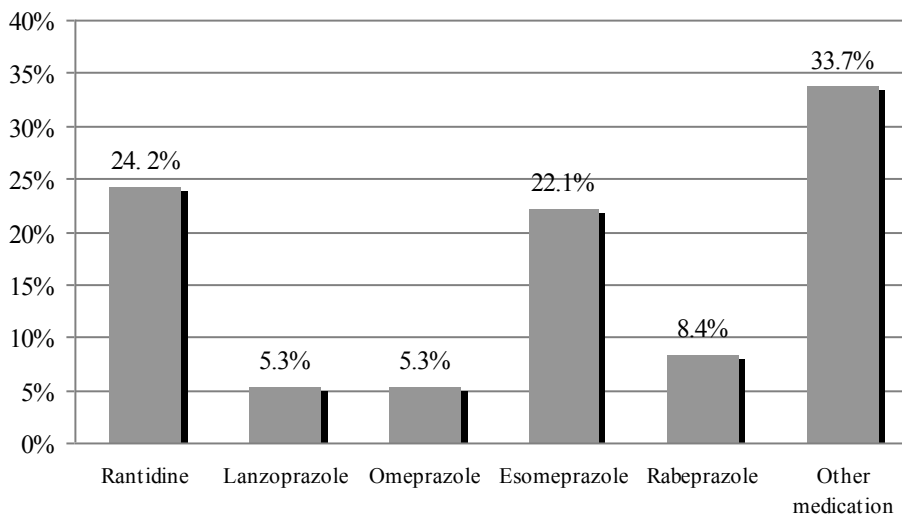


Figure 32: Which medication do you take?

A total of 27.3% reported they were on constant medication. Most individuals (85.6%) reported taking medication only when they experienced symptoms (Table 27). (There was some overlap here between groups). Six subjects reported having had an operation for reflux disease.

Table 27: Heartburn and relationship to medication, food /beverages and tiredness

Variable	No.	% of heartburn prior week
On constant medication	30	27.3
Medication only when experiencing symptoms	77	85.6
Tiredness (lethargy)		
Frequent	20	13.2
Sometimes/seldom	73	48.0
Never	59	38.8
Heartburn caused by food and beverages		
Very often	32	20.0
Sometimes/seldom	118	73.8
Never	10	6.3
Increased heartburn caused by specific food		
Very often	35	22.7
Sometimes/seldom	92	59.7
Never	27	17.5

Tiredness or lethargy was reported as occurring frequently by 13.2%, reported rare or seldom by 48%, and reported as never having occurred by 38.8% (table 27).

Heartburn caused by food or beverages was reported as occurring very often by 20%, 73.8% reported some or minimum and 6.3% never. Increase in heartburn caused by a specific food was reported as occurring very often by 22.7% and sometimes by 59.7%. A specific food significantly more often provoked considerable heartburn in women than in men (table 27).

As can be seen in table 28 heartburn can affect symptoms or activities in many cases. Three out of four heartburn subjects claimed that they felt badly sometimes or seldom. One out of three heartburn subjects felt hopeless, anxious or impatient. Moreover, one out of three were also worried or scared because of heartburn every week

Only 1.9% of the subjects reported that heartburn frequently affected their daily activities, whereas one fifth claimed that their daily activities were only sometimes or seldom affected by heartburn. Three out of four subjects reported that heartburn made them irritable. One out of four heartburn subjects reported that heartburn caused less family activities, affected their daily activities and were unable to move in sports, hobbies and outside of home. Half of the heartburn subjects reported trouble with sleeping because of heartburn.

Many heartburn subjects reported less food and beverage consumption and that they neglected specific food or alcohol because of the heartburn.

Table 28: Symptoms or activities affected by heartburn

Variable	No.	% of heartburn prior week
Felt bad		
Frequent	21	13,1
Sometimes/seldom	119	74,4
Never	20	12,5
Less food and beverages consumption		
Frequent	9	5,9
Sometimes/seldom	77	50,3
Never	67	43,8
Less family activities		
Frequent	1	0,6
Sometimes/seldom	32	20,8
Never	121	78,6
Trouble with sleeping		
Frequent	9	5,8
Sometimes/seldom	70	45,2
Never	76	49,0
Felt hopeless, worried or impatient		
Frequent	9	5,8
Sometimes/seldom	42	27,3
Never	103	66,9
Felt worried or scared for their health		
Frequent	5	3,2
Sometimes/seldom	47	30,3
Never	103	66,5
Felt irritable		
Frequent	21	13,6
Sometimes/seldom	80	51,9
Never	53	34,4
Neglect specific food or alcohol		
Frequent	36	23,1
Seldom	66	42,3
Never	54	34,6
Affects their daily activities		
Frequent	3	1,9
Sometimes/seldom	32	20,5
Never	121	77,6
Unable to move (sports, hobbies and outside of home)		
Frequent	3	1,9
Sometimes/seldom	34	21,80
Never	119	73,6

4 DISCUSSION

The main finding in the present thesis will be discussed briefly below and compared with other findings in the literature.

4.1 Natural history of Functional Gastrointestinal Disorders (IV)

There are three long-term studies which have focused on the natural history of FGIDs. The first one was a Swedish questionnaire survey of 1059 individuals conducted over a one year period (Agréus L, 1995), and followed up with the same subjects seven years later (Agréus L, 2001). Then there was a US population-based study from Olmsted County which followed 1365 subjects over a 12 year period (Halder SLS, 2007). The third one was the UK 10 year follow-up study from Leeds and Bradford with 3819 subjects (Ford AC, 2008). Comparison of responders of those studies can be seen in table 29.

Table 29: Comparison of respondents of four long-term studies (Agréus L, 2001; Halder SLS, 2007; Ford AC, 2008)

	Sweden	UK	Olmsted County	Iceland
Number of subjects in initial survey	1290	8407	4816	2000
Response rate	90%		79%	67%
Mean age (years)	48		47	43
Women responding	50%		55%	55%
Number of subjects in final survey	1172	6416	2914	1.180
Subjects who responded to both initial and final surveys	65% (843/1290)	48% (4003/8407)	28% (1365/4816)	40% (779/2000)
Mean age (years)	54	55	57	53
Women responding	53%	56%	52%	58%
Mean (\pm SD) time between completion of the initial and final surveys	7 years	10 years	12 years (\pm 2)	10 years
Study period	1988/1995	1994/2004	1988/2003	1996/2006
IBS initial	10.8%	1.8%	8.3%	16.9%
IBS final	13.5%	5.3%	11.4%	17.2%
IBS-D initial			3.3%	6.8%
IBS-D final			4.9%	9.1%
IBS-C initial			2.7%	9.7%
IBS-C final			2.4%	6.8%
IBS-M initial			1.3%	2.8%
IBS-M final			1.2%	3.6%
IBS at both initial and final (stable)	23% *	19%	24%	20%
Developed IBS symptoms at final	79% *	50%	16%	11%
Lost IBS symptoms at final	77% *	81%	55%	56%

*based on subjects who responded to all three questionnaire of the study

Numbers do not necessarily represent lost or developed numbers.

*Age- and sex adjusted in order to represent sex- and age distribution in the population

Our study was conducted by using similar methodology and based on the same questionnaire as the Olmsted County study. The current study makes it therefore possible for the first time to compare two large FGID longitudinal studies using the same methodology but performed in different populations. The Icelandic and Olmsted County studies document the natural history of IBS and its subgroups, as well as constipation, diarrhea, functional dyspepsia and abdominal pain over a long time period, 10 and 12 years. These studies were based on predominantly Caucasian populations. There were some differences in the mean age, response rates of those who responded to both the initial and final surveys, and the time settings.

In line with the Olmsted County study we confirmed that these disorders are common. The prevalence of IBS (any), FD and frequent abdominal pain were much higher in Iceland than in the Olmsted County study, but lower for constipation and for diarrhea than in the Olmsted County study. There was also a great difference in onset of FGID except for FD, but the difference was not as great in the disappearance of FGID, except for diarrhea and frequent abdominal pain.

The absolute numbers of people who reported onset of symptoms were greater than those reporting disappearance for all FGID in the Olmsted County study (Halder SLS, 2007). Onset of symptoms assessed by the transition model showed twice as high rates in the Olmsted County study than in the Icelandic study (23% vs. 11%).

It is of interest that subjects without any GI symptoms, neither in the initial nor the final surveys, constituted more than half of the study population in Iceland (52%) and 40% in the Olmsted County study. The numbers of subjects without GI symptoms in the Olmsted County is in line with the result as the Leeds and Bradford study (41%) (Ford AC, 2008) as well as the Swedish study (42%) (Agr  us L, 2001). This makes the Icelandic population with the highest proportion of subjects without any GI symptoms. This may suggest more symptom stability in Iceland, since half of the subjects stayed asymptomatic over the ten year period. However, a large proportion of the study population continued to experience symptoms in some form ten years later. Our study also shows a possible birth cohort effect on the prevalence of subjects without any GI symptoms. It has to be taken into consideration that both the Swedish study and the Leeds and Bradford study used different criteria to identify GI symptoms. The Swedish study used the Abdominal Symptom Questionnaire (Agr  us L, 2001) and the Leeds and Bradford study used the Leeds Dyspepsia Questionnaire and a questionnaire based on the Manning criteria to identify IBS (Ford AC, 2007, 2008).

In both our study and the Olmsted County study the symptom stability, symptom increase and symptom decrease were very similar. In the Swedish study by Agr  us et al. IBS was the most stable disorder, with 55% remaining in this subgroup. There was a considerable change between the dyspepsia and IBS subgroups (Agr  us L, 2001). The Leeds and Bradford study showed that there was an increase in prevalence of GI symptoms over 10 years (Ford AC, 2008) and that more than 70% of individuals meeting diagnostic criteria for a symptom

subgroup at baseline still reported GI symptoms at the 10 year follow-up. In our study more than half of the subjects reported no symptoms at both initial and final surveys and only 7% had symptoms stability during the ten year period.

Another study, the DIGEST study, was the first to examine population prevalence of GI symptoms at multiple international sites. It provided valuable cross-country data on the three month prevalence of upper GI symptoms and the disparities between the different survey sites (Stanghellini, 1999). The DIGEST study investigated populations in ten countries which can all be classified as highly developed with a westernized lifestyle.

Our study and the Olmsted County study expanded the epidemiology to the natural history dimension. It is clear that there was a difference in prevalence and natural history of various FGID in Olmsted County and in Iceland. The cross-country effect could contribute to this difference but the specific details of and reasons for the cross-country effect in these studies are no better understood than in the DIGEST study. There is no obvious difference in sociodemographic or risk factors between the two populations. The socioeconomic development of Iceland in the latter half of the 20th century was at least three decades behind Scandinavian and western European countries (Thjodleifsson B, 2007) and probably behind Olmsted County as well. This has been manifested in differences in *Helicobacter pylori* birth cohort prevalence in Sweden and Iceland (Thjodleifsson B, 2007), which can be regarded as a surrogate marker of hygiene and sanitary development.

Our study suggested a birth cohort effect for IBS with a high prevalence in the youngest age group born in 1971-80. It is therefore a tempting hypothesis that FGID prevalence is related to birth cohorts.

4.2 Stability of irritable bowel syndrome and subgroups as measured by three diagnostic criteria (II)

It is common that IBS patients ask the question whether their symptoms will worsen, remain the same or subside over time. The symptoms duration and severity in IBS patients can change depending upon different factors including food consumption, environmental factors including stress and/or anxiety, and the presence of other aggravating factors including bacterial overgrowth syndrome or acute gastroenteritis.

The importance of a precise diagnostic tool to diagnose IBS is essential for the study of its epidemiology and in clinical practice. In recent years the development of diagnostic criteria for IBS has been ongoing, leading to the introduction recently of the Rome III criteria. There is no doubt that diagnostic criteria constitute a useful and important tool to help physicians make a positive diagnosis of IBS without resorting simply to excluding other diseases. Individual symptoms have limited accuracy for diagnosing IBS in patients referred with lower gastrointestinal tract symptoms (Ford AC, 2008). The accuracy of the Manning criteria

was only modest according to Ford et al. (Ford AC, 2008). Whitehead and Drossman have stated that there are no consistent differences in sensitivity or specificity between Manning, Rome I, and Rome II but tests of Rome III are needed (Whitehead WE, 2010). According to Digesu et al. the Rome III Criteria Questionnaire is a reliable and reproducible tool to diagnose IBS constipation predominant (Digesu GA, 2010). Dorn et al. suggested that IBS subtypes when defined by either Rome II or Rome III are similar in their prevalence and their behavior over time (Wong RK, 2010). This is not the case in our findings where the Rome III criteria were more sensitive than the Rome II criteria.

The main focus of our prospective study was to compare three criteria for the diagnosis of IBS and its subgroups and on the potential usefulness of the criteria in clinical praxis, research and drug development. This comparison included age- and sex-related prevalence and retention and loss of diagnosis over the 10 year period. Furthermore, associations with sociodemographic variables and medical conditions like appendectomy and cholecystectomy were assessed.

The sensitivity of the criteria for diagnosing IBS varied widely in our study. The average prevalence in 2006, according to the Manning criteria, self-report and Rome III was 32%, 16% and 13%, respectively. The age- and sex-related prevalence was concurrent for all criteria, with a higher prevalence in females and young age groups. Prevalence decreased with age up to 75 but increased in the age group 76-85. An interesting finding was a cohort (1971-78) which showed a trend in prevalence manifested according to the Manning criteria, but this increase did not reach statistical significance. There was no change in prevalence over time for the Manning criteria or self-report (33/32 and 17/16, respectively for 1996/2006) but the prevalence for the Rome III criteria showed an increase from 10% to 13% over the 10 year period, which was confined to young females. The subgroup analysis revealed that the increase was due to females with IBS-D in the 26-55 age group. The Minnesota study also reported an increase in IBS-D with time (Halder SLS, 2007) (Table 29).

The prevalence profile in our study suggests that the Manning and self-report criteria have high sensitivity and low specificity, whereas Rome III has low sensitivity and high specificity in detecting IBS. This interpretation is complicated, however, by the fact that there was a flux of subjects in and out of all IBS categories as well as into functional dyspepsia and heartburn.

Stability was greatest in the Manning group 38.2%, and 27.3% in the Rome III subgroups, as against 11.8% in the self-report group. Over the ten year period a similar proportion of IBS subjects developed and lost IBS according to the Manning criteria and self-report groups, whereas many more subjects developed IBS in the Rome III group than lost the symptoms.

When we compared the prevalence and stability of IBS over the 10 year period to other longitudinal studies we saw that the prevalence of IBS in our study was almost the same after 10 years. The Olmsted County study, which followed 1365 patients with functional disorders between 1998 and 2003 (Table 29), the prevalence of IBS symptoms did not

change significantly from the baseline assessment to the final survey (Halder SLS, 2007). The prevalence was however much higher in our study ($p < 0.001$), both at initial and final surveys. These two studies used the same methodology and the same criteria to identify IBS. We also saw that the stability of IBS symptoms was similar in these two studies as well as the lost IBS symptoms at final survey. However, there was a higher prevalence of developed IBS symptoms at final survey in the Olmsted County study than in Iceland (< 0.001).

Two other longitudinal studies have demonstrated change in IBS symptoms over time (Table 29). Agréus et al. reported in a 7 year follow-up study that there was an increase in prevalence of IBS at the final survey (Table 29) (Agréus L, 2001). Ford et al. also reported, in a 10 year follow-up study, an increase in IBS prevalence (Table 29) (Ford AC, 2008). All four studies (Iceland, Olmsted County, Sweden and UK) showed a stability of IBS in the range of 19-24%, with the highest stability in Iceland.

When comparing our result to a meta-analysis by El-Serag et al. on the natural history of IBS in 14 published studies in 2004 (El-Serag HB, 2004), 2-18% of patients developed worsening symptoms over the time frame of 6 months to 6 years of follow-up assessment. It is difficult to compare these numbers with ours since the time frame is so broad: our study showed 11% developing IBS symptoms over the 10 year period. The meta-analysis also showed that symptoms remained unchanged in 30-50% of the cohort (Waller SL, 1969; Hillman LC, 1984; Svendsen JH, 1985; Fowlie S, 1992), which was higher than in our study which showed a stability of 20% in 10 years. Approximately one out of three of IBS patients reported disappearance of their symptoms over a mean follow-up period of two years (El-Serag HB, 2004). This is a somewhat lower prevalence than our study showed but the follow-up period (2 years) was much shorter than ours.

Previous studies have reported various associations between sociodemographic factors and IBS. Our study showed a significant relationship between level of education and Rome II IBS. Employment status was not associated with IBS, except for Rome III in 1996. It is of interest that Body Mass Index (BMI) and alcohol consumption were not associated with IBS for any criteria. A recent study showed that high BMI was associated with fast regional bowel transit and may therefore influence some stool-related symptoms in IBS (Sadik R, 2010). Smoking was not associated with IBS with the exception of Manning criteria 2006.

Several reports and an extensive review (Longstreth GF, 2004) have established an association between IBS and appendectomies, cholecystectomies and abdominal surgery. The present study established this relationship for Manning and Rome II criteria. Patients with IBS according to the Rome III criteria did not show this association except for cholecystectomy in 2006.

Our study gives a profile of the IBS criteria and their potential usefulness in clinical practice, research and drug development. It is however difficult to assess the relative merits of the various

criteria in view of the fact that there is no gold standard for the diagnosis and not even a solid biological marker. The Manning and Rome II criteria detect the symptom cluster of IBS and associated factors but are not stable enough to be useful in the assessment of prognosis. Their main merit is to open the possibility of a positive diagnosis of IBS. The unsophisticated self-report gives an intermediate prevalence to the Manning and Rome II and detects the associated factors equally well but is even more unstable. The self-report has no clinical value but it can give a zero level for the assessment of other criteria. The sophisticated Rome III criteria and its subtypes are based solely on stool consistency as measured using the Bristol Stool Scale (BSS) (Heaton KW, 1989). Stool consistency is regarded as the best surrogate for transit time, which is a potential biological marker of IBS (O'Donnell LJ, 1990; Probert CS, 1994). A recent study by Wong et al. reported that patients identified by Rome III criteria for FC and IBS-C are not distinct groups (Wong RK, 2010). Rome III criteria gave by far the lowest prevalence but the subtypes did not show great stability and therefore raise a question as to potential usefulness in the development of 5-HT-like drugs which have specificity for either constipation or diarrhea, at least not for long-term use. Three patient-based studies have shown a short term instability of Rome III subtypes (Drossman DA, 2005; Longstreth GF, 2006; Dorn SD, 2009). Heitkemper et al. recently reported that distress of IBS is more strongly related to the severity of abdominal pain/discomfort than is the predominant stool pattern in patients with IBS (Heitkemper M, 2011).

The results of our study highlight the problem of defining the IBS as an entity or condition. No single set of criteria seems to hold the answer. The main contribution of our study is perhaps to emphasize the notion that there is no single IBS entity but only a cluster of symptoms that float in time between different IBS categories, functional dyspepsia and heartburn. These conditions presumably have a common pathophysiology.

4.3 Physician's awareness and patient's experience (V)

A critical component of a good patient-physician relationship is the understanding of the patient's expectations (Halpert A, 2010). Most physicians have used a method of exclusion when diagnosing patients with IBS. Most community providers also believe IBS is a diagnosis of exclusion rather than using positive criteria to support the diagnosis (Spiegel BM, 2010). This approach – or lack of one - has therefore been time consuming and costly for the health care system.

The current study has revealed the proportion of Icelandic physicians in two medicine specialities that are aware of the criteria for diagnosing the disease. The study has addressed not only the question of how informed physicians are of the criteria for diagnosing IBS but also the importance of consensus about the diagnosis of the disease. This study has also addressed the IBS patient's perspective, how many sought health care and how they experienced their condition.

According to the results of this study, most IBS patients were seen by GPs, and this is most likely also the case in other countries, underlining the importance of awareness and knowledge of IBS on the part of GPs. Although 64% of all GPs reported that they were aware of the fact that special criteria to identify IBS existed, most of them (81%) did not know the criteria and therefore did not rely on them in clinical practice. Most of them, however, seemed to make a positive diagnosis of IBS without the use of endoscopy. A US study showed that only 30% of family practitioners knew that the Manning, Rome and Rome II criteria are used to diagnose IBS, which is in line with the results of the current study (Longstreth GF, 2003). GPs are more likely than hospital specialists to perceive functional gastrointestinal disorders as having a psychological basis, are far less likely to be familiar with diagnostic criteria, and are more likely to use other methods to make such diagnoses (Gladman LM, 2003). However, physicians are aware of and use the most common IBS symptoms such as abnormal bowel movements, abdominal pain and bloating in their diagnostic approach, and these were the most common symptoms of IBS subjects in the present study.

In the current study, physicians reported in most cases that they gave advice on diet and education on IBS as a treatment of IBS symptoms. This finding underlines the importance of providing reliable and useful information on IBS to patients, as well as the fact that there are no specific treatment options for IBS that are useful for all patients.

It is of interest that among interviewer - diagnosed IBS subjects, only one out of five was diagnosed with IBS even though more than half of the IBS subjects saw a physician because of IBS symptoms. These results were irrespective of whether the subjects fulfilled the Manning or Rome III criteria for IBS. This was also interesting because the majority of IBS subjects reported that IBS affected daily activities. This raises and highlights the question of whether IBS subjects reveal to physicians the low quality of life caused by IBS. It is also conceivable that physicians do not recognize IBS as a disorder that leads to impaired quality of life. The absence of a positive diagnosis of IBS might lead to lack of relevant treatment for specific symptoms of IBS such as abdominal pain. There is a need for a simple, practical and reliable diagnostic tool to be used in everyday clinical practice for more accurate diagnoses of IBS, a tool which will encourage physicians to make a reliable diagnosis and to provide effective treatment (Malagelada, 2005; Quigley EMM, 2006).

In a study from the US, the patients' ideal expectations from their recent healthcare providers relate to obtaining more information and relationship needs of receiving support and hope (Halpert A, 2010). Ideal expectations were found to be different from what patients perceived happened during their recent encounter with an IBS healthcare provider. A better understanding of a patient's needs and different types of expectations are necessary in order to construct an effective therapeutic relationship, which is critical for the management of IBS.

4.4 Natural history of irritable bowel syndrome in women and dysmenorrhea (VI)

The current study makes it possible for the first time to follow up women with and without dysmenorrhea over a ten year period and to observe how the FGID symptoms are associated with the dysmenorrhea. Analysis of women with IBS, either based on the Rome III criteria and/or the Manning criteria, showed that they were more likely to have dysmenorrhea.

A meta-analysis based on a small number of studies compared gastrointestinal symptoms in pre- and post menopausal women (Adeyemo MA, 2010). The authors concluded that there was insufficient evidence to determine the effect of menopausal status on IBS symptoms. The current study demonstrated an increase in prevalence in women having IBS after menopause using both IBS criteria. Increase in gastrointestinal symptoms around the time of menses and early menopause occurs at times of declining or low ovarian hormones, suggesting that estrogen and progesterone withdrawal may contribute either directly or indirectly (Heitkemper MM, 2009). One study has shown that the burden of gastrointestinal symptoms was higher in postmenopausal women than in men, but these differences mostly disappeared when controlled for age (Cain KC, 2009).

Women with dysmenorrhea report more gastrointestinal symptoms prior to or concurrent with uterine cramping pain at menses than women who are nondysmenorrheic (Kane SV, 1998). Gastrointestinal symptoms tend to be increased across all cycle phases in women with IBS compared to healthy women, but both groups demonstrated a similar increase in severity immediately prior to or at the onset of menses (Heitkemper MM, 2003)

The current study compared the FGIDs and dysmenorrheal severity and demonstrated that the great majority of women with dysmenorrhea had other FGID symptoms than related to IBS. Women reported more severe abdominal pain after menopause than before. One study has shown that abdominal pain is the most disruptive IBS symptom (Cain KC, 2006).

The current study observed the transition between symptoms and revealed a substantial difference between women with and without dysmenorrhea. Women without dysmenorrhea remained more often asymptomatic than women with dysmenorrhea. FGID symptoms were more stable in 10 years for women with dysmenorrhea and they also had more increase in symptoms than women without dysmenorrhea. This demonstrated a significant difference between these two groups of women. The prevalence of menstrually related symptoms has been shown to be high and appears to affect bowel patterns (Kane SV, 1998). A recent meta-analysis revealed a significant menstrual cycle effect for loose stools, bloating, abdominal pain, stool frequency and other changes in bowel habit (Adeyemo MA, 2010).

4.5 Natural history of functional dyspepsia (I)

The FD and DS criteria are not consistent with the new Rome III criteria. The Rome III diagnostic criteria for FD must include one or more of the following: (1) Bothersome postprandial fullness, (2) Early satiation, (3) Epigastric pain and (4) Epigastric burning, with no evidence of structural disease that is likely to explain the symptoms. The focus on the Rome III criteria for FD is mostly on fullness and satiation, which is not the case in the two other criteria used in this study.

In our study the FD criteria revealed a lower prevalence (14.0% 1996, 16.7% 2006) than the DS (24.1% 1996, 24.3% 2006) criteria. The prevalence of FD was rather low compared to other studies which indicated a prevalence of 20-40% (R H Jones, 1990; Talley NJ, 1992; Arg  us L, 1995; Douglas A. Drossman, 2006; Tack J, 2006; Alexander C. Ford, 2007). The prevalence of DS was higher (24.1-24.3%) than of FD and was higher than Choung et al. have reported (15%) (Choung RS, 2007). The difference in prevalence may be explained by the use of different criteria and possibly ethnicity, and quantitative comparison is not valid except possibly with the study by Choung et al. (Choung RS, 2007) which also used the BDQ criteria.

In our study younger subjects and females were more likely to report FD and this finding was also reported in the Olmsted County study (Halder SLS, 2007). In the DS group, nausea or vomiting was reported significantly more often by women than by men.

Our study showed a higher FD prevalence in younger age groups, but for DS there was a variation between subgroups where MR showed a significant difference in age groups. It is of interest that there were fewer FD subjects in the DS group than vice versa. The prevalence of FD in our study was stable over time but there was a considerable turnover in symptoms. Transition analysis showed that around half of the FD subjects fulfilled the FD criteria at the 10 year follow-up and 22% had moved into the IBS group, but that 10% had no symptoms. One third of the IBS subjects still had IBS and 25% had developed FD but 20% had no symptoms. Of the heartburn group, 39% remained stable whereas 11% had moved into the FD group and 12% into the IBS group. These figures are in line with results in the Swedish and the Olmsted County studies (Talley NJ, 1992; Halder SLS, 2007). There was considerable transition in the dyspepsia subgroups except in the MR category, which was relatively stable. These findings are not supported, however, in a study by Ford et al. (Ford AC, 2008) who found that 5% of those with dyspepsia had symptoms compatible with IBS at 10 years, compared to 15% going on to meet criteria for GERD. They also demonstrated that of those who were symptomatic at baseline, almost three-quarters remained symptomatic at ten years, but more than 40% changed symptom subgroups (Ford AC, 2008).

In recent studies questions about the best classification of dyspepsia subgroups have persisted, mainly because of the overlap of symptoms in defined subgroups or the lack of association with pathophysiology (Talley NJ, 1992; Stanghellini V, 1999; Karamanolis G, 2006; Choung RS, 2007).

In 2006 a relationship between FD and smoking could be seen but not to alcohol consumption in either 1996 or 2006. Alcohol consumption has been associated with dyspepsia and frequent abdominal pain (Halder SLS, 2006), which is not supported by the current study.

Our study showed a strong relationship between FD and heartburn as well as IBS. The association of FD and heartburn is not unexpected since dysmotility is common to FD and acid reflux. The fact that H2 blockers and proton pump inhibitors did not relieve the gastrointestinal pain suggests that gastro-esophageal reflux disease did not appreciably interfere with the FD diagnosis. FD subjects were more likely to have experienced gastrointestinal pain as a child than others.

In our study the proportion of FD subjects seeking medical care was high. Every fifth subject that had visited a physician more than six times in the previous year had FD and more than a third of all subjects who consulted a physician because of gastro-pain had FD. Researchers have reported higher consultation rates for dyspepsia in those with coexisting functional GI disorders (Talley NJ, 1998; Koloski NA, 2002), and upper GI symptoms have been reported to be associated with a significant loss of work and activity days (Camilleri M, 2005). Those that make use of sick leave from work are more likely to have FD, the prevalence increasing over the ten year period, indicating a heavy burden on health care resources and society. But as has been shown in a study by Ford et al. the reasons for consulting a physician can be multifactorial (Ford AC, 2007).

Various definitions of dyspepsia and FD have been used in previous studies (Westbrook JI, 2002; Tack J, 2006). One of the most important factors affecting prevalence is the demographics. The DIGEST study observed the three-month prevalence rate of upper gastrointestinal symptoms in the general population in 10 locations around the world and reported prevalence of dyspeptic symptoms from 9.4% in Japan to 41.8% in the US, using the same criteria in all places (Stanghellini, 1999). However, variations in the definition of dyspepsia and functional dyspepsia will also affect the prevalence (Gschossmann JM, 2001). In our study we used two criteria to identify dyspepsia symptoms, which resulted in different prevalence rates. However, we used the same definitions consistently throughout the study and were able to compare two different approaches to definitions of dyspepsia. A recent study has shown that neither clinical impression nor computer models that incorporate patient demographics, risk factors, history items and symptoms adequately distinguish between organic and functional disease in patients referred for endoscopic evaluation of dyspepsia (Moayyendi P, 2006).

Since our publication at least three studies using the Rome III criteria for FD have been published. Two of these studies are from Asia and one from Sweden (Lee HJ, 2010; Kaji M, 2010; Aro P, 2011). They all deal with the impact on FD HRQoL. The Japanese study by Kaji et al. showed that, in 2680 eligible subjects, FD, GERD and IBS had a significant impact on HRQoL scores in all physical and psychological domains of the Short Form-8

questionnaire and overlap among FD, GERD and IBS was common and was associated with impaired HRQoL (Kaji M, 2010). The Korean study concluded that depressive mood was significantly related to FD and FD-IBS overlap but not to IBS based on Rome III criteria and that FD-IBS overlap patients have a worse quality of life than patients with FD-alone or IBS-alone (Lee HJ, 2010). A study by Aro et al. of a Swedish population, shows that FD impacts all main domains and noted the physical, mental and social aspects of HRQoL in the general population (Aro P, 2011). Overlap of functional dyspepsia with irritable bowel syndrome or gastro-esophageal reflux symptoms impacts the domain related to bodily pain.

4.6 Natural history of heartburn - A 10 year population-based study (III)

The prevalence of heartburn is high in Iceland. More than two out of five reported heartburn in the preceding year. Half of those reported heartburn in the preceding week. Heartburn was reported as still existing after 10 years for 2 out of 3 subjects in the study. The study by Agréus et al. showed that the prevalence of predominant gastroesophageal reflux symptoms appear to be stable over time (Agréus L, 2001). Results from studies of patients suggest that gastroesophageal reflux disease is a chronic disease in most cases (Kuster E, 1994; McDougall NI, 1996; Agréus L, 2001). One third of subjects who did not report heartburn in 1996 had developed heartburn 10 years later and one third had overcome symptoms. So even though the total prevalence was almost the same in both 1996 and 2006, there was a change among over one third of subjects reporting heartburn.

Heartburn subjects with a BMI either lower than or higher than normal weight were more likely to experience heartburn than subjects with normal weight. A study by Aro et al. found that reflux symptoms are linked to obesity and specifically that the presence of gastroesophageal reflux symptoms was linked to reflux esophagitis in the population (Aro P, 2005). Festi et al. concluded that it was likely that GERD and obesity are in some way linked and that it was possible to hypothesize that GERD may be a curable condition through the control of body weight (Festi D, 2009). This may also be true for heartburn.

The transition analysis showed a substantial change in numbers in all the categories. The stability of each disease varied. FD subjects were the most stable throughout the ten years (52.3%). Of the heartburn group 39.3% were stable, as was 30.3% of the IBS group and 15.4% of the frequent abdominal pain group. A quarter of the heartburn group had increased symptoms in ten years, 4.6% decreased symptoms, and one third developed no symptoms in 10 years. There was a significant relationship between IBS and heartburn as well as FD and heartburn.

Since our publication a study by Haag et al. was published. The aim was to determine the prevalence of upper gastrointestinal symptoms in 13 European countries (Haag S, 2011). The predominant symptoms in all countries were heartburn and symptoms of gastrointestinal origins. In subjects with heartburn, symptoms occurred on average 16.5 times during the

previous 12 months and heartburn was significantly greater in women than in men (18.1 vs. 14.7 episodes / 12 months) and increasing with age. This comparison between 13 European countries shows that there are marked differences in the country specific prevalence of UGI complaints. These differences are associated with socioeconomic indicators such as the gross domestic product (GDP) per capita.

Half (45.1%) of the subjects that reported heartburn in the prior year experienced heartburn in the prior week. Food and beverages play a large part in eliciting heartburn, very often in 20.0% of the cases and sometimes in 73.8% of the cases. Subjects also very often experienced increased heartburn caused by a specific food in 22.7% of the cases. Heartburn did not seem to be the cause leading to less food and beverage consumption, but one out of five heartburn subjects did avoid a specific food or alcohol because of heartburn. Festi et al. report that no definitive data exist regarding the role of diet and specific foods or drinks in GERD clinical manifestations (Festi D, 2009).

Heartburn is associated with feeling tired (61.2%), feeling bad (87.5%) and irritation (65.5%). One third felt worried or scared for their health because of heartburn symptoms and one third also felt that heartburn caused them to feel hopeless, worried or impatient (33.1%). Every fifth heartburn subject reported that heartburn affected activities such as daily and family activities, as well as that heartburn caused them to be unable to move normally and therefore affected their participation in sports, hobbies and outdoor activities. This effect of heartburn on normal life and activities may have affected the subjects as a chronic condition throughout the ten years of the study and therefore had a great impact on quality of life. This finding is in line with McDougall et al., who showed in their study on reflux esophagitis and quality of life that it was not bodily pain and vitality that were impaired, but general health and social function (McDougall NI, 1996).

Three out of five of all the heartburn subjects in 2006 reported taking medicine for heartburn. Almost all the subjects who were on medication for heartburn reported relief offered by the medication. Age was a significant factor for the use of medication for heartburn. Most subjects took ranitidine or esomeprazole for their symptoms.

A few studies have addressed the impact of nocturnal reflux symptoms in heartburn subjects. A study by Nocon et al. has shown that the prevalence of nighttime heartburn in GERD patients under routine care was high, up to 49% for 1 of 3 years (Nocon M, 2007). A population-based survey in the United States found that the overall prevalence of nocturnal GERD symptoms was 10%, with 74% of subjects with GERD symptoms fitting the criteria for nocturnal GERD (Farup C, 2001). In our study sleep was frequently affected in 5.8% cases and 45.2% of heartburn subjects were sometimes or seldom troubled with sleeping in the prior week. These numbers could be expected to be higher for the preceding year, since we asked specifically about the preceding week.

4.7 Strengths and weaknesses

Our study has significant strengths. The main one is the use of a stable homogeneous and well-defined population. The sample was randomly selected from the National Registry of Iceland and represented the nation as a whole in selected age groups. The population of Iceland was around 300 thousand inhabitants at the time of the study and the sample was $\approx 1\%$ of the whole population from all around the country. Extensive use of health care by IBS subjects is well established (Eisen GM, 2000; Ganguly R, 2001; Longstreth GF, 2003) and the present study confirms this. Clinical overlap and transition of IBS to heartburn and functional dyspepsia is common (Corsetti M, 2004; Wang AJ, 2008) and confirmed by our study.

It is of particular importance that the same methodology was used in the present study as in the Olmsted County study, i.e. the Bowel Disease Questionnaire (BDQ) (Talley NJ, 1989; O'Keefe EA, 1992), thereby ensuring a reasonable degree of comparability. The BDQ assesses the whole range of gastrointestinal functional disorders, though the present study reports predominantly on functional dyspepsia.

Only a minority of IBS patients seek medical care and population-based studies are therefore essential for studying IBS.

There are some limitations of our study. The subjects were not specifically interviewed or examined to evaluate the possibility of organic disease. However there were some questions addressing this issue, for example peptic ulcer disease (PUD). Subjects reporting PUD were excluded from dyspepsia analysis. Furthermore, a 10 year (postal) follow-up went some way to making an organic cause of symptoms unlikely. Moreover, since the response rate was 66.8% in 1996 and 68.9% in 2006, a dropout bias cannot be excluded. A similar mean age in the respondent group and the non-respondent group does not indicate an age dropout bias in the study, but a significantly larger proportion of women responded again in 2006, which may indicate a gender bias.

It should also be pointed out that the natural history of FGID in this study is based on the assessment of subjects at two time points, 1996 and 2006. Our use of the Manning criteria to diagnose IBS can be challenged. We made the decision to use the Manning criteria at baseline because our study was designed when the Rome process was in its infancy and also to be able to compare our results to the Olmsted County study. However, we did include the Rome II criteria into the latter questionnaire and we also made a close approximation of the Rome III criteria. The data were re-evaluated retrospectively to conform to Rome III criteria.

Another limitation of this study was the relatively low response rate in the physician study, which raises the question as to whether the level of awareness and knowledge of diagnostic criteria might be even lower than the result obtained. The strength of the study, however, was

that all physicians in Iceland in the relevant fields of general practice and gastroenterology were invited to participate in the study and was also enhanced by the fact that all IBS subjects who were contacted by telephone participated in the telephone survey.

5 CONCLUSIONS

5.1 Conclusions

Prevalence of FGID

Prevalence of FGID symptoms was stable over time but the turnover in symptoms was high. There was a difference in prevalence of symptoms between studies and transition probabilities. A higher number of subjects had no symptoms in Iceland than in Olmsted County and there was a greater variation in subjects having different symptoms at follow up.

This makes the Icelandic population with the highest proportion of subjects without any GI symptoms. This may suggest more symptom stability in Iceland,

Stability of irritable bowel syndrome and subgroups as measured by three diagnostic criteria

IBS prevalence remained stable over a 10 year period with a turnover in symptoms. The results of our study highlight the problem of defining the IBS as one entity. No single set of criteria seems to hold the answer. IBS in Iceland is very common and indicates a chronic condition which poses a heavy burden on the health care system. The main contribution of our study is perhaps to emphasize the notion that there is no single IBS condition but only a cluster of symptoms that float in time between different IBS categories, functional dyspepsia and heartburn. These conditions presumably have a common pathophysiology.

Physician's awareness and patient's experience

Approximately half of the IBS subjects seeking physician physicians received a diagnosis of IBS. The knowledge of IBS seems to be very limited among IBS subjects. This study suggests that few physicians use IBS criteria and that the awareness and knowledge of the diagnostic criteria for IBS differed between SGs on the one hand and GPs on the other hand. One out of four physicians used a diagnosis of exclusion.

More widespread knowledge and use of the diagnostic criteria among physicians can be expected to support a more accurate diagnosis of IBS.

Natural history of irritable bowel syndrome in women and dysmenorrhea

Women with IBS were more likely to experience dysmenorrhea than women without IBS which seems to be a part of the symptomatology in most women with IBS. FGID symptoms were more stable in 10 years for women with dysmenorrhea than women without dysmenorrhea. IBS symptom severity seemed to increase after menopause.

Natural history of functional dyspepsia

The study showed a higher prevalence of dyspepsias as diagnosed by DS than by conventional FD criteria. Younger subjects and females were more likely to have FD and in the subgroup category females more often reported symptoms in the meal-related, nausea or

vomiting and combination subgroups, whereas males reported predominantly upper abdominal pain. FD was stable over the 10 year period but there was a turnover in symptoms. There was a strong correlation between FD and IBS and heartburn. The main risk factors for dyspepsia were female gender, young age and smoking.

Natural history of heartburn

Heartburn is a common condition in the population of Iceland. The prevalence is slightly higher than reported elsewhere. Heartburn is a chronic condition, affecting every fifth person every week. Heartburn subjects with a BMI lower or higher than normal weight were more likely to experience heartburn than subjects of normal weight. Heartburn did not seem to lead to a lower food and beverage consumption, but one out of five heartburn subjects did avoid a specific food or alcohol because of the heartburn. Heartburn had a great impact on daily activities and quality of life. Half of the heartburn subjects experienced sleep disturbances because of heartburn.

5.2 Future directions

Further studies are needed to explore the prevalence of FGIDs based on Rome III. There are great opportunities for future directions in epidemiology with larger follow-up studies over a longer period of time. It would be interesting to connect our study with other Icelandic databases which could add information to our questionnaire, such as the cancer registries and the Reykjavik Study.

The current study was not designed to answer questions about the etiology of FGIDs. The study has highlighted several aspects of FGIDs, however, that can help to focus studies on the pathophysiology. Among the most interesting findings has been the great fluctuation between FGID symptoms and the development of symptom clusters over time, rather than different diseases.

Additional longitudinal studies are needed that investigate further the differences between the criteria. What, for example, happens to subjects who fulfill the Manning criteria but do not fulfill the Rome III criteria? What becomes of these subjects and which diagnosis are they receiving for their syndromes?

More research is also needed to find the predictors of FGID symptoms. Will we be able to predict which subjects are more likely to get FGIDs and will we be able to prevent it?

Our studies have shown that subjects who seek physician with IBS symptoms do not necessarily get a diagnosis of IBS. There is therefore also a need for further study of the patient – physician relationship as well as to study why physicians do not provide a diagnosis of IBS.

Studies have revealed gender differences. More research is therefore needed to investigate the association between dysmenorrhea and FGIDs, as well as to study what happens to women after menopause.

Other interesting fields are now being studied. One of those fields is post-infectious IBS. Evidence is beginning to mount which indicates that IBS develops in some individuals following an acute bacterial infection in the digestive system. A better understanding of the role of microbiota and immune activation in the pathophysiology of IBS could provide novel pharmacological targets for this common troublesome disorder.

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PAPERS I-VI

Paper I

Natural History of Functional Dyspepsia: A 10-Year Population-Based Study

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Key Words

Functional bowel disorders • Follow-up • Questionnaire study • Epidemiology • Dyspepsia

Abstract

Background: Functional dyspepsia (FD) is a common disorder, but information on its natural history is limited. **Aim:** To study the natural history of FD as assessed by 2 criteria over a 10-year period. **Method:** A population-based study conducted by mailing a questionnaire to the same age- and gender-stratified random sample of the Icelandic population aged 18–75 in 1996 and again in 2006. FD was estimated by the Functional Dyspepsia Score List and by dyspepsia subgroups categorized into 4 groups: (1) frequent upper pain, (2) meal-related, (3) nausea or vomiting, and (4) combinations of these groups. **Results:** FD was diagnosed in 13.9% of the subjects in the 1996 sample (11.3% male, 15.8% female) and 16.7% in 2006 (12.3% male, 20.2% female) with a significant difference between males and females in 2006. Dyspepsia subgroup criteria showed a higher prevalence than conventional FD criteria. The proportion of FD subjects in one of the dyspepsia subgroups was low. There was a significant relationship between FD and heartburn and irritable bowel syndrome. A high proportion of subjects who seek medical care have FD. **Conclusion:** FD was stable over the

10-year period, but there was turnover in symptoms and increased intensity and frequency of gastrointestinal pain. Dyspepsia subgroup criteria showed a higher prevalence than FD, which was more common in young subjects and females. FD poses a heavy burden on the health care system.

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Introduction

Functional dyspepsia (FD) is a syndrome characterized by central upper abdominal pain or discomfort in the absence of any organic disease that can explain the symptoms. The syndrome is heterogeneous, and the symptoms reported include epigastric pain, postprandial fullness, bloating, early satiety or discomfort, belching, nausea, vomiting, and epigastric burning. FD has been defined as the presence of one or more dyspepsia symptoms that are considered to originate from the gastroduodenal region in the absence of any organic, systemic or metabolic disease that is likely to explain the symptoms [1].

The natural history of FD is largely unknown and epidemiological studies are difficult to perform. Although FD can be positively diagnosed, it is predominantly a di-

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agnosis of exclusion and most patients with FD do not seek medical care [2]. Population-based surveys are therefore necessary for assessing the epidemiology of these conditions in the community, and they are mainly conducted by postal surveys. Population-based studies have to rely on symptom criteria for the diagnosis of FD, like the Rome II-III criteria [1].

A bowel disease questionnaire, which can be used in epidemiological studies, has also been developed and shown to have adequate validity to diagnose gastrointestinal (GI) functional disorders, including FD [3–5], and has been used in a recent publication [6].

The Rome II criteria attempted to further classify FD into subgroups according to the most predominant or most bothersome single dyspeptic symptom reported by the subject. However, the heterogeneity and instability of the proposed dyspepsia subgroups and lack of agreement on what predominant means made this attempt unsuccessful [7–11].

A recent population-based study of outpatients, using factor analysis, suggests that distinct subgroups of uninvestigated dyspepsia do exist in the general population. Three subgroups were found: (1) an epigastric pain factor group, (2) an early satiety factor group and (3) a nausea/vomiting factor group [12].

Dyspepsia is a common condition in the general population [13, 14]. With the absence of predominant heartburn in dyspepsia, 20–40% of individuals report chronic or recurrent dyspeptic symptoms [1, 7, 15–18]. The variations in prevalence are due both to different ethnic populations and the methods used to diagnose dyspepsia [19].

Follow-up epidemiological studies on FD are rare. The aim of the present study was to evaluate the natural history of FD, as defined by The Bowel Disease Questionnaire (modified) [20, 21], in the Icelandic population prospectively over a 10-year period and, furthermore, to evaluate the natural history over a 10-year period of dyspepsia subgroups [12] with symptoms compared to the FD criteria.

Methods

The National Bioethics Committee of Iceland and The Icelandic Data Protection Authority (Personuvernd) gave permission for the research.

Participants and Setting

In 1996, an epidemiological study of GI diseases was performed in Iceland [22]. 2,000 inhabitants 18–75 years of age were involved. The individuals were randomly selected from the Na-

tional Registry of Iceland. An equal distribution of sex and age was secured in each age group. In 2006, we attempted to contact all the participants from 1996, as well as adding 300 new individuals with an age range of 18–27 years. They were randomly selected from the national registry as well. A questionnaire and an explanatory letter were mailed to eligible individuals at baseline and in 2006. Reminder letters were mailed at 2, 4 and 7 weeks, using the total method of Dillman [23]. Individuals who, at any point, indicated that they did not want to participate in the study were not contacted further.

The Questionnaire

The Bowel Disease Questionnaire (BDQ) [20, 21] was translated and modified for this study. The BDQ was the best available instrument to assess dyspepsia in 1995–1996, when the original study was planned and performed. The questionnaire was designed as a self-report instrument to measure symptoms experienced over the previous year and to collect past medical history [6].

The Icelandic version of the BDQ questionnaire (1996) addresses 47 GI symptoms and 32 items that measure past illness, health care use, and sociodemographic and psychosomatic symptoms. It also includes a valid measure of non-GI somatic complaints, the Somatic Symptom Checklist [24]. The Somatic Symptom Checklist consists of items concerning 12 non-GI and 5 GI symptoms or illnesses. Individuals are instructed to indicate, on a 5-point scale, how often each symptom occurs and how bothersome it is. There were few changes in the later questionnaire used in 2006, which addresses 51 GI symptoms and includes 33 items that measure past illness, health care use, and sociodemographic and psychosomatic symptoms. Furthermore, the 2006 questionnaire addresses 17 items to identify heartburn and items related to heartburn. The Icelandic version of the BDQ was tested on previously uninvestigated subjects in GI outpatient clinics for possible misunderstandings and ambiguities, and the translation was modified and developed accordingly.

Criteria for Identifying Dyspepsia

Functional Dyspepsia Score List. Subjects were classified with dyspepsia if they reported symptoms from the Functional Dyspepsia Score List [20]: Pain from the upper abdomen more than 6 times in the preceding year and 19 dyspepsia-related symptoms (in our study we combined 2 symptoms, nausea and vomiting, into 1 question and, therefore, had 18 dyspepsia-related symptoms). Each set of questions in figure 1 was ranked according to the method by Talley et al. [20]. These calculations provided an average rank for each subject and were divided into 3 categories: mild, moderate and severe. Subjects with significant FD were classified as having moderate to severe symptoms, but a report of ulcer disease was an exclusion criterion.

Dyspepsia Subgroups. Subjects were categorized into 4 groups: (1) frequent upper pain (FUP; more than 6 times per year), (2) meal-related discomfort (MR; discomfort related to eating), (3) nausea or vomiting (NV; once a week or more), and (4) combination (COMB; more than 1 of the 3 symptom complexes above).

Criteria for Identifying Irritable Bowel Syndrome and Heartburn

Irritable bowel syndrome (IBS) subjects were classified as having IBS using 2 criteria: fulfilling 2 or more symptoms of the Man-

Abdominal pain score above the navel >6 times in the past year
 Severity of ache or pain
 Ache or pain awakens subject from sleep at night
 Pain comes and goes periodically
 Ache or pain occurs before meals or when hungry
 Ache or pain occurs immediately after meals
 Ache or pain occurs 30 min to 2 h after meals
 Pain relieved by burping
 Pain relieved by eating
 Pain relieved by antacids
 Pain intensified by consumption of food or milk
 Pain intensified by drinking beer, wine or other alcoholic beverages
 Number of times subject had pain in the last year
 Radiation of pain
 Initial occurrence of pain
 Nausea or vomiting in the past year
 Change in weight in the past year
 Change in appetite in the past year

Fig. 1. Functional dyspepsia score.

ning criteria [25] or fulfilling the Rome II criteria [26]. Heartburn subjects were classified with heartburn if they identified symptoms of heartburn in a question that included a definition of heartburn.

Mortality Data

For the 2006 survey, we identified all deceased individuals with the assistance of the National Registry of Iceland (Thjodskra).

Statistical Analysis

Tables were constructed for frequency and percentages. Categorical data were analyzed using the χ^2 test. The type I error protection rate was set at 0.05. The exact p value is listed in the tables and text. All the research data were imported into SPSS (Statistical Package of Social Science) software.

Transition between Disorders from Initial and Final Surveys

A transition model used by Halder et al. [6] was modified and applied for this study (fig. 4). The responses from the initial (1996) and final (2006) surveys were matched for each subject to examine the changes between disorders at an individual level for the 9 categories (FD, COMB, FUP, MR, NV, IBS, heartburn, frequent abdominal pain and no symptoms). A 9×9 table was used to model these multiple changes and collapsed into 6 groups, as illustrated in figure 4. Those with the most symptoms were prioritized higher. Those who developed more symptoms and those who reported fewer symptoms could be categorized into groups. There were 6 patterns of symptoms, identified as follows: (1) 'symptom stability', (2) 'symptom increase', (3) 'symptom decrease', (4) 'symptom onset', (5) 'became asymptomatic' and (6) 'none of these symptoms'.

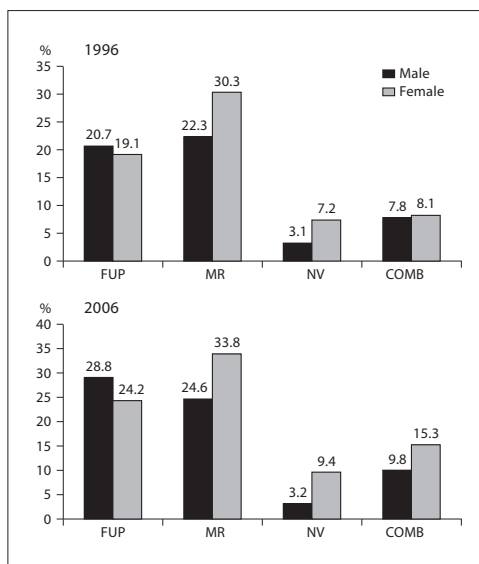


Fig. 2. Change in dyspepsia subgroups during the 10-year period.

Results

Demographic Data of Participants

The response rate in 1996 was 66.8% (1,336/2000). Of the 1,336 individuals that participated in 1996, 81 were deceased in 2006, 5 were unable to answer (mainly because of old age) and 70 could not be traced to a current address. This left 1,180 individuals in 2006, of whom 813 responded. Therefore, the response rate in 2006 was 68.9% (813/1,180). The mean age of the individuals in 2006 was 53, and 341 were male (42.3%). The responders represented the population in all major factors concerning sex and age distribution. The response rate was slightly higher for women, which is common in similar studies, and the response rate was also higher for older subjects than younger ones. Age distribution and demographic details of the study cohort are presented in tables 1 and 2.

Functional Dyspepsia 1996–2006

Of those who answered the questionnaire in both 1996 and 2006, FD was diagnosed in 13.9% in 1996 (11.3% male, 15.8% female) and 16.7% in 2006 (12.3% male,

Table 1. Age and sex distribution of study population

	Population 2006, %	Respondents 2006, %
Gender		
Men	50.3	42.3
Women	49.7	57.7
Age		
28–35	19.5	14.71
36–45	24.9	20.15
46–55	22.8	22.25
56–65	15.6	19.65
66–75	10.4	14.96
76–85	6.8	8.28
Total, n	173,859	806 (809)

20.2% female), with a statistical significance between sexes in 2006 [χ^2 (1, n = 806) = 8.750, $p < 0.01$]. Females were more likely to develop FD over the 10-year period than males. More females developed FD than got over the symptoms.

Younger subjects were significantly more likely to experience FD than older ones. Employment status was not associated with FD. Those who used sick leave from work were more likely to have developed FD during the 10-year time period (table 2).

BMI and Weight

BMI was not associated with the development of FD over the 10-year period (table 2). Those who lost weight without dieting were more likely to have FD. Those who had a lower or greater than normal appetite were also more likely to have FD.

Smoking and Alcohol

Smoking was associated with the development of FD from 1996 to 2006 (table 2), but there was no association between FD and the number of cigarettes smoked. There was no significant association with the development of FD and alcohol consumption.

Gastrointestinal Pain

Those who reported a greater frequency of pain were significantly more likely to fulfill FD criteria. The same applied to those who had experienced GI pain as children or were relieved of pain by burping or eating. The more intense the GI pain, the higher the odds of having FD (significant at the 0.05 level for 2006; significant at the 0.05 level for 1996 when combining the alternatives intense and very intense). It is of interest that administra-

tion of H_2 blockers and protein pump inhibitors did not relieve the pain.

Medical Care

Those who consulted a doctor were more likely to have FD and also more frequently because of gastric (abdominal) pain. There was an association between FD and abdominal operations as well as FD and appendectomy in 1996. There was an association between FD and cholecystectomy in 2006.

The Relationship of FD, Heartburn and IBS

There was a strong relationship between heartburn and FD. There was a significant relationship between IBS and FD. In 2006, 43.5% of IBS subjects were identified with FD when applying the Manning criteria and 61.9% when using the Rome II criteria.

Dyspepsia Subgroups

According to the dyspepsia subgroup criteria, for subjects in one or more dyspepsia subgroup, the prevalence of dyspepsia was 24.1% in 1996 and 24.3% in 2006. Subjects who answered all questions in 2006 and fell into a dyspepsia subgroup numbered 162. Of these, the percentages for each dyspeptic subgroup were as follows: 47% had frequent upper abdominal pain, 23% had nausea/vomiting and 56% had meal-related discomfort (fig. 3).

Because of overlap among these groups, the percentages add up to more than 100%; of the total, 25% fell into the combination group. Table 3 shows the proportion of gender and age and FD subjects in each subgroup of dyspepsia.

Of those who did not report any dyspepsia subgroup symptoms in 1996, 12.9% reported symptoms 10 years later.

Figure 2 shows the changes in the dyspepsia subgroups over the 10-year period. There was an increase in all cases during the 10 years. Meal-related discomfort and nausea/vomiting were more prevalent in females than males, as well as in combination in 2006. In contrast, upper abdominal pain was more prevalent in males than females.

In table 4 the proportion of dyspepsia subgroup and FD subjects can be seen in each group, showing that the proportion of dyspepsia subgroup subjects in the FD group was significantly higher than vice versa.

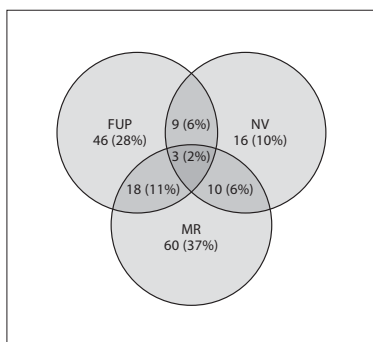
Transitions Among Symptom Subgroups between the Initial and Final Surveys

As described in the methods section, the groups in this analysis were defined as mutually exclusive using the

Table 2. Sociodemographic characteristics and the development and disappearance of FD

	Number	Never had FD, %	Lost FD, %	Retained FD, %	Developed FD, %	χ^2	p
Gender						10.427	<0.05*
Male	341	81.8	5.9	5.3	7.0		
Female	465	72.3	7.5	8.6	11.6		
Age group, years						25.615	<0.001***
66–85	188	86.7	4.8	4.3	4.3		
36–65	502	75.7	7.2	6.8	10.4		
28–35	119	63.0	8.4	13.4	15.1		
BMI						8.861	0.182
>30	161	68.9	8.1	10.6	12.4		
>25 to ≤30	330	78.5	5.2	7.0	9.4		
≤25	300	77.7	8.0	5.7	8.7		
Level of education						5.840	0.756
>4 years of further education	232	74.57	7.76	7.76	9.91		
3–4 years of further education	288	76.04	6.94	8.33	8.68		
<3 years of further education	100	73.00	9.00	5.00	13.00		
No further education	173	80.35	4.62	6.36	8.67		
Employment status						3.842	0.279
Employed	594	75.59	7.07	6.57	10.77		
Unemployed	208	78.37	6.25	8.65	6.73		
Alcohol						8.246	0.221
≥7 drinks per week	44	88.64	2.27	4.55	4.55		
1–6 drinks per week	422	74.17	6.64	7.11	12.09		
No alcohol	328	77.44	7.32	7.62	7.62		
Smoking						10.0834	<0.05*
Smokers	182	70.3	9.9	11.0	8.8		
Nonsmokers	516	79.1	5.6	5.8	9.5		

* p < 0.05, *** p < 0.001.

**Fig. 3.** Distribution and overlap of dyspepsia subgroups.**Table 3.** Non-overlapping dyspepsia subgroups by gender, age and FD

Dyspepsia subgroups	%	FD %	Age, %			Female	
			28–35	36–65	66–85	%	Male %
FUP	25.8	38.5 ^a	16.4	28.2	26.9	24.2	28.8
MR	30.9	39.4 ^b	47.5 ^c	24.6 ^c	35.3 ^c	33.8	24.6
NV	6.8	18.0 ^c	11.9	6.1	5.1	9.4 ^f	3.2 ^f
COMB	13.3	22.1 ^d	17.5	12.0	13.5	15.3	9.8

^a FUP – FD: $\chi^2 = 19.59$, p < 0.001.^b MR – FD: $\chi^2 = 7.52$, p = 0.006.^c NV – FD: $\chi^2 = 32.26$, p < 0.001.^d COMB – FD: $\chi^2 = 15.54$, p < 0.001.^e MR – Age: $\chi^2 = 12.21$, p = 0.002.^f NV – female/male: $\chi^2 = 11.12$, p < 0.001.

Fig. 4. Transitions among symptom subgroups between the initial and final surveys.

FGID in 1996	Proportion of FGID in 2006 based on primary survey disorder								
	FD %	IBS %	DS Comb. %	DS FUP %	DS MR %	DS NV %	Heartburn %	Frequent Abd. Pain %	No symptoms (%)
FD (n = 113)	51.3	22.1	2.7	1.8	1.8	0.9	8.0	1.8	9.7
IBS (n = 157)	24.8	31.2	1.3	1.3	1.3	1.3	17.2	1.9	19.7
DS Combination (n = 5)	20.0	60.0	0.0	0.0	0.0	0.0	0.0	0.0	20.0
DS FUP (n = 16)	6.3	0.0	0.0	0.0	6.3	6.3	25.0	0.0	56.3
DS MR (n = 11)	27.3	18.2	0.0	9.1	18.2	0.0	27.3	0.0	0.0
DS NV (n = 5)	40.0	20.0	0.0	0.0	0.0	0.0	0.0	0.0	40.0
Heartburn (n = 153)	11.1	11.8	0.7	3.9	0.7	0.7	38.6	1.3	31.4
Frequent Abdominal Pain (n = 29)	6.9	31.0	0.0	0.0	3.4	10.3	10.3	10.3	27.6
No symptoms (n = 324)	4.0	9.9	0.3	0.9	0.3	1.9	16.0	5.2	61.4

FGID - Functional Gastrointestinal Disorder
 FD - Functional Dyspepsia
 FUP - Frequent Upper Pain
 MR - Meal-Related Pain
 NV - Nausea or vomiting
 Combination - Combination of FUP, MR, NV
 IBS - Irritable Bowel Syndrome
 DS - Dyspepsia subgroup

Remaining asymptomatic (white)
 Became asymptomatic (green)
 Stable (blue)
 Developed symptoms (pink)
 Decreased symptoms (red)
 Increased symptoms (yellow)

Table 4. Proportion of dyspepsia subgroup (DS) and FD in each group

	1996	2006
Proportion of DS subjects in the FD group	55.8%	70.6%
Proportion of FD subjects in the DS group	36.8%	51.3%

symptom hierarchy so that each subject appears in only one category for both the 1996 and 2006 surveys. There was a ‘no symptoms’ category for those who did not meet any of the criteria applied for functional GI disorders. Due to the hierarchical classification, few numbers occurred in some categories.

There was a substantial change in numbers in all the categories (fig. 4). The group ‘no symptoms’ was the most common. More than half of FD subjects remained FD for the 10 years and 9.7% reported ‘no symptoms’ in 2006. Of all the dyspepsia subgroups, only MR remained stable (18.2%), whereas the majority of the dyspepsia subgroups showed an increase in symptoms over the 10 years.

Almost one third had a stable IBS in both years but 24.8% developed FD (increased symptoms) in 2006 and 19.7% had moved into the ‘no symptoms’ group.

Of the heartburn group, 38.6% remained stable, whereas 11.1% had moved into the FD group and 11.8% into the

IBS group. The category ‘frequent abdominal pain’ was stable in 1 of 10 cases, whereas 31.0% had moved into the IBS category, 10.3% into NV, 6.9% into FD and 27.6% into the ‘no symptoms’ category.

The distribution of the 6 transition groups was 21.0% symptom stability, 14.1% symptom increase, 11.4% symptom decrease, 15.3% developed symptoms, 13.5% became asymptomatic and 24.5% had no symptoms in either 1996 or 2006.

Discussion

The main focus of our study was on the natural history of dyspepsia and its subgroups over a 10-year period. The only two other long-term studies to our knowledge are the natural history of functional GI disorder study, which was a 12-year longitudinal population-based study in Minnesota (USA) [6] and the long-term community study in Sweden for a maximum of 7 years [27]. There are strengths and weaknesses in all three studies, but taken together they give a reasonably accurate picture of the natural history of functional GI disorders.

The strength of our study is the use of a stable, homogeneous and well-informed population. The sample was randomly selected from the National Registry of Iceland and represented the nation as a whole in selected age groups. The population of Iceland was around 300,000

inhabitants at the time of the study and the sample was approximately 1% of the whole population from all around the country. It is of particular importance that the same methodology was used in the present study as in the Minnesota study, i.e. the BDQ [3, 4], thereby ensuring a reasonable degree of comparability. The BDQ assesses the whole range of GI functional disorders, though the present study reports predominantly on FD.

The FD and dyspepsia subgroup criteria are not consistent with the new Rome III criteria. The Rome III diagnostic criteria for FD must include one or more of the following: (1) bothersome postprandial fullness, (2) early satiation, (3) epigastric pain and (4) epigastric burning, with no evidence of structural disease that is likely to explain the symptoms. The focus in the Rome III criteria for FD is mostly on fullness and satiation, which is not the case in the two other criteria used in this study. Since no studies have been published as of yet, we are not able to compare our method and criteria for FD to the Rome III criteria.

In our study, the FD criteria revealed a lower prevalence (14.0% in 1996, 16.7% in 2006) than the dyspepsia subgroup criteria (24.1% in 1996, 24.3% in 2006). The prevalence of FD was rather low compared to other studies, which indicated a prevalence of 20–40% [1, 7, 15–18]. The prevalence of a dyspepsia subgroup was higher (24.1–24.3%) than FD, and was higher than Choung et al. [12] reported (15%). The difference in prevalence may be explained by the use of different criteria and ethnicity, and quantitative comparison is not valid except, possibly, with the study by Choung et al. [12], which also used the BDQ criteria.

In our study, younger subjects and females were more likely to report FD, a finding which was also reported in the Minnesota study [6]. In the dyspepsia subgroups, nausea or vomiting was reported significantly more often by women than by men.

Our study showed a higher FD prevalence in younger age groups, but for the dyspepsia subgroups, there was a variation between subgroups where MR showed a significant difference in age groups. It is of interest that there were fewer FD subjects in the dyspepsia subgroups than vice versa.

The prevalence of FD in our study was stable over time, but there was considerable turnover in symptoms. Transition analysis showed that around half of the FD subjects fulfilled the FD criteria at the 10-year follow-up and 22% had moved into the IBS group, but approximately 10% had no symptoms. One third of the IBS subjects still had IBS and approximately 25% had developed FD,

but 20% had no symptoms. Of the heartburn group, 38.6% remained stable, whereas approximately 11% had moved into the FD group and approximately 12% into the IBS group. These figures are in line with the results of the Swedish and the Minnesota studies [6, 28]. There was considerable transition in the dyspepsia subgroups except in the MR category, which was relatively stable.

In recent studies, questions about the best classification of dyspepsia subgroups have persisted, mainly because of the overlap of symptoms in defined subgroups or the lack of association with pathophysiology [12, 18, 29, 30].

In 2006, a relationship between FD and smoking could be seen, but not to alcohol consumption in either 1996 or 2006. Alcohol consumption has been associated with dyspepsia and frequent abdominal pain [31].

Our study showed a strong relationship between FD and heartburn as well as IBS. The association of FD and heartburn is not unexpected since dysmotility is common to FD and acid reflux. The fact that H₂ blockers and protein pump inhibitors did not relieve GI pain suggests that gastroesophageal reflux disease did not appreciably interfere with the FD diagnosis. FD subjects were more likely to have experienced GI pain as a child than others.

In our study the proportion of FD subjects seeking medical care was high. Every fifth subject that had visited a physician more than 6 times in the previous year had FD and more than a third of all subjects who consulted a physician because of gastric pain had FD. Researchers have reported higher consultation rates for dyspepsia in those with coexisting functional GI disorders [32, 33], and upper GI symptoms have been reported to be associated with a significant loss of work and activity days [34]. Those that used sick leave from work were more likely to have FD, which increased over the 10-year period, indicating a heavy burden on health care resources and society. But as has been shown in a study by Ford et al. [15], the reasons for consulting a physician can be multifactorial.

Various definitions of dyspepsia and FD have been used in previous studies [17, 35]. One of the most important factors affecting prevalence is demographics. The DIGEST study observed the 3-month prevalence rate of upper GI symptoms in the general population in 10 locations around the world and reported prevalence of dyspeptic symptoms from 9.4% in Japan to 41.8% in the USA, using the same criteria in all places [36]. However, variations in the definition of dyspepsia and FD will also affect the prevalence [37]. In our study, we used two criteria to identify dyspepsia symptoms, which resulted in different

prevalence rates. However, we used the same definitions consistently throughout the study and were able to compare two different approaches to the definitions of dyspepsia. A recent study has shown that neither clinical impression nor computer models that incorporate patient demographics, risk factors, history items and symptoms adequately distinguish between organic and functional disease in patients referred for endoscopic evaluation of dyspepsia [38].

There are some limitations of our study. The subjects were not specifically interviewed or examined to evaluate the possibility of organic disease, but there were some questions addressing this issue, e.g. peptic ulcer disease. Subjects reporting peptic ulcer disease (113) were excluded from dyspepsia analysis. Furthermore, a 10-year (post-al) follow-up went some way to making an organic cause of symptoms unlikely. Though the response rate was 66.8% in 1996 and 68.9% in 2006, a dropout bias cannot be excluded.

Conclusion

In summary, our study showed a higher prevalence of dyspepsia as diagnosed by dyspepsia subgroup than by conventional FD criteria. Younger subjects and females were more likely to have FD; in the subgroup categories, females more often reported symptoms in the MR, NV and COMB subgroups, whereas males predominantly reported upper abdominal pain. FD was stable over the 10-year period, but there was turnover in symptoms. There was a strong correlation between FD and IBS and heartburn. The main risk factors for dyspepsia were female gender, young age and smoking.

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Paper II

Stability of the irritable bowel syndrome and subgroups as measured by three diagnostic criteria - a 10-year follow-up study

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SUMMARY

Background

The irritable bowel syndrome (IBS) is a common disorder, but information on its natural history is limited.

Aim

To study the performance of four IBS criteria in detecting incidence and stability of categories over a 10-year period.

Method

This study was a population-based postal study. Questionnaire was mailed to the same age- and gender-stratified random sample of the Icelandic population aged 18–75 years in 1996 and again in 2006. IBS was estimated by the Manning criteria, Rome II, Rome III, subgroups and self-report.

Results

Prevalence of IBS varied according to criteria: Manning showed the highest (32%) and Rome II the lowest (5%). Younger subjects and females were more likely to have IBS. Prevalence was stable over 10 years for all criteria except Rome III. There was a turnover in all IBS subgroups and a strong correlation among IBS, functional dyspepsia and heartburn.

Conclusions

The prevalence of the IBS remained stable over a 10-year period with a turnover in symptoms. The study suggests that IBS is a cluster of symptoms that float in time between different IBS categories, functional dyspepsia and heartburn. The irritable bowel syndrome in Iceland is very common and indicates a chronic condition, which poses a heavy burden on the health care system.

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INTRODUCTION

Irritable bowel syndrome (IBS) is a functional bowel disorder in which abdominal pain or discomfort is associated with defecation or a change in bowel habits, and with features of disordered defecation.¹ Patients often experience additional symptoms such as bloating, sensation of incomplete evacuation, straining (constipation) and urgency (diarrhoea).² Previous studies report that IBS is one of the most common disorders observed in the general population^{3–5} with a major effect on quality of life and health care.^{4, 6, 7} IBS is one of the leading causes of gastroenterology and primary care consultations.^{8, 9}

IBS prevalence is estimated to range from 3% to 28%^{3–5, 10} depending on the country and the diagnostic criteria. The prevalence of IBS in the Western countries is estimated to be 10–15%.^{4, 11} Recent studies from around the world where the Rome II criteria were used have reported a lower frequency of IBS, 5% or even lower than 3%.^{12–14} The criteria available to identify IBS are the Manning criteria,¹⁵ Rome I,¹⁶ Rome II¹⁷ and Rome III.^{1, 18} The Rome criteria are more refined than the Manning criteria and include symptom duration.² No consistent differences in sensitivity or specificity between Manning, Rome I and Rome II have been reported¹⁹ and the stability over time has not been examined. A recent study has shown that more than bowel habits and abdominal pain drive IBS symptom severity.²⁰

Health examinees with physician-diagnosed IBS had reported rates of cholecystectomy three times the rate of examinees without IBS, twice the rate of appendectomies and hysterectomies, and back surgery 50% more often. IBS is independently associated with these surgical procedures²¹ in physician-diagnosed IBS.

Although altered rectal perception has been proposed as a marker of IBS,^{22, 23} no clinically useful or reliable biomarkers have been identified. The diagnosis therefore relies upon diagnostic criteria and normal findings on routine clinical investigations.²⁴ (The subtypes of IBS are of crucial importance for defining drug targets since the 5-HT drugs act predominantly on diarrhoea²⁵ or constipation.²⁶

Population-based studies are essential for studying IBS as only a minority of IBS patients seek medical care; self-medication is common,²⁷ and differences have been noted in IBS patients and non-IBS patients from the community.^{28, 29} A great majority of IBS studies are patient-based.

The IBS diagnostic criteria have not been tested over time and population-based follow-up epidemiological studies on IBS are rare. A recent 12-year longitudinal study suggests that many episodes of symptom disap-

pearance were due to changed symptom in subjects rather than total symptom resolution.³⁰ A patient-based study by Garrigues *et al.* shows that changes in IBS subtypes over time are common, but changes between constipation and diarrhoea are rare,³¹ at least over a 1-year period. Symptom report is one of several issues that are unresolved regarding prognosis and classification of IBS. Another large population-based study on the natural history of symptoms and factors that influence consultation behaviour of IBS has shown that the prevalence of IBS increased over the 10 years of the study, with an annual incidence of 1.5%.³²

The objective of our study was to compare the prevalence and stability of IBS according to the Manning criteria, Rome II, Rome III subtypes and self-reported IBS over a 10-year period.

A parallel study based on the same database, focusing on Functional Dyspepsia, has been published.³³

METHODS

Participants and setting

In 1996, an epidemiological study of gastrointestinal diseases was performed in Iceland.³⁴ Involved were 2000 inhabitants in the age range of 18–75 years. The individuals were randomly selected from the National Registry. Equal distribution of gender and age was secured in each age group. In 2006, we attempted to contact all the individuals from 1996 as well as adding 300 new individuals in the age group of 18–27 years who were randomly selected from the National Registry of Iceland. A questionnaire was mailed to individuals at baseline and the study questionnaire and an explanatory letter mailed to all eligible individuals. Reminder letters were mailed at 2, 4 and 7 weeks, using the Total Method of Dillman.³⁵ Individuals who indicated at any point that they did not want to participate in the study were not contacted further.

The questionnaire

The Bowel Disease Questionnaire (BDQ)^{36, 37} was translated from English into Icelandic and modified for this study. The questionnaire was designed as a self-report instrument to measure symptoms experienced over the previous year and to collect the participant's past medical history.³⁰

The Icelandic version of the BDQ questionnaire addressed 47 gastrointestinal symptoms and 32 items that measure past illness, health care use, and socio-demographic and psychosomatic symptoms, together

with a valid measure of non-GI somatic complaints, the Somatic Symptom Checklist (SSC).³⁸ The SSC consists of 12 non-GI and five GI symptoms or illnesses. Individuals are instructed to indicate, on a 5-point scale, how often each symptom appears and how bothersome it is. There were only a few changes in the latter questionnaire (2006) which addressed 51 gastrointestinal symptoms and 33 items that measure past illness, health care use, and sociodemographic and psychosomatic symptoms. The 2006 Questionnaire furthermore addressed 17 items to identify heartburn and symptoms related to heartburn.

Criteria to identify IBS

The criteria for identification of IBS are presented in Table 1.

Diagnosis of IBS according to the Manning criteria¹⁵ required two or more of the six symptoms listed in Table 1 and abdominal pain six or more times during the previous year.^{39, 40}

Rome II: the 2006 questionnaire included Rome II criteria¹⁷ to identify IBS. The 1996 questionnaire made it possible with minor modification to create surrogate Rome II criteria.

Rome III: a close approximation of the Rome III criteria was used. The data were re-evaluated retrospectively to conform to Rome III criteria.

Self-report IBS: subjects were asked whether or not they had IBS. Two commonly used Icelandic translations were given (ristilkrampar and idraolga). No further explanation of the disease was provided.

Transition between disorders from the initial to the final survey

A transition model used by Halder *et al.* was modified and applied to this study³⁰ (Figure 4). The responses from the initial (1996) and final (2006) surveys were matched for each subject to examine the changes between disorders at an individual level for the six categories (IBS Rome, IBS Manning, IBS self-report, FD, frequent abdominal pain and no symptoms). A 6 × 6 table was used to model these multiple changes and collapsed into six groups, as illustrated in Figure 3. Those with the most symptoms were prioritized higher. Those who developed more symptoms and those who reported fewer symptoms could be categorized into groups. There were six patterns of symptoms, identified as follows: (i) symptom stability, (ii) symptom increase, (iii) symptom decrease, (iv) symptom onset, (v) becoming asymptomatic and (vi) none of these symptoms.

Table 1 | Criteria to identify IBS

Manning
Pain eased after BM
Looser stools at onset of pain
More frequent BM at onset of pain
Abdominal distension
Mucus per rectum
Feeling of incomplete emptying
Rome II criteria
At least 12 weeks (which need not be consecutive) in the preceding 12 months, of abdominal discomfort or pain that has two of three features:
Relieved with defecation; and/or
Onset associated with a change in frequency of stool, and/or
Onset associated with a change in form (appearance) of stool
Rome III criteria
Recurrent abdominal pain or discomfort at least 3 days/month in the last 3 months, association with two or more of the following:
Improvement with defecation
Onset associated with a change in frequency of stool
Onset associated with a change in form (appearance) of stool
Subgroups of Rome III
Subjects fulfilling the Rome III criteria were divided into four subgroups according to their bowel habits:
Diarrhoea-predominant (IBS-D), IBS-D is determined by predominantly loose or watery stools ≥25% of the time
Constipation-predominant (IBS-C), IBS-C is determined by predominantly hard or lumpy stools ≥25% of the time
Diarrhoea and constipation (IBS-M), categories for mixed [mixed irritable bowel syndrome (IBS-M): meeting criteria for IBS-D and IBS-C ≥25% of time]
No diarrhoea or constipation, un-subtyped [un-subtyped irritable bowel syndrome (IBS-U): not meeting criteria for IBS-C nor IBS-D, i.e. both are <25% of the time]
BMs, bowel movements.

Mortality data

For the 2006 survey, we identified all deceased individuals with the assistance of the National Registry of Iceland (Thjodskra).

Statistical analysis

Tables were constructed for frequency and percentage. Categorical data were analysed using the Chi-squared test. Type I error protection rate was set at 0.05. The exact p is listed in the Tables and text. All the research data were imported into SPSS (Statistical Package of Social Science; SPSS Inc., Chicago, Illinois, USA) software.

Ethics

The National Bioethics Committee of Iceland and The Icelandic Data Protection Authority (Personuvernd) gave their permission for the research.

RESULTS

Demographic data of involved individuals

In 1996, the response rate was 66.8% (1336/2000). Of the 1336 individuals who participated in 1996, 81 were deceased by 2006, five subjects were unable to answer, mainly because of old age, and 70 could not be traced to a current address. This left 1180 individuals, out of which 799 responded in 2006. Therefore, the response rate in 2006 was 67.7% (799/1180). The mean age of the individuals in 1996 was 42 years, in 2006 it was 43 years, and 41 years for nonrespondents in 2006. Women were more likely to respond than men in both years. A larger proportion of women responded again in 2006 (57.8%) than those who had responded in 1996, but not in 2006 (49.8%) ($P < 0.01$). The responders represented the population in all major factors concerning gender- and age-distribution. The response rate was a little higher for women, which is common in similar studies, and the response rate was also higher for older subjects than younger ones. Age distribution and demographic details of the study cohort are presented in Tables 2–5.

Irritable bowel syndrome. The prevalence of IBS according to the Manning criteria showed similar results in 1996/2006 or 31%/32% respectively (Figure 1). According to the Rome II criteria, the prevalence of IBS in 2006 was significantly lower than for the Manning criteria or 5.0%. The Rome II criteria were not part of the questionnaire in 1996. The Rome III criteria showed a prevalence of IBS in 1996/2006 as 10%/13% respectively. Self-reported IBS showed the same prevalence in 1996/2006 or 16%/16%. The yield from the different criteria can be seen in Figure 1. Women were significantly more likely to report IBS than men when diagnosed with Manning, self-report IBS, Rome II and Rome III. There was no significant relationship between gender and Rome III for

Table 2 | Study population. Age- and gender-distribution

	Population 2006 (%)	Respondents 2006 (%)
Gender		
Men	50.3	42.2
Women	49.7	57.8
Age		
28–35	19.5	14.52
36–45	24.9	20.40
46–55	22.8	22.15
56–65	15.6	19.52
66–75	10.4	15.14
76–85	6.8	8.26
Total number	173 859	799

IBS in 1996, but there was a significant increase in prevalence of IBS (Rome III) for women between 1996 and 2006 (10% and 17% respectively). This increase can only be seen in younger groups of women (age 26–55 years). The mean age was significantly lower for Manning, self-report, Rome II and Rome III criteria for IBS (2006), but this was not a significant factor in Rome III in 1996 (Tables 3–5). Comparison of age group prevalence in each IBS category showed that the Manning and self-report criteria did not change significantly over the 10-year period. As can be seen in Figure 2, the prevalence of each birth cohort stayed pretty much the same during the 10 years (the 26–35 age group in the 2006 Manning group had a prevalence of 46.5% in 2006 and 41.8% in 1996, the 36–45 age group had a prevalence of 31.4% in 2006 and 28.9% in 1996). The prevalence therefore within age groups therefore remained fairly constant in most cases (Figure 2). In the IBS Rome III group, there were some changes in the age group 46–75 (Figure 2).

Data in Figure 3 suggest a birth cohort effect on the prevalence of IBS, particularly with regard to the Manning criteria for subjects born 1971–1978, but the difference did not reach a statistical significance.

Education and employment status

There was a significant relationship between level of education and the Rome II IBS criteria (Table 4); other criteria showed no relationship. Employment status was associated with IBS in 1996 using both Manning and Rome III IBS criteria (Tables 3 and 4).

Table 3 | Sociodemographic factors and comorbidity in subjects fulfilling the Manning criteria in 1996 and 2006

	1996			2006		
	IBS-neg.	IBS-pos.	P	IBS-neg.	IBS-pos.	P
Gender (% female)	52.9	66.8	<0.001	52.1	69.2	<0.001
Mean age (years)	43.9	39.8	<0.001	53.7	49.1	<0.001
Employment status (% employed)	85.5	77.5	0.008	76.2	76.2	0.980
Sick leave from work						
≥6 times a year	4.1	13.8	<0.001	4.6	12.8	<0.001
1-5 times a year	51.7	57.3	50.5		56.6	
Never	44.2	28.9		44.9	30.6	
Smoking						
Smokers >15 cigarettes per day	19.8	26.4	0.091	7.5	11.1	0.017
Smokers ≤15 cigarettes per day	32.5	36.4	15.4		22.6	
No smokers	48.6	37.2		77.2	66.3	
Gastrointestinal pain as a child	14.1	27.4	<0.001	16.8	30.2	<0.001
Appendectomy	19.4	31.9	<0.001	22.9	29.1	0.077
Cholecystectomy	2.5	7.8	<0.001	4.7	8.6	0.043
Gastroduodenal ulcer	7.6	13.9	0.008	8.8	14.9	0.016
Abdominal operation	18.3	28.3	0.002	22.4	28.3	0.095
Seeking physician in last 12 months						
Never	23.7	12.6	<0.001	22.9	10.8	<0.001
1-5 times	69.0	64.5	67.5		68.5	
>6 times	7.3	22.9		9.6	20.7	
Seeking physician because of gastro-pain	4.3	34.6	<0.001	4.5	26.0	<0.001
Heartburn	34.1	60.5	<0.001	35.4	60.8	<0.001
Functional dyspepsia	4.9	34.5	<0.001	6.9	41.1	<0.001

Smoking and alcohol

Smoking was associated with IBS for only one set of criteria (Table 3). There was no significant association with IBS and alcohol consumption for any of the criteria.

Gastrointestinal pain and operations

For all criteria, the frequency of pain was greater for subjects with IBS than for others. The intensity of gastrointestinal pain was significantly greater than for others in the Rome II and III subjects in 2006. In the Manning IBS and Rome III criteria (2006) subjects, there was a significant relationship between gastrointestinal pain as a child and IBS (Tables 3–5).

For the Manning criteria subjects, there was a significant relationship with having had an appendectomy and IBS subjects in 1996, but not in 2006. There was a signif-

icant relationship between cholecystectomy and the Manning and Rome III (2006) criteria in IBS subjects. There was also a significant relationship between abdominal surgery and the Manning criteria for IBS in 1996 and Rome II. There was a relationship with gastroduodenal ulcer and subjects diagnosed with IBS for the Manning criteria and Rome III. Subjects with Rome III IBS indicated no relationship between operations such as appendectomy and other abdominal surgery (Tables 3 and 4).

Medical care

Subjects with IBS according to Manning and Rome II/III criteria sought physicians more often than others. Subjects who sought a physician because of gastro-pain significantly more often had IBS as diagnosed by Manning and Rome III criteria than others (Tables 3–5).

Stability of the irritable bowel syndrome

Table 4 | Sociodemographic factors and comorbidity in subjects fulfilling the Rome criteria in 1996 and 2006

	Rome III 1996			Rome II 2006			Rome III 2006		
	IBS-neg.	IBS-pos.	P	IBS-neg.	IBS-pos.	P	IBS-neg.	IBS-pos.	P
Gender (% female)	57.0	60.5	0.559	56.4	78.1	0.015	55.2	73.5	<0.001
Mean age (years)	43.4	40.8	0.142	53.6	47.7	0.028	53.4	48.0	<0.001
Level of education									
>4 years' further education	16.8	12.0	0.731	26.6	45.2	0.042	29.4	33.0	0.529
3-4 years' further education	41.8	44.0	38.3	25.8		37.6		29.9	
<3 years' further education	18.7	21.3	12.5	19.4		12.6		13.4	
No further education	22.8	22.7	22.5	9.7	20.4			23.7	
Employment status (% employed)	83.7	71.1	0.006	73.6	81.3	0.335	74.9	75.3	0.937
Sick leave from work									
≥6 times a year	5.9	14.3	0.019	6.1	23.2	<0.001	6.1	16.3	<0.001
1-5 times a year	53.5	54.3	52.0		56.7	51.2		57.0	
Never	40.6	31.4	41.9		20.0	42.6		26.7	
Gastrointestinal pain as a child	17.7	24.3	0.161	20.9	29.0	0.278	19.4	36.5	<0.001
Cholecystectomy	3.3	12.2	NV	6.1	21.9	NV	5.2	14.3	<0.001
Gastroduodenal ulcer	8.8	18.7	0.006	10.2	16.7	NV	10.3	17.7	0.034
Abdominal operation	21.7	28.4	0.193	24.2	43.8	0.013	23.6	31.9	0.081
Seeking physician in last 12 months									
Never	21.7	5.3	<0.001	19.0	9.4	0.025	20.1	8.2	0.002
1-5 times	67.6	69.7	68.7		62.5	68.2		70.1	
>6 times	10.7	25.0		12.4	28.1		11.7	21.6	
Seeking physician because of gastro-pain	10.9	46.1	<0.001	6.9	46.9	NV	7.9	38.1	<0.001
Heartburn	40.6	59.2	0.003	39.1	71.9	<0.001	41.0	61.9	<0.001
Functional dyspepsia	10.6	43.4	<0.001	11.1	65.6	NV	11.5	57.1	<0.001

Table 5 | Development of IBS, retained, lost and developed in 10 years

	n	Never IBS (%)	Lost IBS (%)	Retained IBS (%)	Developed IBS (%)
Manning	674	56.2	12.2	19.1	12.5
Self-report	621	74.9	8.5	8.2	8.4
Rome III	749	81.4	5.7	4.3	8.7

Heartburn and functional dyspepsia

There was a significant relationship between subjects with heartburn and IBS subjects according to all the criteria. There was also a significant relationship between subjects reporting functional dyspepsia and Manning and Rome III criteria for IBS (Tables 3 and 4).

Development of IBS in 10 years

The development of IBS symptoms over the 10-year period showed a similar proportion of IBS subjects who developed and lost IBS in the Manning and self-report groups, whereas many more subjects developed IBS in the Rome III group than became free of the symptoms (Table 5). A much higher proportion of IBS subjects retained IBS (18.7%) in the Manning group than in the self-report (8.2%) and the Rome III (4.4%) groups.

Transitions among symptom subgroups between the initial and final surveys

As described in the methods section, the groups in this analysis were defined as mutually exclusive using the symptom hierarchy so that each subject appears in only one category for both the 1996 and 2006 surveys. There was a 'no symptoms' category for those who did not

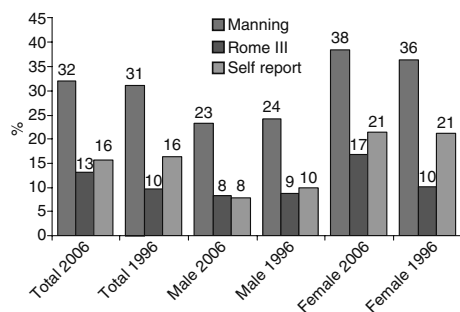


Figure 1 | Prevalence of IBS for three IBS criteria and gender.

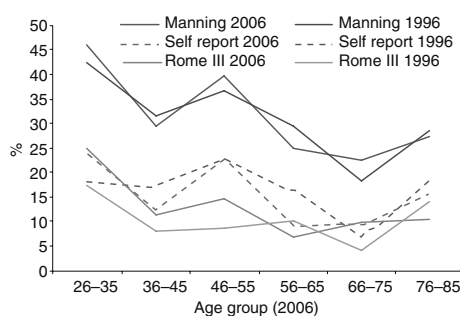


Figure 2 | Birth cohort of IBS for three IBS criteria by age.

meet any of the criteria applied for FGIDs. Due to the hierarchical classification, only a few subjects occurred in some categories.

There was a substantial change in numbers in all the categories. The group 'no symptoms' was the most common. Of the Rome III group, 39% were stable. Most of the subjects were in the Manning group and 37% were

stable over the 10-year period; 26% reported 'no symptoms' in 2006 and 17% showed an increase in symptoms over the 10 years. Of the self-report subjects, 12% were stable, 42% reported 'no symptoms' and 34% had increased symptoms in 2006 (Figure 4).

One of five subjects had a stable FD in both years, but 50.0% developed FD (increased symptoms) in 2006 and 7% had moved into the 'no symptoms' group.

The category 'frequent abdominal pain' was stable in 18% cases, whereas 34% moved into the 'increased symptoms' category and 48% into the 'no symptoms' category.

The distribution of the six transition groups was 12% symptom stability, 11% symptom increase, 10% symptom decrease, 14% developed symptoms, 14% became asymptomatic and 40% had no symptom in either 1996 or 2006.

Subjects who were diagnosed with IBS in 1996 moved into other IBS groups, FD, FAP and no symptom groups (Figure 5). Only 39% of subjects diagnosed with IBS by the Rome III criteria remained in the same IBS group, 23% moved into the Manning criteria group and 18% into the no symptom group. Only 37% of the Manning group (1996) remained in the same group, 26% were in the no symptom group and 17% in the Rome III. Of the self-report group from 1996, 42% moved into the no symptom group, 21% into the Manning group and 15% into the Rome III group. Only 12% remained in the same self-report group.

Subgroups of Rome III

Subjects fulfilling the Rome III criteria were divided into four subgroups: (i) diarrhoea-predominant (IBS-D), which is determined by predominantly loose or watery stools $\geq 25\%$ of the time, (ii) constipation-predominant (IBS-C) determined by predominantly hard or lumpy stools $\geq 25\%$ of the time, (iii) diarrhoea and constipation (IBS-M), meeting criteria for IBS-D and IBS-C $\geq 25\%$ of time and (iv) no diarrhoea or constipation, un-subtyped (IBS-U): not meeting criteria for of IBS-C nor IBS-D,

	Self report		Rome III		Manning	
	1996	2006	1996	2006	1996	2006
Born 1971–78	17.7	24.1	17.0	25.7	41.8	46.5
Born 1961–70	16.3	12.1	7.4	11.5	31.4	28.9
Born 1951–60	22.7	22.9	8.6	14.4	37.2	38.6
Born 1941–50	15.1	8.6	10.5	7.2	28.6	24.0
Born 1931–40	5.5	9.4	4.1	9.9	16.5	21.8
Born 1921–30	18.4	15.4	14.1	10.5	28.6	26.0

Figure 3 | Birth cohort effect on the prevalence (%) of IBS according to three criteria.

Stability of the irritable bowel syndrome

	Rome III	Manning	Self report	FD	Frequent abd. pain	No symptoms
Rome III (n = 71)	39%	23%	10%	4%	6%	18%
Manning (n = 165)	17%	37%	6%	8%	6%	26%
Self report (n = 33)	15%	21%	12%	3%	6%	42%
FD (n = 28)	14%	36%	0%	21%	21%	7%
Frequent abdominal pain (n = 77)	8%	21%	1%	4%	18%	48%
No symptoms (n = 425)	3%	9%	2%	2%	9%	75%

Remaining asymptomatic	Developed symptoms
Became asymptomatic	Decreased symptoms
Stable	Increased symptoms

Figure 4 | Transitions among symptom subgroups between the initial and final surveys.

FGID, Functional Gastrointestinal Disorder; FD, Functional Dyspepsia
D, Diarrhea; C, Constipation; N, Normal

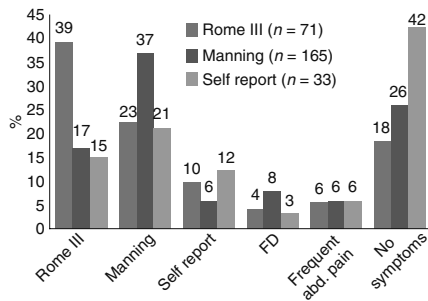


Figure 5 | Distribution of subjects in 2006 who were diagnosed with Rome III, Manning and Self-report in 1996.

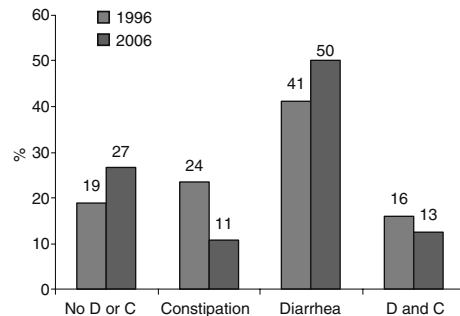


Figure 6 | Subgroups of Rome III.

that is, both <25% of the time. The IBS-D was the most prevalent group in both 1996 and 2006. There was a significant increase in prevalence of IBS-D in the year 2006. There was a significant decrease in the IBS-C group and an increase in the IBS-U group (Figure 6).

DISCUSSION

The main focus of our prospective study was on the comparison of three criteria in the diagnosis of IBS and its subgroups and on the potential usefulness of the criteria in clinical praxis, research and drug development. This comparison included age- and gender-related prevalence and retention and loss of diagnosis over the 10-year period. Furthermore, associations with sociodemographic variables and medical conditions like appendectomy and cholecystectomy were assessed.

The sensitivity of the criteria for diagnosing IBS varies widely in our study. The average prevalence in 2006, according to the Manning criteria, self-report and Rome III was 32%, 16% and 13% respectively. The age- and gender-related prevalence is concurrent for all criteria, with a higher prevalence in women and young age groups. Prevalence decreased with age up to 75 years, but increased in the age group 76–85. An interesting finding was a cohort (1971–1978) related increase in prevalence manifested according to the Manning criteria, but this increase was not significant. There was no change in prevalence over time for the Manning criteria or self-report (33/32 and 17/16 respectively for 1996/2006), but the prevalence for the Rome III criteria showed an increase from 10 to 13 over the 10-year period, which was confined to young women. The subgroup

analysis revealed that the increase was due to women with IBS-D in age group 26–55. The Minnesota study also reported an increase in IBS-D with time.³⁰

The prevalence profile in our study suggests that the Manning and self-report criteria have high sensitivity and low specificity, whereas Rome III criteria have low sensitivity and high specificity in detecting IBS. This interpretation is complicated, however, by the fact that there was a flux of subjects in and out of all IBS categories as well as into functional dyspepsia and heartburn.

Stability was greatest in the Manning group 38.2%, and 27.3% in the Rome III subgroups, but 11.8% were stable in the self-report group. Over the 10-year period, a similar proportion of IBS subjects developed and lost IBS according to the Manning criteria and self-report groups, whereas many more subjects developed IBS in the Rome III group than lost the symptoms.

Previous studies have reported various associations between sociodemographic factors and IBS. Our study showed a significant relationship between level of education and Rome II IBS. Employment status was not associated with IBS, except for Rome III in 1996. It is of interest that Body Mass Index (BMI) and alcohol consumption were not associated with IBS for any criteria. Smoking was not associated with IBS with the exception of Manning criteria 2006.

Several reports and an extensive review²¹ have established an association between IBS and appendectomies, cholecystectomies and abdominal surgery. The present study has established this relationship for Manning and Rome II criteria. The Rome III criteria did not detect this association except for cholecystectomy in 2006.

Our study gives a profile of the IBS criteria and their potential usefulness in clinical practice, research and drug development. It is, however, difficult to assess the relative merits of the various criteria in view of the fact that there is no gold standard for the diagnosis and not even a solid biological marker. The Manning and Rome II criteria detect the symptom cluster of IBS and associated factors, but are not stable enough to be useful in the assessment of prognosis. Their main merit is to open the possibility of a positive diagnosis of IBS. The unsophisticated self-report gives an intermediate prevalence to the Manning and Rome II and detects the associated factors equally well, but is even more unstable. The self-report has no clinical value, but it can give a zero level for the assessment of other criteria. The sophisticated Rome III criteria and its subtypes are based solely on stool consistency as measured using the Bristol Stool Scale (BSS)⁴¹ Stool consistency is

regarded as the best surrogate for transit time, which is a potential biological marker of IBS.^{42, 43} Rome III criteria gave by far the lowest prevalence, but the subtypes did not show great stability and therefore raise a question as to potential usefulness in the development of 5-NT-like drugs, which have a specificity for either constipation or diarrhoea, at least not for long-term use. Three patient-based studies have shown a short-term instability of Rome III subtypes.^{24, 44, 45}

The results of our study highlight the problem of defining the IBS disease or condition. No single set of criteria seems to hold the answer. The main contribution of our study is perhaps to emphasize the notion that there is no single IBS disease, but only a cluster of symptoms that float in time between different IBS categories, functional dyspepsia and heartburn. These conditions presumably have a common pathophysiology.

The strength of our study is the use of a stable and homogeneous population. The sample was randomly selected from the National Registry of Iceland and represented the nation as a whole in selected age groups. Only a minority of IBS patients seek medical care and population-based studies are therefore essential for studying IBS. The population of Iceland was around 300 thousand inhabitants at the time of the study and the sample was ≈1% of the whole population from all around the country. Extensive use of health care by IBS subjects is well established^{46–48} and the present study confirms this with all criteria. Clinical overlap and transition of IBS to heartburn and functional dyspepsia is common^{49, 50} and our study shows this for all criteria.

There are some limitations to our study. The subjects were not specifically interviewed or examined to evaluate the possibility of organic disease. However, a 10-year (postal) follow-up went some way to making an organic cause of symptoms unlikely. Furthermore, as the response rate was 66.8% in 1996 and 68.9% in 2006, a dropout bias cannot be excluded. A similar mean age in the respondent group and the nonrespondent group does not indicate an age dropout bias in the study, but a significantly larger proportion of women responded again in 2006, which may indicate a gender bias.

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Paper III



Natural history of heartburn: A 10-year population-based study

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week was diagnosed in 20.8%. There was a significant relationship between heartburn, dyspepsia and irritable bowel syndrome. Individuals with a body mass index (BMI) below or higher than normal weight were more likely to have heartburn. Heartburn caused by food or beverages was reported very often by 20.0% of subjects.

CONCLUSION: Heartburn is a common and chronic condition. Subjects with a BMI below or higher than normal weight are more likely to experience heartburn. Heartburn has a great impact on daily activities, sleep and quality of life.

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Key words: Heartburn; Follow-up; Questionnaire study; Epidemiology

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Abstract

AIM: To study the natural history and prevalence of heartburn at a 10-year interval, and to study the effect of heartburn on various symptoms and activities.

METHODS: A population-based postal study was carried out. Questionnaires were mailed to the same age- and gender-stratified random sample of the Icelandic population (aged 18-75 years) in 1996 and again in 2006. Subjects were classified with heartburn if they reported heartburn in the preceding year and/or week, based on the definition of heartburn.

RESULTS: Heartburn in the preceding year was reported in 42.8% (1996) and 44.2% (2006) of subjects, with a strong relationship between those who experienced heartburn in both years. Heartburn in the preceding

INTRODUCTION

Gastroesophageal reflux disease (GERD) is one of the most prevalent diseases worldwide^[1]. GERD is a chronic condition which usually manifests symptomatically, is a great burden for patients, and has significant socioeconomic implications^[2]. The prevalence of predominant gastroesophageal reflux symptoms appears to be stable over time^[3]. Heartburn is the typical GERD symptom and may be induced by various physiological and pathophysiological mechanisms^[4]. Heartburn, coupled with acid regurgitation and odynophagia, are considered to be highly specific for GERD^[1].

Functional heartburn is defined as episodic retrosternal burning in the absence of GERD, histopathology-based motility disorders or structural explanations^[5]. Heartburn alone has a prevalence of 17%–42% in Western populations^[2,3,5–7].

The prevalence of upper gastrointestinal symptoms in the general population is high and symptoms are associated with significant health-care utilization and diminished quality of life^[6]. In contrast, the natural history of heartburn has received limited attention and few epidemiological studies have focused on heartburn. Subjects with upper gastrointestinal symptoms are more likely to use prescription medication and are more likely to have seen a physician about symptoms than those with heartburn^[6]. There has been more focus on GERD than heartburn.

The aim of this present study was therefore to evaluate the natural history of heartburn in the Icelandic population prospectively over a 10-year period, as well as to evaluate different factors which are affected by heartburn both physically and sociodemographically. A parallel publication based on the same database, focusing on functional dyspepsia (FD), has been published^[8] as has another parallel publication regarding irritable bowel syndrome (IBS)^[9].

MATERIALS AND METHODS

Participants and setting

In 1996 an epidemiological study of gastrointestinal diseases was carried out in Iceland^[10], involving 2000 inhabitants in the range of 18–75 years of age. The individuals were randomly selected from the National Registry of Iceland. Equal distribution of sex and age was secured in each age group. In 2006 we attempted to contact all the same individuals as in 1996 as well as adding 300 new individuals in the 18–27 age group who were also randomly selected from the National Registry. A study questionnaire and explanatory letter were mailed to all eligible individuals at baseline. Reminder letters were mailed at 2, 4 and 7 wk, using the Total Method of Dillman^[11]. Individuals who indicated at any point that they did not want to participate in the study were not contacted further.

The questionnaire

The Bowel Disease Questionnaire (BDQ)^[12,13] was translated and modified for this study. The questionnaire was designed as a self-report instrument to measure symptoms experienced over the previous year and to collect the subject's past medical history^[14].

The Icelandic version of the BDQ questionnaire addresses 47 gastrointestinal symptoms and 32 items that measure past illness, health care use, items on sociodemographic and psychosomatic symptoms, together with a valid measure of non-gastrointestinal (non-GI) somatic complaints ascertained through the Somatic Symptom Checklist (SSC)^[15]. The SSC includes questions on 12 non-GI and 5 GI symptoms or illnesses. Individuals are instructed to indicate, on a 5-point scale, how often each symptom has appeared and how bothersome it has been. There were few changes to the later questionnaire (2006)

which addressed 51 gastrointestinal symptoms and 33 items that measure past illness, health care use, and sociodemographic and psychosomatic symptoms items. The 2006 Questionnaire furthermore addressed 17 items to identify heartburn and items related to heartburn.

Criteria for identifying heartburn

Subjects were classified with heartburn if they reported heartburn according to the following definition: Heartburn is a burning sensation in the retrosternal area (behind the breastbone). The pain often rises in the upper abdomen and may radiate to the chest.

Transition between disorders from initial and final surveys

A transition model used by Halder *et al.*^[14] was modified and applied for this study. The responses from the initial (1996) and final (2006) surveys were matched for each subject to examine the changes between disorders at an individual level for the 5 categories (FD, IBS, heartburn, frequent abdominal pain and no symptoms). A 5 × 5 table was used to model these multiple changes and collapsed into 6 groups, as illustrated in Table 1. Those with the most symptoms were prioritized higher. Those who developed more symptoms and those who reported fewer symptoms could be categorized into their respective groups. There were six patterns of symptoms, identified as follows: (1) symptom stability; (2) symptom increase; (3) symptom decrease; (4) symptom onset; (5) became asymptomatic; and (6) none of these symptoms.

Mortality data

For the 2006 survey we identified all deceased individuals with the assistance of the National Registry of Iceland (*Thjodskera*).

Statistical analysis

Tables were constructed to show frequency and percentage. Categorical data were analyzed using the χ^2 test. The type I error protection rate was set at 0.05. The exact *P* is listed in the tables and text. All the research data were imported into SPSS (Statistical Package of Social Science) software.

Ethics

The National Bioethics Committee of Iceland and The Icelandic Data Protection Authority (*Personuvernd*) gave their permission for the research.

RESULTS

Demographic data of involved individuals

In 1996 the response rate was 66.8% (1336/2000). Of the 1336 individuals who participated in 1996, 81 were deceased by 2006, five subjects were unable to answer, mainly because of old age, and 70 could not be traced to a current address. This left 1180 individuals, out of whom 799 responded. Therefore, the response rate in 2006 was 67.7% (799/1180). The mean age of the individuals in

Table 1 Transition among symptom subgroups between the initial and final surveys

FGID in 1996	Proportion of FGID in 2006 based on primary survey disorder (%)				
	FD	IBS	Heartburn	Frequent abdominal pain	No symptoms
FD (<i>n</i> = 111)	52.3 ¹	21.6 ³	14.4 ¹	1.8 ³	9.9 ⁴
IBS (<i>n</i> = 152)	25.0 ²	30.3 ³	19.7 ³	4.6 ³	20.4 ⁴
Heartburn (<i>n</i> = 173)	12.1 ²	12.1 ²	39.3 ³	4.6 ³	31.8 ⁴
Frequent abdominal pain (<i>n</i> = 39)	12.8 ²	23.1 ²	17.9 ²	15.4 ⁴	30.8 ⁴
No symptoms (<i>n</i> = 324)	3.4 ⁵	9.9 ⁵	17.3 ⁵	6.2 ⁵	63.3 ⁶

¹Stable; ²Increased symptoms; ³Decreased symptoms; ⁴Became asymptomatic; ⁵Developed symptoms; ⁶Remaining asymptomatic. FGID: Functional gastrointestinal disorder; FD: Functional dyspepsia; IBS: Irritable bowel syndrome.

Table 2 Study population: age and sex distribution

	Population 2006 (%)	Respondents 2006 (%)
Gender		
Male	50.3	42.2
Female	49.7	57.8
Age (yr)		
28-35	19.5	14.52
36-45	24.9	20.40
46-55	22.8	22.15
56-65	15.6	19.52
66-75	10.4	15.14
76-85	6.8	8.26
Total number	173859	799

1996 was 42 years, in 2006 it was 43 years, and 41 years for non-respondents in 2006. Women were more likely to respond than men in both years. A larger proportion of women than men responded again in 2006 (57.8%) than had responded in 1996, as is common in similar studies. The responders represented the population in all major factors concerning sex and age distribution. The response rate was also higher for older subjects than for younger ones. The age distribution and demographic details of the study cohort are presented in Tables 2 and 3.

Heartburn 10-year follow-up

At the 10-year follow-up, individuals were asked if they had experienced heartburn in the preceding year; 42.8% in 1996 and 44.2% in 2006 reported heartburn. There was a strong relationship between those who experienced heartburn in 2006 and those who reported heartburn in 1996. Two thirds of those who reported heartburn in 1996 also experienced heartburn in 2006. However, one third of those who reported heartburn in 2006 had not experienced it 10 years earlier.

Almost all who were on medication for heartburn reported relief with the medication. Individuals reported acid reflux once a month or more in 11% of cases in 1996 and 10% of cases in 2006.

There was a significant relationship between heartburn and dyspepsia and between heartburn and IBS, both in 1996 and in 2006.

Individuals of normal weight [body mass index (BMI) 18.5-24.9] were less likely to experience heartburn than individuals with a BMI below or higher than normal weight.

Individuals who smoked were not more likely to have heartburn than those who did not smoke. Individual alcohol consumption within the study group changed during the 10-year period of 1996 to 2006. Alcohol consumption was not associated with heartburn.

Transitions among symptom subgroups between the initial and final surveys

As described in the Methods section, the groups in this analysis were defined as mutually exclusive using a symptom hierarchy so that each subject appears in only one category for both the 1996 and 2006 surveys. There was a “no symptoms” category for those who did not meet any of the criteria applied for functional gastrointestinal disorders. Due to the hierarchical classification only a few participants occurred in some categories.

There was a substantial change in numbers in all the categories over time (Table 1). The group “no symptoms” was the most common (63.3%). Of the heartburn group 39.3% were stable and 31.8% reported “no symptoms”; 24.2% reported increased symptoms and 4.6% decreased symptoms. Of the FD group 52.3% remained stable and 9.9% reported “no symptoms” in 2006. Most of the subjects who were in the IBS group, or 30.3% of the total, were stable over the 10-year period; 20.4% reported “no symptoms” in 2006 and 25.0% showed an increase in symptoms over the 10 years. In 2006, 15.4% of the subjects reported stable frequent abdominal pain, 30.8% reported “no symptoms” and 53.8% reported increased symptoms.

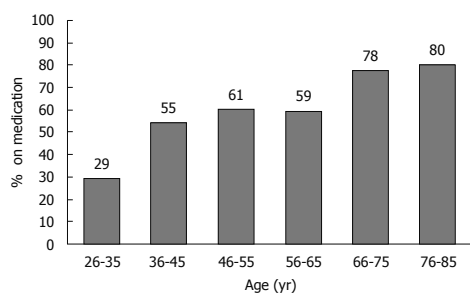
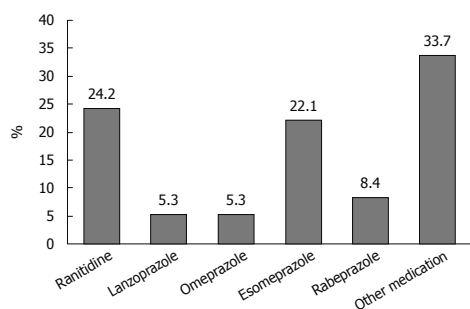
The distribution of the 6 transition groups was: 22.3% symptom stability, 12.6% symptom increase, 10.9% symptom decrease, 14.9% developed symptoms, 13.6% became asymptomatic, and 25.7% had no symptoms in either 1996 or 2006.

Heartburn in subjects in 2006

In the 2006 questionnaire individuals were asked additional questions regarding heartburn during the preceding week. Heartburn during the preceding week was reported by 20.8% of the subjects (19.0% male, 22.1% female). Of these, 60.5% reported taking medicine for heartburn. Increasing age was not a significant factor in prevalence of heartburn/reflux disease. Age was, however, a significant factor associated with the use of medication for heartburn (Figure 1). Most subjects took ranitidine or esomeprazole for their symptoms (Figure 2).

Table 3 Sociodemographic characteristics and the development and disappearance of heartburn

	<i>n</i>	Never HB (%)	Lost HB (%)	Retained HB (%)	Developed HB (%)	χ^2	<i>P</i> -value
Gender						1.687	0.640
Male	330	40.3	14.5	30.3	14.8		
Female	441	41.5	14.7	26.5	17.2		
Age group (yr)						15.542	< 0.05 ^a
66-85	170	54.8	10.6	27.1	10.6		
36-65	488	37.3	16.4	29.3	17.0		
28-35	113	40.7	13.3	24.8	21.2		
BMI (kg/m ²)						21.685	< 0.01 ^b
> 30	154	31.8	14.3	37.0	16.9		
> 25 and ≤ 30	314	37.3	14.3	31.5	16.9		
≤ 25	286	49.3	15.0	19.9	15.7		
Level of education						6.156	0.724
> 4 years' further education	225	39.6	12.9	28.9	18.7		
3-4 years' further education	279	41.9	17.6	25.1	15.4		
< 3 years' further education	92	39.1	13.0	33.7	14.1		
No further education	161	41.6	13.0	29.8	15.5		
Employment status						6.276	0.099
Employed	574	39.7	15.5	27.0	17.8		
No employment	189	44.4	12.2	31.7	11.6		
Alcohol						4.503	0.609
≥ 7 drinks per week	43	37.2	9.3	34.9	18.6		
1-6 drinks per week	404	39.1	14.6	28.2	18.1		
No alcohol	309	43.0	15.5	27.5	13.9		
Smoking						8.773	0.187
Smokers, > 15 cigarettes per day	63	34.9	20.6	25.4	19.0		
Smokers, ≤ 15 cigarettes per day	113	31.9	17.7	34.5	15.9		
No smoking	496	43.5	13.7	26.2	16.5		

^a*P* < 0.05, ^b*P* < 0.01. HB: Heartburn; BMI: Body mass index.**Figure 1** Age and use of medication.**Figure 2** Which medication do you take?**Table 4** Heartburn and relationship to medication, food/beverages and tiredness

Variable	<i>n</i>	% of heartburn prior week
On constant medication	30	27.3
Medication only when experiencing symptoms	77	85.6
Tiredness (lethargy)		
Frequent	20	13.2
Sometimes/seldom	73	48.0
Never	59	38.8
Heartburn caused by food and beverages		
Very often	32	20.0
Sometimes/seldom	118	73.8
Never	10	6.3
Increased heartburn caused by specific food		
Very often	35	22.7
Sometimes/seldom	92	59.7
Never	27	17.5

27.3% reported they were on constant medication. Most individuals (85.6%) reported taking medication only when they experienced symptoms (Table 4), although there was some overlap here between groups. Six subjects reported having had an operation for reflux disease.

Tiredness or lethargy was reported as occurring frequently by 13.2% of subjects, reported rarely or seldom by 48%, and reported as never having occurred by 38.8% (Table 4).

Heartburn caused by food or beverages was reported as occurring very often by 20%, 73.8% reported some or

Table 5 Symptoms or activities affected by heartburn (caused by heartburn)

Variable	n	% of heartburn prior week
Felt bad		
Frequent	21	13.1
Sometimes/seldom	119	74.4
Never	20	12.5
Less food and beverages consumption		
Frequent	9	5.9
Sometimes/seldom	77	50.3
Never	67	43.8
Less family activities		
Frequent	1	0.6
Sometimes/seldom	32	20.8
Never	121	78.6
Trouble with sleeping		
Frequent	9	5.8
Sometimes/seldom	70	45.2
Never	76	49.0
Felt hopeless, worried or impatient		
Frequent	9	5.8
Sometimes/seldom	42	27.3
Never	103	66.9
Felt worried or scared for their health		
Frequent	5	3.2
Sometimes/seldom	47	30.3
Never	103	66.5
Felt irritable		
Frequent	21	13.6
Sometimes/seldom	80	51.9
Never	53	34.4
Neglect specific food or alcohol		
Frequent	36	23.1
Seldom	66	42.3
Never	54	34.6
Affects their daily activities		
Frequent	3	1.9
Sometimes/seldom	32	20.5
Never	121	77.6
Unable to move (sports, hobbies and outside of home)		
Frequent	3	1.9
Sometimes/seldom	34	21.8
Never	119	73.6

minimal heartburn and 6.3% never. Increased heartburn caused by a specific food was reported as occurring very often by 22.7% and sometimes by 59.7%. A specific food significantly more often provoked considerable heartburn in women than in men (Table 4).

As can be seen in Table 5, heartburn can affect symptoms or activities in many cases. Three out of four heartburn subjects claimed that they felt badly sometimes or seldom. One out of three heartburn subjects felt hopeless, anxious or impatient. And one out of three also reported being worried or scared because of heartburn every week.

Only 1.9% of the subjects reported that heartburn frequently affected their daily activities, whereas one fifth claimed that their daily activities were only sometimes or seldom affected by heartburn. Three out of four subjects reported that heartburn made them irritable. And one out of four heartburn subjects reported that heartburn resulted in less family activities, affected their daily activities and meant they were unable to move in sports, hobbies and

outside of home. Half of the heartburn subjects reported trouble with sleeping because of heartburn.

Many heartburn subjects reported less food and beverage consumption and that they avoided specific food or alcohol because of the heartburn.

DISCUSSION

In this study our main focus was on the natural history of heartburn over a 10-year period in an Icelandic population. The only other long-term study, to our knowledge, that has focused on heartburn is a long-term community study in Sweden covering a maximum of 7 years^[3]. There are strengths and weaknesses in both studies, but taken together they give a reasonably accurate picture of the natural history of heartburn.

The strength of our study is the use of a stable, homogeneous and well-informed population. The sample was randomly selected from the National Registry of Iceland and represented the nation as a whole in selected age groups. The population of Iceland was around 300 thousand inhabitants at the time of the study and the sample was approximately 1% of the whole population from all around the country. The BDQ, the questionnaire used, assesses the whole range of gastrointestinal functional disorders.

The prevalence of heartburn is high in Iceland. More than two out of five subjects reported heartburn in the preceding year. Half of those reported heartburn in the preceding week. Heartburn was reported as still existing after 10 years for 2 out of 3 subjects in the study. The study by Agréus *et al.*^[5] showed that the prevalence of predominant gastroesophageal reflux symptoms appears to be stable over time. Results from studies of patients suggest that GERD is a chronic disease in most cases^[3,16,17]. One third of subjects who did not report heartburn in 1996 had developed heartburn 10 years later. So even though the total prevalence of heartburn was almost the same in both 1996 and 2006, there was a change among over one third of subjects reporting heartburn.

Heartburn subjects with a BMI either lower than or higher than normal weight were more likely to experience heartburn than subjects with normal weight. A study by Aro *et al.*^[18] found that reflux symptoms are linked to obesity and specifically that the presence of gastroesophageal reflux symptoms was linked to reflux esophagitis in the obese population. Festi *et al.*^[9] concluded that it was likely that GERD and obesity are in some way linked and that it was possible to hypothesize that GERD may be a curable condition through the control of body weight. This may also be true for heartburn.

The transition analysis showed a substantial change in numbers in all the categories. The stability of each disease varied. FD subjects were the most stable throughout the 10 years (52.3%). Of the heartburn group 39.3% were stable, as were 30.3% of the IBS group and 15.4% of the frequent abdominal pain group. A quarter of the heartburn group had increased symptoms in 10 years, 4.6% decreased symptoms and one third developed no

symptoms in 10 years. There was a significant relationship between IBS and heartburn as well as FD and heartburn.

Half (45.1%) of the subjects who reported heartburn in the preceding year experienced heartburn in the previous week. Food and beverages play a large part in eliciting heartburn; very often in 20.0% of the cases and sometimes in 73.8% of the cases. Subjects also very often experienced increased heartburn caused by a specific food in 22.7% of the cases. Heartburn did not seem to be the cause for less food and beverage consumption, but one out of five heartburn subjects did avoid a specific food or alcohol because of heartburn. Festi *et al.*^[19] report that no definitive data exist regarding the role of diet and specific foods or drinks in GERD clinical manifestations^[19].

Heartburn is associated with feeling tired (61.2%), feeling bad (87.5%) and with irritation (65.5%). One third felt worried or scared for their health because of heartburn symptoms and one third also felt that heartburn caused them to feel hopeless, worried or impatient (33.1%). Every fifth heartburn subject reported that heartburn affected activities such as daily and family activities, as well as that heartburn caused them to be unable to move normally and therefore affected their participation in sports, hobbies and outdoor activities. This effect of heartburn on normal life and activities may have affected the subjects in the manner of a chronic condition throughout the 10 years of the study, and therefore had a great impact on quality of life. This finding is in line with McDougall *et al.*^[17] who showed in their study on reflux esophagitis and quality of life that it was not bodily pain and vitality that were impaired, but general health and social function.

Three out of five of all the heartburn subjects in 2006 reported taking medicine for heartburn. Almost all the subjects who were on medication for heartburn reported relief provided by the medication. Age was a significant factor for the use of medication for heartburn. Most subjects took ranitidine or esomeprazole for their symptoms.

Few studies have addressed the impact of nocturnal reflux symptoms in heartburn subjects. A study by Farup *et al.*^[20] showed that the prevalence of nighttime heartburn in GERD patients under routine care was high, up to 49% for 1 of 3 years. A population-based survey in the United States claimed that the overall prevalence of nocturnal GERD symptoms was 10%, with 74% of subjects with GERD symptoms fitting the criteria for nocturnal GERD^[21]. In our study, sleep was frequently affected in 5.8% of cases and 45.2% of heartburn subjects were sometimes or seldom troubled with sleeping in the prior week. These numbers can be expected to be higher for the preceding year, since we asked specifically about the preceding week.

There are some limitations to our study. The subjects were not specifically interviewed or examined to evaluate the possibility of organic disease. However, a 10-year (postal) follow-up went some way towards making an organic cause of symptoms unlikely. Furthermore, since the response rate was 66.8% in 1996 and 67.7% in 2006, a dropout bias cannot be excluded.

In summary, heartburn is a common condition in the population of Iceland. The prevalence is slightly higher than reported elsewhere. Heartburn is a chronic condition, affecting every fifth person every week. Heartburn subjects with a BMI lower or higher than normal weight were more likely to experience heartburn than subjects of normal weight. Heartburn did not seem to result in less food and beverage consumption, but one out of five heartburn subjects did avoid a specific food or alcohol because of the heartburn. Heartburn had a great impact on daily activities and quality of life. Half of the heartburn subjects experienced sleep disturbances because of this condition.

COMMENTS

Background

Heartburn is a signature symptom of gastroesophageal reflux disease (GERD), which is a cluster of symptoms and signs associated with regurgitation of stomach acid up to the pharynx and mouth. Patient-based studies of GERD have shown high prevalence and chronicity, particularly in Western societies. GERD is associated with significant health-care utilization and diminished quality of life. Heartburn, coupled with acid regurgitation and painful swallowing are considered to be highly specific for GERD. Very few epidemiological studies have been performed with regard to heartburn, and only one has been population-based. The natural history of GERD or heartburn has received little attention. The pathophysiology of GERD and heartburn is basically unknown.

Research frontiers

The prevalence of upper gastrointestinal symptoms in the general population is high and symptoms are associated with significant socioeconomic consequences. The prevalence and natural history of heartburn is of importance as well as its association with functional dyspepsia and irritable bowel syndrome, and sociodemographic factors such as body mass index (BMI). The aim of the present study was therefore to evaluate the natural history of heartburn in the Icelandic population prospectively over a 10-year period, as well as to evaluate different factors which are associated with heartburn both physically and sociodemographically.

Innovations and breakthroughs

The prevalence of heartburn is high in Iceland. More than two out of five subjects reported heartburn in the preceding year. Half of those reported heartburn in the preceding week. Heartburn was reported as still existing after 10 years for 2 out of 3 subjects in the study. Heartburn subjects with a BMI either lower or higher than normal weight were more likely to experience heartburn than subjects with normal weight. There was an association between heartburn, functional dyspepsia and irritable bowel syndrome and patients floated over time between these categories. This suggests a common etiopathogenesis of these disorders. The quality of life was diminished due to a variety of factors such as worries, irritability, intolerance to specific foods and sleep disturbance.

Applications

The prevalence and natural history of heartburn and its risk factors are important for management and prognosis. Heartburn can be regarded as a reliable surrogate marker of GERD. This study creates a database for future studies and hopefully stimulates studies in other countries. Secular prevalence trends and international comparison can contribute towards understanding of the pathophysiology of the disease.

Terminology

A 10-year follow-up population-based, questionnaire study of the Icelandic population was performed. The primary aim was to study the prevalence and natural history of heartburn. Subjects were classified as having heartburn if they reported heartburn according to the following definition: Heartburn is a burning sensation in the retrosternal area (behind the breastbone). The pain often rises in the upper abdomen and may radiate to the chest.

Peer review

Heartburn alone has a prevalence of 17%-42% in Western populations and is associated with extensive health care expenses and diminished quality of life. Comparative international population-based studies are needed to document secular trends and to elucidate the reasons for the different prevalence in various countries.

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Paper IV

Natural history of Functional Gastrointestinal Disorders: Comparison of two longitudinal population-based studies

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ABSTRACT

Background: Functional gastrointestinal disorders (FGID) are common but information on their natural history is limited.

Aims: To document the natural history of FGID in a population based study of the Icelandic population and to compare the results with the Olmsted County (OC) study.

Method A questionnaire was mailed to the same age- and gender-stratified random sample of the Icelandic population aged 18-75 in 1996 and again in 2006. Results were compared to the Olmsted County (OC) study, which used the same methodology. Birth cohort effects were studied.

Results: Prevalence of FGID symptoms was stable between these periods in time: 16.9% and 17.2% for IBS, and 4.8% and 6.1% for functional dyspepsia. Onset of each disorder was higher in the OC study for IBS and frequent abdominal pain. Disappearance rates were similar for IBS and FD in both studies. Transition probabilities varied across the different subgroups and were different between studies. The same proportion had the same symptoms in the initial and final studies. More subjects had no symptoms in Iceland (52% vs. 40%) and had different symptoms at follow up in Iceland (38% vs. 23%). Birth cohort analysis suggest a higher prevalence of IBS in the youngest age group born in the years 1971-78 in Iceland.

Conclusion: Prevalence of FGID symptoms was stable over time but the turnover in symptoms was high. There was a difference in prevalence of symptoms between studies and transition probabilities. A higher number of subjects had no symptoms in Iceland than in Olmsted county and there was a greater variation in subjects having different symptoms at follow up.

Key Words: *Functional gastrointestinal disorders, Irritable bowel syndrome, functional dyspepsia, follow up, questionnaire study, epidemiology, Manning criteria, Rome III.*

INTRODUCTION

Functional gastrointestinal disorders (FGID) are common in the community and pose a significant health-care burden [1, 2]. The prevalence of FGID has been reported up to 40% [1] and other studies report that more than one third of the general population have one or more FGID [3]. There is an increasing interest in the epidemiology of these diseases [1, 4], but the field has been confounded by rapid introduction of new diagnostic criteria. This has made it very difficult or virtually impossible to compare prevalence rates from different time periods or geographic regions [5]. With more studies based on the same or similar methodology the understanding of the natural history of FGID will improve.

The causes and pathogenic mechanisms of FGID are not fully known. According to the Rome III committee FGID are classified into six major domains [6], three of which will be addressed in this study: 1) functional dyspepsia (FD); 2) functional bowel disorders, including irritable bowel syndrome (IBS), functional constipation and functional diarrhea; and 3) functional abdominal pain syndrome. Studies have shown that individual FGID including IBS and FD often occur together [3, 7]. A recent study found no association between survival and symptoms of IBS, functional diarrhea, dyspepsia or abdominal pain [2]. However, IBS patients with moderate to severe symptoms, experience diminished quality of life compared with the general population [8].

The main advantage of a population-based epidemiological approach is the possibility of studying the spectrum of symptoms in the whole population [7]. Patient-based studies from health institutions are inherently biased by health care seeking because only a minority of subjects consult a health care provider regarding their symptoms [9-11]. IBS patients are often reluctant to consult a physician paradoxically because they either think their symptoms are not serious enough or are afraid that they have a serious life-threatening illness [12, 13].

Three long-term studies have focused on the natural history of FGID, the 12-year longitudinal population-based study from Olmsted County Minnesota USA [1], the 7 year

long-term community study from Sweden [4] and the 10-year longitudinal follow-up study conducted in Leeds and Bradford, UK [14]. These studies have been carried out in three different countries and the methods are not the same so they are not quite comparable. The DIGEST study used the same methods in several populations and registered the three month prevalence of upper GI symptoms. That study provided valuable data on the international prevalence of upper GI symptoms and the disparities between the different survey sites [15]. The results of parallel studies based on the same Icelandic database, focusing on Functional Dyspepsia, the stability of IBS and Functional Heartburn, have been published [18-20].

Comparison of studies from different populations using the same criteria is essential for understanding the natural history of FGID. The primary objective of our study was to 1. document the natural history of FGID in the Icelandic population. 2. to compare our study with the Minnesota study, which used the same methodology, i.e. the Bowel Disease Questionnaire (BDQ) [16, 17], thereby ensuring a reasonable degree of comparability for the Rome II data. 3. to assess the birth cohort effect on the prevalence (%) of FGID.

METHODS

Participants and setting

In 1996 an epidemiological study of gastrointestinal diseases was performed in Iceland [21]. A total of 2000 inhabitants aged 18-75 years were studied. The individuals were randomly selected from the National Registry of Iceland. Equal distribution of sex and age was secured in each age group. In 2006 we attempted to contact all the individuals from the 1996 study as well as adding 300 new individuals in the age group 18-27, who were also randomly selected from the National Registry. A questionnaire was mailed to individuals at baseline and the study questionnaire and an explanatory letter mailed to all eligible individuals. Reminder letters were mailed at 2, 4, and 7 weeks, using the Total Method of Dillman [22]. Individuals who indicated at any point that they did not want to

participate in the study were not contacted further. The study was conducted in compliance with the guidelines for Good Epidemiology Practice (GEP).

The questionnaire

The Bowel Disease Questionnaire (BDQ) [17, 23] was translated from English into Icelandic and modified for this study. The questionnaire was designed as a self-report instrument to measure symptoms experienced over the previous year and to collect the participant's past medical history [1]. The Icelandic version of the BDQ questionnaire addresses 47 gastrointestinal symptoms and 32 items that measure past illness, health care use, and sociodemographic and psychosomatic symptoms items, together with a valid measure of non-GI somatic complaints, the Somatic Symptom Checklist (SSC) [24]. The SSC consists of 12 non-GI and 5 GI symptoms or illnesses. Individuals are instructed to indicate, on a 5-point scale, how often each symptom appears and how bothersome it is. There were only a few changes in the latter questionnaire when used in 2006, which addressed 51 gastrointestinal symptoms and 33 items that measure past illness, health care use, and sociodemographic and psychosomatic symptoms items. The 2006 Questionnaire furthermore addressed 17 items to identify heartburn and items related to heartburn.

Symptom Categories [1]

Subjects were classified according to the methodology used by Halder et al. (Table I) [1] into a priori symptom groups based on their responses to each of the questionnaires, which recorded their symptoms over the previous year. A subject could have more than one disorder. The same modification of Rome II was used to categorize subjects as in the study by Halder et al.[1].

Table I: Diagnostic criteria used by Halder et al.

IBS
The criteria for identification of IBS were a slight modification of Rome II criteria. IBS was defined as a combination of frequent (more than 6 times per year) abdominal pain and an altered bowel habit. The abdominal pain had to have 2 of the following 3 characteristics: <ol style="list-style-type: none">1. relieved by defecation2. associated with a change in stool frequency3. associated with a change in stool form. <i>Rome II:</i> the 2006 questionnaire included Rome II criteria [25] to identify IBS.
IBS-constipation predominant
IBS-constipation predominant (IBS-C) fulfils the criteria of IBS and reports 2 or more of the following symptoms: <ol style="list-style-type: none">1. less than 3 bowel movements per week2. straining to have a bowel movement3. often passing hard stools4. incomplete evacuation.
IBS-diarrhea predominant (IBS-D)
IBS-diarrhea predominant (IBS-D) fulfills the definition of IBS and reports often passing loose or watery stools.
IBS-both
IBS-both meets the definitions for both IBS-C and IBS-D.
IBS neither C nor D
IBS-neither meets the definitions for IBS with the exclusion of IBS-C and IBS-D.
Functional constipation
Functional constipation (C) in the absence of frequent abdominal pain is defined as having 2 or more of the following symptoms: <ol style="list-style-type: none">1. less than 3 bowel movements per week2. straining to have a bowel movement3. often passing hard stools4. incomplete evacuation.
Functional diarrhea
Functional diarrhea (D) in the absence of frequent abdominal pain has 1 or more of the following symptoms: <ol style="list-style-type: none">1. reporting diarrhea as the usual bowel pattern2. more than 3 bowel movements per day3. having loose or watery stools4. urgency to have a bowel movement.
Both C and D
Both C and D meet the definition for both constipation and diarrhea with no abdominal pain.
FD
FD was defined as when 2 or more of the following are present <ol style="list-style-type: none">1. frequent upper pain (>6 times per year)2. nausea (at least weekly ≥ 3)3. vomiting (at least weekly ≥ 3)4. early satiety5. loss of appetite
Abdominal pain
Subjects who reported having had more than 6 episodes of abdominal pain in the prior year were considered to have frequent abdominal pain; those who reported fewer episodes were not included to remove those experiencing only gastroenteritis or other acute illness.

Transition between disorders from the initial to the final survey

A transition model used by Halder et al. was modified and applied for this study [1] . The responses from the initial (1996) and final (2006) surveys were matched for each subject to examine the changes between disorders at an individual level for the 10 categories (IBS subgroups, constipation, diarrhea, FD, frequent abdominal pain and none of these symptoms). A 10 x 10 table was used to model these multiple changes and collapsed into 6 groups, as illustrated in Figure 1. Those with the most symptoms were prioritized higher. Those who developed more symptoms and those who reported fewer symptoms could be categorized into groups. There were six patterns of symptoms, identified as follows: (1) symptom stability, (2) symptom increase, (3) symptom decrease, (4) symptom onset, (5) becoming asymptomatic, and (6) none of these symptoms.

FGID in 1996	Proportion of FGID in 2006 based on primary survey disorder									
	IBS-both %	IBS-C %	IBS-D %	IBS-no C or D %	Both C and D %	C %	D %	FD %	Frequent Abd. Pain %	No symptoms
IBS-both (n=16)	18.8 (23.5)	0.0 (0.0)	12.5 (29.4)	12.5 (0.0)	6.3 (0.0)	0.0 (0.0)	0.0 (5.9)	0.0 (0.0)	31.3 (11.8)	18.8 (29.4)
	11.5 (12.0)	17.3 (12.0)	3.8 (0.0)	5.8 (16.0)	3.8 (0.0)	1.9 (8.0)	0.0 (0.0)	7.7 (0.0)	21.2 (24.0)	26.9 (20.0)
	3.1 (2.5)	3.1 (0.0)	34.4 (20.0)	6.3 (17.5)	0.0 (0.0)	0.0 (0.0)	3.1 (15.0)	6.3 (5.0)	9.4 (5.0)	34.4 (33.0)
IBS-D (n=32)	0.0 (1.3)	0.0 (7.9)	18.2 (7.9)	9.1 (30.3)	0.0 (2.6)	0.0 (5.3)	0.0 (2.6)	9.1 (0.0)	36.4 (11.8)	27.3 (30.3)
	10.0 (0.0)	40.0 (0.0)	10.0 (12.5)	10.0 (0.0)	0.0 (12.5)	10.0 (0.0)	0.0 (0.0)	0.0 (0.0)	20.0 (12.5)	0.0 (62.5)
Both C and D (n=10)	0.0 (0.0)	10.0 (6.7)	10.0 (0.0)	0.0 (4.4)	0.0 (4.4)	0.0 (22.2)	0.0 (0.0)	10.0 (6.7)	0.0 (8.9)	70.0 (46.7)
C (n=10)	0.0 (0.0)	0.0 (1.1)	4.5 (5.8)	9.1 (4.6)	0.0 (2.3)	0.0 (4.6)	4.5 (28.7)	9.1 (0.0)	31.8 (6.9)	40.9 (42.5)
D (n=22)	0.0 (3.5)	0.0 (0.0)	10.5 (0.0)	5.3 (25.0)	0.0 (0.0)	0.0 (0.0)	15.8 (0.0)	15.8 (0.0)	15.8 (25.0)	36.8 (50.0)
FD (n=19)	5.4 (2.5)	9.9 (4.6)	6.3 (10.6)	3.6 (9.1)	1.8 (0.5)	1.8 (3.5)	1.8 (6.6)	7.2 (0.0)	22.5 (22.2)	39.6 (40.4)
Frequent Abdominal Pain (n=111)	1.2 (1.0)	0.6 (1.0)	2.0 (3.4)	2.6 (8.7)	0.8 (1.9)	0.6 (3.9)	2.0 (7.6)	0.6 (0.2)	7.9 (9.9)	81.8 (62.3)

Remaining asymptomatic	Developed symptoms
Became asymptomatic	Decreased symptoms
Stable	Increased symptoms

FGID - Functional Gastrointestinal Disorders

FD - Functional Dyspepsia

D - Diarrhea

C - Constipation

Numbers in italics = Olmsted County study

Mortality data

For the 2006 survey we identified all deceased individuals with the assistance of the National Registry of Iceland (Thjodskra).

Statistical Analysis

Tables were constructed for frequency and percentage. Categorical data were analyzed using the χ^2 test (Chi square test). The type I error protection rate was set at 0.05. The exact p is listed in the tables and text. All the research data were imported into SPSS (Statistical Package of Social Science) software.

RESULTS

Demographic Data of Involved Individuals

Comparison of the demographics of the Minnesota and Iceland studies: the number of subjects in initial survey is for the Olmsted County (OC) 4,816 and 2,000 for the Icelandic study. The initial response rate for the OC study was 79% and 67% for the Icelandic study. The mean age was 57 years for the OC study and 43 years for the Icelandic study. Women responding were 52% for the OC study and 55% for the Icelandic study. In the final study the number of subject was 2,914 for the OC study and 1,180 for the Icelandic study. The number of subjects who responded to both initial and final surveys was 28% (1,365/4,816) for the OC study and 40% (799/2,000) for the Icelandic study. The mean age was 47 years for the OC study and 53 years for the Icelandic study. Women responding in the final survey were 55% for the OC study and 58% for the Icelandic study. The mean (\pm SD) time between completion of the initial and final surveys was 12 years (\pm 2) for the OC study and 10 years for the Icelandic study. The study period was 1988/2003 for the OC study and 1996/2006 for the Icelandic study.. The major difference between these two studies is the mean age as the Icelandic study population is younger. The time points of the initial and final surveys of the studies are also different.

Prevalence of each disorder and comparison with the Olmsted County study

The prevalence of any of the FGID in Iceland over the 10 year period was 36.8% in 1996 and 35.7% in 2006. The prevalence rates for each FGID studied can be seen in table II. In the Olmstead County study there was a higher prevalence of any of the FGID over the 12 year period, with an aggregated rate of 42.3%.

Table II. Prevalence (%) of functional GI disorders in Iceland.

FGID	Initial (baseline - 1996)			Final (follow up - 2006)		
	Female (95% CI)	Male (95% CI)	All (95% CI)	Female (95% CI)	Male (95% CI)	All (95% CI)
IBS (any)	20.5 (16.5-24.5) <i>(9.7)</i>	13.4 (10.0-16.7) <i>(7.0)</i>	16.9 (14.3-19.6) <i>(8.3)</i>	22.7 (18.3-27.2) <i>(13.0)</i>	11.6 (8.4-14.8) <i>(9.5)</i>	17.2 (14.4-19.9) <i>(11.4)</i>
IBS-C	12.2 (9.0-15.5) <i>(3.0)</i>	7.2 (4.6-9.7) <i>(2.4)</i>	9.7 (7.6-11.8) <i>(2.7)</i>	9.4 (6.4-12.4) <i>(3.1)</i>	4.2 (2.2-6.2) <i>(1.6)</i>	6.8 (5.0-8.6) <i>(2.4)</i>
IBS-D	8.0 (5.2-10.7) <i>(3.9)</i>	5.6 (3.3-8.0) <i>(3.2)</i>	6.8 (5.0-8.6) <i>(3.6)</i>	10.6 (7.4-13.8) <i>(5.7)</i>	7.7 (5.0-10.5) <i>(4.0)</i>	9.1 (7.0-11.3) <i>(4.9)</i>
IBS-both	2.5 (0.9-4.1) <i>(1.6)</i>	3.0 (1.3-4.7) <i>(1.0)</i>	2.8 (1.6-3.9) <i>(1.3)</i>	4.3 (2.2-6.4) <i>(1.2)</i>	2.9 (1.2-4.6) <i>(1.0)</i>	3.6 (2.2-4.9) <i>(1.2)</i>
C	3.2 (1.4-4.9) <i>(4.5)</i>	2.5 (0.9-4.0) <i>(4.1)</i>	2.8 (1.7-4.0) <i>(4.3)</i>	2.5 (0.9-4.1) <i>(5.3)</i>	1.7 (0.4-3.0) <i>(3.1)</i>	2.1 (1.1-3.1) <i>(4.1)</i>
D	5.1 (3.0-7.3) <i>(5.0)</i>	3.3 (1.5-5.0) <i>(6.2)</i>	4.2 (2.8-5.6) <i>(5.6)</i>	3.9 (1.9-5.9) <i>(5.4)</i>	3.4 (1.6-5.3) <i>(6.2)</i>	3.7 (2.3-5.0) <i>(5.7)</i>
Both C and D	1.6 (0.4-2.9) <i>(1.0)</i>	1.0 (0.0-2.0) <i>(0.8)</i>	1.3 (0.5-2.1) <i>(0.9)</i>	1.7 (0.4-3.0) <i>(0.8)</i>	0.4 (0.0-1.0) <i>(1.0)</i>	1.0 (0.3-1.8) <i>(0.9)</i>
Functional dyspepsia	6.4 (3.9-8.8) <i>(2.0)</i>	3.3 (1.5-5.0) <i>(1.8)</i>	4.8 (3.3-6.3) <i>(1.9)</i>	9.8 (6.7-13.0) <i>(4.2)</i>	2.5 (1.0-4.1) <i>(2.3)</i>	6.1 (4.4-7.9) <i>(3.3)</i>
Frequent abdominal pain	39.4 (34.5-44.2) <i>(21.9)</i>	24.0 (19.8-28.1) <i>(18.2)</i>	31.6 (28.2-35.0) <i>(20.1)</i>	40.1 (34.6-45.7) <i>(22.3)</i>	26.6 (22.1-31.1) <i>(17.8)</i>	33.3 (29.8-36.9) <i>(20.2)</i>

FGID, functional gastrointestinal disorders; IBS, irritable bowel syndrome; C, constipation; D, diarrhea.
Numbers in *italic* = from the Olmsted County study

IBS and subgroups. In comparison to the Olmsted County study (Table II) the IBS numbers in Iceland were much higher. IBS (any) in the Olmsted County study had the initial prevalence of 8.3% and 11.4% in the final survey.

Constipation and diarrhea. The prevalence of functional diarrhea and constipation was higher in the Olmsted County study than in the Icelandic study (Table II).

Functional dyspepsia. The prevalence of functional dyspepsia was much higher in the Icelandic study (1996: 4.8%/2006: 6.1%) than in the Olmsted County study (initial: 1.9%/final: 3.3%) (Table II).

Abdominal pain. The prevalence of abdominal pain was much higher in the Icelandic study (1996: 31.6%/2006: 33.3%) than in the Olmsted County study (initial: 20.1%/final: 20.2%) (Table II).

Table III. Onset (%) of different functional GI disorders in 2006 in comparison to 1996.

FGID	Number at baseline	n	Iceland Onset (95% CI)	<i>n</i> ^{OC}	<i>Olmsted County Onset (95% CI)^{OC}</i>
IBS-any	668	74	11.1 (8.7-13.5)	195	16.2 (14.1-18.4)
IBS neither C nor D	764	26	3.4 (2.1-4.7)	100	7.8 (6.4-9.4)
IBS-C	719	34	4.7 (3.2-6.3)	22	1.6 (1.0-2.5)
IBS-D	721	43	6.0 (4.2-7.7)	56	4.2 (3.2-5.5)
IBS-both	752	18	2.4 (1.3-3.5)	17	1.3 (0.7-2.0)
Constipation	770	15	1.9 (1.0-2.9)	51	3.9 (2.9-5.1)
Diarrhea	763	25	3.3 (2.0-4.5)	90	7.0 (5.7-8.6)
Both C and D	780	9	1.2 (0.4-1.9)	23	1.7 (1.1-2.5)
Functional dyspepsia	748	39	5.2 (3.6-6.8)	67	5.1 (4.0-6.4)
Frequent abdominal pain	545	97	17.8 (14.6-21.0)	235	24.0 (21.4-26.8)

NOTE. For each condition, the left column shows the number of people *without* the condition at baseline. The right column shows the number and percentage (with 95% CI) of those people who did report the condition at follow up. FGID, functional gastrointestinal disorders; IBS, irritable bowel syndrome; C, constipation; D, diarrhea. Numbers in italics = from the Olmsted County (OC) study

Onset and disappearance rates between the initial and final surveys

Table III shows the onset of different functional GI disorders in 2006 as compared to 1996. Subjects could be categorized into more than one FGID group. Onset rates were based on those who were free of symptoms of a specified disorder at the time point of the first survey and were then identified with symptoms of that specific disorder in the latter survey. Subjects could have had that specific disorder during more than one year prior to the initial survey. Compared to the Olmsted County study the numbers in Iceland were lower for the IBS-any (11.1% vs. 16.2%). The rates were also lower for the IBS neither C

nor D. However, the rates were higher for subjects in Iceland in the IBS-C, IBS-C and IBS-both. The frequency of onset of constipation, diarrhea, functional dyspepsia and frequent abdominal pain was lower in the Icelandic study (see table III).

In table IV the disappearance of different functional GI disorders can be seen.. These rates were similar in the Olmsted County study for IBS-any (55.6%/55.1%). The disappearance rates were somewhat higher in the Icelandic study for IBS neither C nor D, IBS-C and IBS-both, and somewhat lower for IBS-D.

Table IV. Disappearance (%) of different functional GI disorders in 2006 in comparison to 1996

FGID	Number at baseline	n	Iceland <i>Disappearance</i> (95% CI)	<i>n^{OC}</i>	<i>Olmsted County</i> <i>Disappearance</i> (95% CI) ^{OC}
IBS-any	126	70	55.6 (46.9-64.2)	87	55.1 (47.0-63.0)
IBS neither C nor D	22	19	86.4 (72.0-100.0)	40	52.6 (40.8-64.2)
IBS-C	68	46	67.6 (56.5-78.8)	15	60.0 (38.7-78.9)
IBS-D	48	26	54.2 (40.1-68.3)	24	60.0 (43.3-75.1)
IBS-both	16	10	62.5 (38.8-86.2)	8	47.1 (23.0-72.2)
Constipation	20	17	85.0 (69.4-100.0)	35	77.8 (62.9-88.8)
Diarrhea	32	31	96.9 (90.8-100.0)	62	71.3 (60.6-80.5)
Both C and D	10	10	100.0 (100.0-100.0)	7	87.5 (47.4-99.7)
Functional dyspepsia	35	22	62.9 (46.8-78.9)	28	66.7 (50.5-80.4)
Frequent abdominal pain	252	89	35.3 (29.4-41.2)	165	42.6 (37.7-47.7)

NOTE. For each condition, the left column shows the number of people *with* the condition at baseline. The right column shows the number and percentage (with 95% CI) of those people who did not report the condition at follow-up. FGID, functional gastrointestinal disorders; IBS, irritable bowel syndrome; C, constipation; D, diarrhea. Numbers in *italic* = from the Olmsted County (OC) study

The high disappearance rates for constipation and diarrhea (85.0% and 96.9%) were higher than in the Olmsted County study (77.8% and 71.3%). There was also a high disappearance rate for functional dyspepsia, 62.9%, which was similar to the Olmsted County study (66.7%). The disappearance rate for frequent abdominal pain was lower in this study (35.3%) than in the Olmsted County study (42.6%).

Direct comparison on the onset and disappearance of FGID symptoms could not be done because of different denominators. But the absolute numbers suggested that there was not a great difference between the number of subjects with onset and disappearance of symptoms. The only difference was in subjects reporting functional dyspepsia and frequent abdominal pain, with more subjects in the onset group. In comparison, a greater number of subjects had onset of different functional GI disorders than disappearance in most cases in the Olmsted County study compared with our study.

Transition between disorders from the 1996 and 2006 surveys

As described in the methods section, the groups in this analysis were defined as mutually exclusive, using the symptom hierarchy so that each subject appears in only one category for both the 1996 and 2006 surveys. There was a “no symptoms” category for those who did not meet any of the criteria applied for FGID. Due to the hierarchical classification only a few participants occurred in some categories.

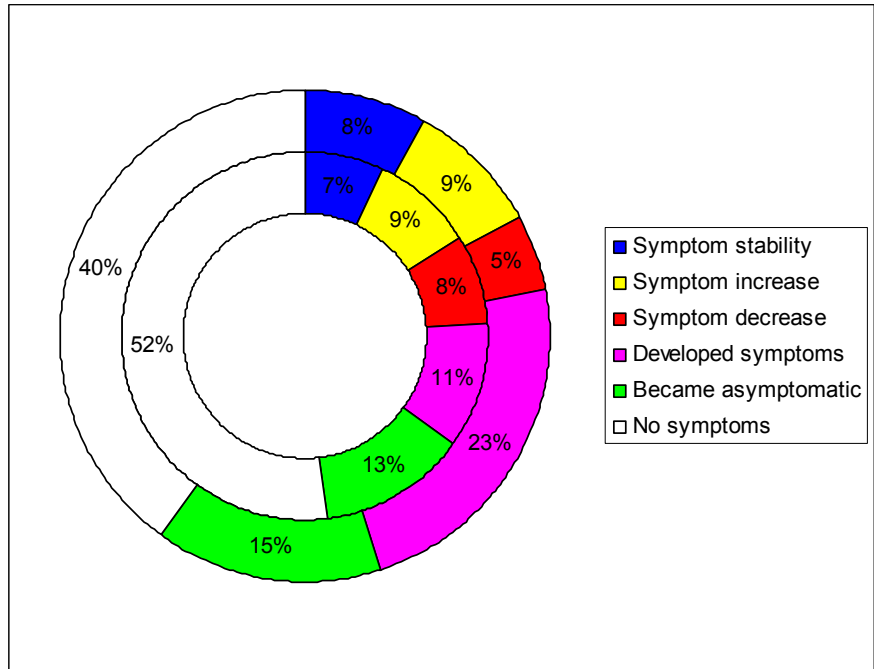
There was a substantial change in numbers in all the categories between the two surveys. The group “no symptoms” was the most common. Of the IBS groups the IBS-D was the most stable with 34.4%, and one third reported no symptoms at follow up. IBS-both and IBS –C were similar with almost one fifth in those categories, but more of the IBS-C moved into the no symptoms category. Few of the IBS-C moved into the IBS-D over the 10 year period and vice versa. That did not happen in the Olmsted County study where IBS-C did not show a transition into the IBS-D nor did the IBS-D subjects move into the IBS-C. None of the IBS-C transitioned into the diarrhea group and none of the IBS-D moved into the constipation group. No one of those having IBS-neither C nor D was stable over the 10 year period. (Figure 1)

A total of 15.8% had a stable FD in both years but 31.6% developed FD (increased symptoms) in 2006 and 36.8% had moved into the “no symptoms” group.

The category “frequent abdominal pain” was stable in 22.5% of cases, whereas 34.2% moved into the “increased symptoms” category and 39.6% into the “no symptoms” category.

The distribution of the 6 transition groups is illustrated in figure 2. These rates were similar in the Olmsted County study except for the symptom onset which was 11% for this study and 23% for the Olmsted County study, and for the subjects who had no symptoms in both the initial and final surveys 52% in this study and 40% in the Olmsted County study.

Figure 2. Six-group transition model, change from initial to the final survey. Iceland (n=799) in the inner circle and Olmsted County (n=1365) in the outer circle.



Birth cohort effect of functional gastrointestinal disorders

Data in table V suggest a birth cohort effect in IBS subjects with high prevalence in the age group born 1971-78. There was a trend for lower prevalence in the diarrhea category in the same age group.

Table V. Birth cohort effect on the prevalence (%) of functional gastrointestinal disorders

	IBS (any)		Constipation		Diarrhea		Both C and D		FD		Abdominal pain		No symptoms	
	1996	2006	1996	2006	1996	2006	1996	2006	1996	2006	1996	2006	1996	2006
Born 1971-78	26,7%	27,6%	0,0%	1,7%	2,6%	0,9%	3,4%	1,7%	0,9%	4,3%	15,5%	9,5%	50,9%	54,3%
Born 1961-70	13,5%	15,3%	0,6%	0,6%	1,8%	3,1%	1,2%	2,5%	3,1%	4,3%	11,0%	11,7%	68,7%	62,6%
Born 1951-60	16,9%	16,4%	3,4%	1,1%	5,1%	3,4%	1,1%	0,6%	1,7%	3,4%	14,1%	16,9%	57,6%	58,2%
Born 1941-50	10,9%	9,0%	0,6%	1,3%	2,6%	2,6%	0,6%	0,6%	3,2%	1,3%	14,1%	17,3%	67,9%	67,9%
Born 1931-40	8,3%	11,6%	0,8%	0,0%	0,8%	0,8%	0,8%	0,0%	1,7%	3,3%	15,7%	7,4%	71,9%	76,9%
Born 1921-30	18,2%	13,6%	1,5%	0,0%	3,0%	0,0%	0,0%	1,5%	4,5%	1,5%	13,6%	12,1%	59,1%	71,2%

DISCUSSION

The current study makes it possible for the first time to compare two large FGID longitudinal studies using the same methodology but performed in different populations. The Icelandic and Olmsted County studies document the natural history of IBS and its subgroups, as well as constipation, diarrhea, functional dyspepsia and abdominal pain over a long time period, 10 and 12 years. These studies were based on predominantly Caucasian populations. There were some differences in the mean age, response rates of those who responded to both the initial and final surveys, and the time settings.

In line with the Olmsted County study we confirmed that these disorders are common. The prevalence of IBS (any), FD and frequent abdominal pain were much higher in Iceland than in the Olmsted County study, but lower for constipation and for diarrhea than in the Olmsted County study. There was also a great difference in onset of FGID except for FD, but the difference was not as great in the disappearance of FGID, except for diarrhea and frequent abdominal pain.

The absolute numbers of people who reported onset of symptoms were greater than those reporting disappearance for all FGID in the Olmsted County study[1]. Onset of symptoms assessed by the transition model showed twice as high rates in the Olmsted County study than in the Icelandic study (23% vs. 11%).

It is of interest that subjects without any GI symptoms, neither in the initial nor the final surveys, constituted more than half of the study population in Iceland and two out of five in the Olmsted County study. In both studies symptom stability, symptom increase and symptom decrease were very similar.

More subjects in the Icelandic study remained in the no symptom category (52%) than in the Olmsted County study (40%). This may suggest more symptom stability in Iceland, since half of the subjects stayed asymptomatic over the ten year period. However, a large proportion of the study population continued to experience symptoms in some form ten years later. Of those subjects symptomatic at baseline, who participated in the Leeds and Bradford study, almost three-quarters remained symptomatic at 10 years, but over 40% changed symptom subgroup [14].

The DIGEST study was the first to examine the population prevalence of GI symptoms at multiple international sites. It provided valuable cross-country data on the three month prevalence of upper GI symptoms and the disparities between the different survey sites [15]. The DIGEST study investigated populations in ten countries which can all be classified as highly developed with a westernized lifestyle.

Our study and the Olmsted County study expand the epidemiology to the natural history dimension. It is clear that there is a difference in prevalence and natural history of various FGID in Olmsted County and in Iceland. The cross-country effect could contribute to this difference but the specific details of and reasons for the cross-country effect in these studies are no better understood than in the DIGEST study. There is no obvious difference in sociodemographic or risk factors between the two populations. The socioeconomic development of Iceland in the latter half of the 20th century was at least

three decades behind Scandinavian and western European countries [26] and probably behind Olmsted County as well. This has been manifested in differences in *Helicobacter pylori* birth cohort prevalence in Sweden and Iceland [26], which can be regarded as a surrogate marker of hygiene and sanitary development. It is a tempting hypothesis that FGID prevalence is related to birth cohorts.

Our study suggested a birth cohort effect for IBS with a high prevalence in the youngest age group born in the years 1971-80.

The strength of our study is the use of a stable and homogeneous population. The sample was randomly selected from the National Registry of Iceland and represented the nation as a whole in selected age groups. Only a minority of IBS patients seek medical care and population-based studies are therefore essential for studying IBS. The population of Iceland was around 300 thousand inhabitants at the time of the study and the sample was $\approx 1\%$ of the whole population from all around the country. Extensive use of health care by IBS subjects is well established [27-29] and the present study confirms this. Clinical overlap and transition of IBS to heartburn and functional dyspepsia is common [30, 31] and confirmed by our study.

There are some limitations to our study. The subjects were not specifically interviewed or examined to evaluate the possibility of organic disease. However, the 10-year (postal) follow up went some way to making an organic cause of symptoms unlikely. Furthermore, since the response rate was 66.8% in 1996 and 68.9% in 2006, a dropout bias cannot be excluded. A similar mean age in the respondent group and the non-respondent group does not indicate an age dropout bias in the study, but a significantly larger proportion of women responded again in 2006, which may indicate a gender bias.

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Paper V

Irritable Bowel Syndrome: Physician's awareness and patient's experience

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ABSTRACT

AIM: To study if and how physicians use the IBS diagnostic criteria and to assess treatment strategies among physicians in IBS patients.

METHOD: A questionnaire was sent to 191 physicians regarding IBS criteria, diagnostic methods and treatment. Furthermore, 94 subjects who were diagnosed with IBS underwent telephone interview.

RESULTS:

A total of 80/191 (41.9%) physicians responded to the survey. Overall 13 subjects were diagnosed monthly with IBS by specialists in gastroenterology (SG) and 2.5 subjects by physicians in general practice (GP). All the SGs knew of criteria to diagnose IBS and 46/70 (65.7%) of the GPs. 79% used the patient's history, 38% used a physical examination and 38% exclusion of other diseases to diagnose IBS. Only 18/80 (22.5%) of all physicians used specific IBS criteria.

Of the subjects interviewed, 59/94 (62.8%) knew they had experienced IBS. Two out of five subjects knew IBS and had seen a physician because of IBS symptoms. Half of those received the diagnoses of IBS. A total of 13% were satisfied with treatment. IBS affected daily activities in 43% cases.

CONCLUSION: Approximately half of the IBS subjects seeking physician receive the diagnoses of IBS. The knowledge of IBS seems to be very limited among IBS subjects. Awareness and knowledge of diagnostic criteria for IBS differ between SGs and GPs. More widespread use of the diagnostic criteria among physicians would lead to more accurate diagnosis of IBS.

Key Words: *Irritable bowel syndrome, questionnaire study, diagnostic criteria, Manning criteria, Rome criteria, physician's knowledge*

INTRODUCTION

Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder. The prevalence of IBS is estimated to range from 3% to 28% depending on the country studied (Drossman DA, 1993; Talley, 1999; Hungin APS, 2003; Akhter AJ, 2006). The prevalence of IBS in the Western countries is estimated to be 10-15% (Hungin APS, 2003). However, ascertaining prevalence is based on various approaches in studies using different diagnostic criteria.

The criteria that have been used to identify IBS patients are the Manning criteria (Manning AP, 1978), Rome I (Drossman DA, 1994), Rome II (Thompson WG, 1999) and the most recent Rome III criteria (Douglas A. Drossman, 2006; Drossman, 2006). The Rome criteria are more refined than the Manning criteria and include the duration of symptoms as part of the definition of IBS (Hungin APS, 2005). Studies have also shown that the Manning criteria are relatively sensitive but lack specificity (Fass R, 2001). (Table I)

It has been questioned whether the Rome criteria are sensitive enough to diagnose patients in general practice. The current lack of interest in these criteria, especially among GPs, is unlikely to change unless they can be considerably improved (Lea R, 2004). The challenges and uncertainties for diagnosis of IBS have been listed as follows (Spiegel, 2007; Spiegel BM, 2010):

- (1) There is currently no consistent biological marker of IBS, leaving clinicians to rely on patient symptoms alone to make the diagnosis
- (2) The symptoms of IBS are often difficult to quantify objectively
- (3) Symptoms can vary among individuals with IBS
- (4) Many organic conditions can masquerade as IBS

With these uncertainties many physicians approach IBS as a diagnosis of exclusion (Spiegel BM, 2010). A recent study concluded that: (i) the best practise diagnostic guidelines have not been uniformly adopted in IBS, particularly among primary care providers; (ii) most community providers believe IBS is a diagnosis of

exclusion (this belief is associated with increased diagnostic resource use); and (iii) despite the dissemination of guidelines regarding diagnostic testing in IBS, there remains extreme variation in beliefs among both experts and non-experts (Spiegel BM, 2010).

Patients diagnosed with IBS exhibit a higher use of outpatient visits, inpatient stays, outpatient prescriptions and number of hospitalizations than those not diagnosed with IBS (Eisen GM, 2000; Ganguly R, 2001; Longstreth GF, 2003). A recent study showed that knowledge and use of the Rome criteria or their positive predictive values for IBS did not correlate with reduced use of diagnostic tests (Charapata C, 2006). The cost for outpatient visits, drugs and diagnostic testing has been shown to be 51% higher for IBS patients than for others (Eisen GM, 2000; Ganguly R, 2001; Longstreth GF, 2003). IBS subjects have shown to lose time from work more often than others and are less productive while at work (Hulisz, 2004). This may reflect the morbidity in this relatively benign disorder, although up to 70% of IBS patients in the United States do not consult a health care provider regarding their symptoms (Drossman DA, 2002). IBS patients are often reluctant to consult a physician, often because they think their symptoms do not warrant a visit to a physician or are afraid that they have a serious life-threatening illness (Hungin APS, 2003; Hulisz, 2004). US family practitioners have attitudes about IBS patients which include difficulties in satisfying patients and difficulties in making a strategy decision and finding the time required, and their lack of knowledge could interfere with patient care (Longstreth GF, 2003). No specific treatment options for IBS are available. In clinical practice the decision as to treatment is up to the discretion of the physician (Hulisz, 2004). While some physicians recommend lifestyle modification or trials with OTC (over the counter) products, others recommend antispasmodics and antidepressants.

In our study we aimed to analyze IBS from the physician's and the IBS patient's point of view. The specific aims of this study were the following:

(A) *The physician study*, to assess if and how physicians (general practitioners - GPs, specialists in gastroenterology - SGs): (i) use the diagnostic criteria to identify IBS; (ii)

diagnose patients with IBS, and which symptoms of IBS they identify; and (iii) which treatment they recommended.

(B) *The patient study*, to assess how subjects with IBS based on criteria are diagnosed and treated by physicians and which treatment they received, as well as studying the ideas the subjects have of IBS.

MATERIAL AND METHODS

The patient study

Participants and setting

In 1996 an epidemiological study of gastrointestinal diseases was performed in Iceland (Ólafsdóttir LB, 2005). Involved were 2000 inhabitants in the age range of 18-75 years. The individuals were randomly selected from the National Registry. Equal distribution of sex and age was secured in each age group. In 2006 we attempted to contact all the individuals from 1996 as well as adding 300 new individuals in the age group of 18-27 years of age who were also randomly selected from the National Registry of Iceland. A questionnaire was mailed to individuals at baseline and the study questionnaire and an explanatory letter mailed to all eligible individuals. Reminder letters were mailed at 2, 4, and 7 weeks, using the Total Method of Dillman (Dillman, 1978). Individuals who indicated at any point that they did not want to participate in the study were not contacted further.

The questionnaire

The Bowel Disease Questionnaire (BDQ) (Talley NJ, 1989; Nicholas J. Talley, 1990) was translated from English into Icelandic and modified for this study. The questionnaire was translated by two gastroenterologists and a pharmacist. A specialist in the Icelandic language at the University of Iceland made a linguistic modification. The questionnaire was piloted within a small group of IBS patients diagnosed by gastroenterologist. The questionnaire was designed as a self-report instrument to measure symptoms experienced over the previous year and to collect the participant's past medical history (Halder SLS, 2007).

The Icelandic version of the BDQ questionnaire addressed 47 gastrointestinal symptoms and 32 items that measure past illness, health care use, and sociodemographic and psychosomatic symptoms, together with a valid measure of non-GI somatic complaints, the Somatic Symptom Checklist (SSC) (Attanasio V, 1984). The SSC consists of 12 non-GI and 5 GI symptoms or illnesses. Individuals are instructed to indicate, on a 5-point scale, how often each symptom appears and how bothersome it is. There were only a few changes in the 2006 questionnaire which addressed 51 gastrointestinal symptoms and 33 items that measure past illness, health care use, and sociodemographic and psychosomatic symptoms. The 2006 questionnaire furthermore addressed 17 items to identify heartburn and symptoms related to heartburn.

Telephone survey

In the questionnaire subjects were asked to write down their telephone number and give their permission to participate in a telephone survey. Subjects who were diagnosed with IBS based on the Manning criteria and/or the Rome III criteria and had written down their telephone number were called and interviewed.

Physician study

In Iceland (population approximately 300,000) there are 177 physicians working in general practice (GP) and 17 specialists in gastroenterology (SG) (3 physicians who were involved in carrying out this study were excluded). A questionnaire was sent to these 191 physicians regarding awareness and application of the 3 sets of criteria used to diagnose IBS (table I) as well as diagnostic methods and treatment of this disorder. We assessed the knowledge of validated symptom-based criteria for IBS.

Statistical Analysis

Tables were constructed for frequency and percentage. Categorical data were analyzed using the χ^2 test (Chi square test). The type I error protection rate was set at 0.05. The exact p is listed in the tables and text. All the research data were imported into SPSS (Statistical Package of Social Science) software

Manning

Pain eased after BM
Looser stools at onset of pain
More frequent BM at onset of pain
Abdominal distension
Mucus per rectum
Feeling of incomplete emptying

Rome I criteria

Three months or more of continuous or recurrent symptoms

- Abdominal pain or discomfort
 - Relieved with defecation; and/or
 - Associated with a change in frequency of stool; and/or
 - Associated with a change in consistency of stool; and
- Two or more of the following, at least 25% of occasions or days
 - Altered stool frequency (>3 BMs per day or <3 per week)
 - Altered stool form (lumpy/hard or loose/watery stool),
 - Altered stool passage (straining, urgency, tenesmus)
 - Passage of mucus
 - Bloating or feeling of abdominal distension

Rome II criteria

At least 12 weeks (which need not be consecutive)
in the preceding 12 months, of abdominal discomfort or
pain that has two out of three features

- Relieved with defecation; and/or
- Onset associated with a change in frequency of stool, and/or
- Onset associated with a change in form (appearance) of stool

Rome III criteria

Recurrent abdominal pain or discomfort at least 3 days/month
in the last 3 months association with
two or more of the following:
Improvement with defecation
Onset associated with a change in frequency of stool
Onset associated with a change in form (appearance) of stool

BM, bowel movements.

Table I. Manning, Rome I, II and Rome III criteria for irritable bowel syndrome(Manning AP, 1978; Drossman DA, 1994; Thompson WG, 1999; Drossman DA, 2006).

Ethics

The National Bioethics Committee of Iceland and The Icelandic Data Protection Authority (Personuvernd) gave their permission for the research.

RESULTS

The patient study

A total of 94 subjects underwent telephone interview (29.8% male, 70.2% female) with a mean age of 47 years. Of these, all subjects had IBS according to the Manning criteria and 56.0% according to the Rome III criteria (the Rome III criteria being more refined and stricter than Manning criteria). When subjects were asked if they had experienced IBS (self assessed), 62.8% reported yes and 21.3% said they had received an IBS diagnosis from a physician, 60% of these had a Rome III-based diagnosis, and 100% had a Manning-based diagnosis.

Table II. Interviewer-diagnosed subjects; awareness of the disorder, the diagnoses and treatment

	All subjects n=94 % (n)
Diagnosed with IBS	22.2 (20)
Knowledge of IBS	39.4 (37)
Seen a physician because of IBS symptoms	39.4 (37)
Satisfied with treatment for IBS	12.8 (12)
IBS affects daily activities	42.6 (40)
Think they will be cured of IBS	30.9 (29)
Think they will always suffer from IBS	28.7 (27)
Takes medication for IBS	11.7 (11)
Uses untraditional medication	16.0 (15)
Thinks dietary modification is important for the treatment of IBS	55.3 (52)

Table II shows the awareness of IBS. Two out of five subjects had heard of IBS and the same number had seen a physician because of IBS symptoms but only half of those had received a diagnosis of IBS. Only 12/94 (12.8%) of IBS subjects were satisfied with the treatment they had been given. IBS did affect daily activities in approximately 43% of the

cases. One third of the IBS subjects thought they would be cured of IBS but a similar proportion thought they would always suffer from IBS (Table II). IBS subjects were found to use more untraditional medication than prescribed drugs. More than half of subjects believed that dietary modification is important for the treatment of IBS.

Three out of five IBS subjects were diagnosed by a gastroenterologist and two out of five by general practitioners. Most IBS subjects reported abdominal pain (73.7%), bloating (21.1%), constipation (5.3%) and diarrhoea (10.5%) as the symptom that led to the diagnosis. More than half (57.9%) of the IBS subjects who received management for their IBS symptoms were satisfied.

The physician study

An anonymous questionnaire was sent to a total of 191 physicians in Iceland in the fields of primary care or SG (excluding 3 physicians involved in carrying out this study). A total of 80 physicians (41.9%) replied (83% male, 17% female) and completed the questionnaire. Of those who answered, 70 of 175 were GPs and 9 of 15 were SGs.

On average 13 subjects were estimated to be diagnosed with IBS monthly by SGs and 2.5 subjects by GPs.

Physicians reported how they diagnosed subjects with IBS in table III.

Table III. Diagnoses of subjects with IBS

	All subjects (%) n=80*	SG (%) n=9	GP (%) n=70
Patients history	79%	78%	80%
Physical examination	38%	22%	41
Exclusion of other diseases	38%	44%	35%
IBS criteria	22%	33%	19%
GI endoscopy	7%	22%	6%

* One physician did not list his profession

Two thirds of all the physicians knew that special diagnostic criteria exist for defining and diagnosing IBS (Figure 1).

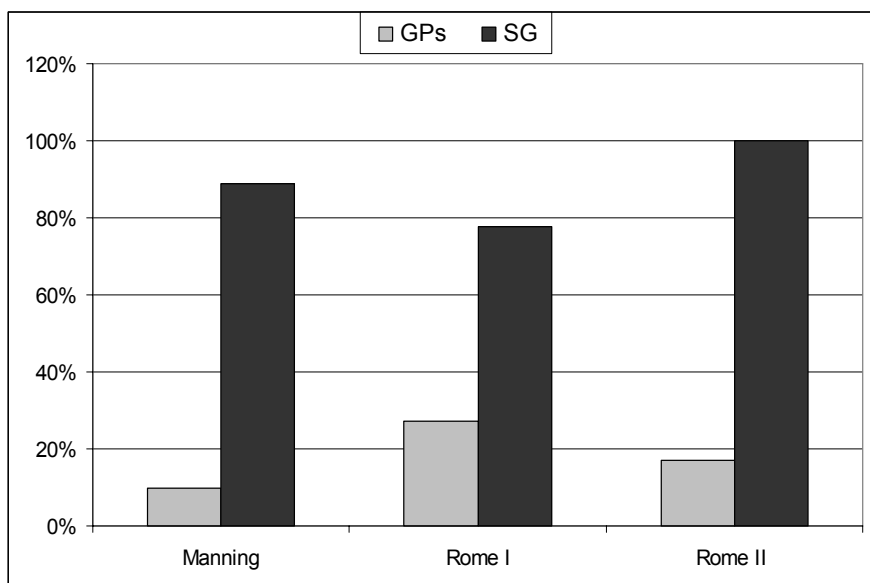


Figure 1. Number of physicians knowing about each set of diagnostic criteria (%)

When physicians were asked if they knew of the IBS diagnostic criteria, 71% said yes (64% of GPs, 100% of SGs). Despite the fact that 64% of GPs claimed they knew that diagnostic criteria existed only 10% had heard of the Manning criteria, 27% of Rome I, and 17% of Rome II (Figure 1).

Physicians stated that abnormal bowel movements such as diarrhoea and constipation, abdominal pain and bloating as the most commonly reported symptoms of IBS (Table IV).

Table IV. The most common IBS symptoms reported

	GPs	SG
Abnormal bowel movements	61%	100%
Abdominal pain	86%	67%

Bloating	20%	56%
Gas	9%	11%
Passage of mucus	5%	0%
Incomplete evacuation with defecation	5%	11%

Physicians reported in most cases that they would give advice on diet and education about IBS as a treatment for IBS symptoms. Both GPs and SGs gave their patients mebeverinum in most cases. Psyllium was frequently used by SGs and chlordiazepoxide, and clidinium was in some cases used by both GPs and SGs (Table V).

Table V. Treatment of IBS.

	GPs	SG
Medication		
Mebeverinum	89%	86%
Husk	31%	43%
Chlordiazepoxide and clidinium	29%	14%
Antidepressants	7%	14%
Other medicines	9%	14%
Lifestyle		
Food	98%	86%
Relaxation	14%	14%
Exercise	16%	14%
Education about IBS	90%	86%
Do not know/something else	27%	14%

DISCUSSION

Most physicians have used the method of exclusion when diagnosing patients with IBS. Most community providers also believe IBS is a diagnosis of exclusion rather than using positive criteria to support the diagnosis (Spiegel BM, 2010). This approach – or lack of one - has therefore been time consuming and costly for the health care system. The importance of a precise diagnostic tool to diagnose IBS is therefore very important. In recent years the development of diagnostic criteria for IBS has been ongoing, leading to the introduction recently of the Rome III criteria. There is no doubt that diagnostic criteria constitute a useful and important tool to help physicians make a positive diagnosis of IBS without resorting simply to excluding other diseases. This study has revealed the proportion of Icelandic physicians in two fields of medicine that are aware of the criteria for diagnosing the disease. The study has addressed not only the question of how informed physicians are of the criteria for diagnosing IBS but also the importance of consensus about the diagnosis of the disease. This study has also addressed the IBS patient's perspective, how many sought physicians and how they experienced the disease.

According to the results of this study, most IBS patients were seen by GPs, and this is most likely also the case in other countries, underlining the importance of awareness and knowledge of IBS on the part of the GPs. Although 64% of all GPs reported that they were aware of the fact that special criteria to identify IBS existed, most of them (81%) did not know the criteria and therefore did not rely on them in practice. Most of them seem to make a positive diagnosis of IBS without the use of endoscopy. A US study showed that only 30% of family practitioners knew that the Manning, Rome and Rome II criteria are used to diagnose IBS which is in line with the results of the current study (Longstreth GF, 2003). GPs are more likely than hospital specialists to perceive functional gastrointestinal disorders as having a psychological basis, are far less likely to be familiar with diagnostic criteria, and are more likely to use other methods to make such diagnoses (Gladman LM, 2003). However, physicians are aware of and use the most common IBS symptoms such as abnormal bowel movements, abdominal pain and bloating in their diagnostic approach, and these were the most common symptoms IBS subjects in the present study.

In the current study, physicians reported in most cases that they gave advice on diet and education on IBS as a treatment of IBS symptoms; this finding underlines the importance of providing reliable and useful information on IBS to patients, as well as the fact that there are no specific treatment options for IBS that is useful for all patients.

It is of interest that among interviewer- diagnosed IBS subjects, only one out of five was diagnosed with IBS even though more than half of the IBS subjects saw a physician because of IBS symptoms. These results were irrespective of whether the subjects fulfilled the Manning or Rome III criteria for IBS. This was also interesting because the majority of IBS subjects reported that IBS affected daily activities. This stresses the question whether IBS subjects reveal to the physicians the low quality of life caused by IBS. It is also conceivable that physicians do not recognize IBS as a disorder that leads to impaired quality of life. The absence of positive diagnosis of IBS might lead to lack of relevant treatment for specific symptoms of IBS such as abdominal pain. There is a need for a simple, practical and reliable diagnostic tool to be used in everyday clinical practice to more accurately diagnose IBS, a tool which will encourage physicians to be able to make a reliable diagnosis and to provide effective treatment (JR, 2005; Quigley EMM, 2006).

The limitation of this study was the relatively low response rate in the physician study, which raises the question as to whether the level of awareness and knowledge of diagnostic criteria might be even lower than the result obtained. The strength of the study, however, was that all physicians in Iceland in the relevant fields of general practice and gastroenterology were invited to participate in the study and was also enhanced by the fact that all IBS subjects who were contacted by telephone participated in the telephone survey.

CONCLUSION

In this study, only half of the IBS subjects who saw a physician received a diagnosis of IBS. The knowledge of IBS is limited among IBS subjects. This study suggests that few

physicians use IBS criteria and that the awareness and knowledge of the diagnostic criteria for IBS differed between SGs on the one hand and GPs on the other hand. One out of four physicians used a diagnosis of exclusion.

More widespread knowledge and use of the diagnostic criteria among physicians can be expected to support a more accurate diagnosis of IBS.

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Competing interests: None.

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Paper VI

Natural history of irritable bowel syndrome in women and dysmenorrhea: A 10-year follow up study

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ABSTRACT

Background: Studies have shown that women are more likely to have IBS and more women seek healthcare because of IBS than men.

Aim: The primary objective of our study was to study the natural history of IBS and dysmenorrhea in women over a 10 year period. The secondary objective was to assess the change in IBS after menopause.

Method: A population-based postal study. A questionnaire was mailed to the same age- and gender-stratified random sample of the Icelandic population aged 18-75 in 1996 and again in 2006.

Results: A total of 254/331 (77 %) premenopausal women had dysmenorrhea in the year 1996 and 74 % in the year 2006. Overall 105/254 (42 %) of women with dysmenorrhea had IBS according to Manning criteria in the year 2006 and 49 % 1996. A total of 39/152 (26 %) of women with dysmenorrhea had IBS according to Rome III 2006 and 11 % in the year 1996. In 2006 46/152 (30 %) women had severe or very severe dysmenorrhea pain severity. Altogether 45/57 (79 %) of those who had FD and 72/80 who had heartburn had dysmenorrhea and 88 % of those who had diarrhea and/or constipation ($p < 0.01$). More women 8/31 (27 %) reported severe abdominal pain after menopause than before menopause 11 %. Women without dysmenorrhea were twice as likely to remain asymptomatic than the women with dysmenorrhea. Women with dysmenorrhea were more likely to have stable symptoms and were twice more likely to have increased symptoms.

Conclusion: Women with IBS are more likely to experience dysmenorrhea than women without IBS which seems to be a part of the symptomatology in most women with IBS. IBS symptom severity seems to increase after menopause.

Key Words:. *Irritable bowel syndrome, functional gastrointestinal disorders, menstruation pain, follow up, questionnaire study, epidemiology,*

INTRODUCTION

In the Western countries more women than men seek health-care services for Irritable bowel syndrome (IBS)(Chial HJ, 2002; Heitkemper M, 2008). This can possibly be explained by factors involving physiological gender differences in gonadal hormones, stress reactivity, and inflammatory responses, as well as sociocultural differences in response to pain and/or bowel pattern changes (Heitkemper M, 2008). A recent study of men and women with IBS, the gender differences found were more complicated than a simple ratio of men:women(Herman J, 2010). Women with IBS report more constipation, nausea, bloating and extraintestinal and psychological symptoms than men with IBS(Chang L, 2002). Gender-related differences in gastrointestinal and somatic symptoms are apparent in persons with IBS but are most prominent in postmenopausal women(Cain KC, 2009). Abdominal pain has been shown to be the most disruptive symptom in IBS and impacts on the quality of life in women with IBS(Cain KC, 2006). The differences between genders in the occurrence of IBS could furthermore be the result of cultural, psychosocial, or healthcare access issues instead of purely physiologic differences(Heitkemper MM, 2008).

Population-based studies are essential for studying IBS since only a minority of IBS patients seek medical care (Penston JG, 1996). Self-medication is common among these patients (Penston JG, 1996) and differences have been noted in IBS patients and non-patients from the community (El-Serag HB, 2004; Jones R, 1992). The great majority of IBS studies are patient or healthcare based. Women overall have a greater prevalence of IBS symptoms than men, particularly those associated with constipation(Adeyemo MA, 2010). Studies suggest that female sex hormones influence the severity of IBS symptoms (Adeyemo MA, 2010). A recent study suggest that an increase in gastrointestinal symptoms around the time of menses and early menopause occurs at times of declining or low ovarian hormones, suggesting that estrogen and progesterone withdrawal may contribute either directly or indirectly(Heitkemper MM, 2009).

The objective of our study was to study the natural history of IBS and dysmenorrhea in women over a 10 year period. The secondary objective was to assess the change in IBS over menopause and the birth cohort effect of dysmenorrhea.

METHODS

Participants and setting

In 1996 an epidemiological study of gastrointestinal diseases was performed in Iceland (Ólafsdóttir LB, 2005). Involved were 2000 inhabitants in the age range of 18-75 years. The individuals were randomly selected from the National Registry. Equal distribution of sex and age was secured in each age group. In 2006 we attempted to contact all the individuals from 1996 as well as adding 300 new individuals in the age group of 18-27 years of age who were randomly selected from the National Registry of Iceland. A questionnaire was mailed to individuals at baseline and the study questionnaire and an explanatory letter mailed to all eligible individuals. Reminder letters were mailed at 2, 4, and 7 weeks, using the Total Method of Dillman (Dillman, 1978). Individuals who indicated at any point that they did not want to participate in the study were not contacted further.

The questionnaire

The Bowel Disease Questionnaire (BDQ) (Nicholas J. Talley, 1990; Talley NJ, 1989) was translated from English into Icelandic and modified for this study. The questionnaire was translated by two gastroenterologists and a pharmacist. A specialist in the Icelandic language at the University of Iceland made a linguistic modification. The questionnaire was piloted within a small group of IBS patients diagnosed by gastroenterologist. The questionnaire was designed as a self-report instrument to measure symptoms experienced over the previous year and to collect the participant's past medical history (Halder SLS, 2007).

The Icelandic version of the BDQ questionnaire addressed 47 gastrointestinal symptoms and 32 items that measure past illness, health care use, and sociodemographic and psychosomatic symptoms, together with a valid measure of non-GI somatic complaints,

the Somatic Symptom Checklist (SSC) (Attanasio V, 1984). The SSC consists of 12 non-GI and 5 GI symptoms or illnesses. Individuals are instructed to indicate, on a 5-point scale, how often each symptom appears and how bothersome it is. There were only a few changes in the latter questionnaire (2006) which addressed 51 gastrointestinal symptoms and 33 items that measure past illness, health care use, and sociodemographic and psychosomatic symptoms.

Criteria to identify dysmenorrhea

Women were asked if they experienced dysmenorrhea in the beginning of their menstruation. Those who had dysmenorrhea were asked to state the magnitude of the pain; minor pain, medium pain, severe pain, very severe pain and no pain. Those who did not have menstruations were excluded.

Criteria to identify IBS

The criteria for identification of IBS are presented in table I.

Diagnosis of IBS according to the Manning criteria (Manning AP, 1978) required two or more of the six symptoms listed in table I and abdominal pain six or more times during the previous year (Drossman, 1989; Talley NJ, 1991).

Transition between disorders from the initial to the final survey

A transition model used by Halder et al. was modified and applied for this study (Halder SLS, 2007). The responses from the initial (1996) and final (2006) surveys were matched for each subject to examine the changes between disorders at an individual level for the 6 categories (IBS, FD, heartburn, frequent abdominal pain and no symptoms). A 5 x 5 table was used to model these multiple changes and collapsed into 6 groups, as illustrated in Figure 1 and 2. Those with the most symptoms were prioritized higher. Those who developed more symptoms and those who reported fewer symptoms could be categorised into groups. There were six patterns of symptoms, identified as follows: (1) symptom stability, (2) symptom increase, (3) symptom decrease, (4) symptom onset, (5) becoming asymptomatic, and (6) none of these symptoms.

FGID in 1996	Proportion of FGID in 2006 based on primary survey disorder				
	FD %	IBS %	Heartburn %	Frequent Abd. Pain %	No symptoms
FD (n=29)	62.1	17.2	6.9	0.0	13.8
IBS (n=37)	29.7	29.7	10.8	5.4	24.3
Heartburn (n=22)	22.7	22.7	22.7	4.5	27.3
Frequent Abdominal Pain (n=4)	0.0	25.0	75.0	0.0	0.0
No symptoms (n=38)	7.9	15.8	15.8	5.3	55.3



FGID - Functional Gastrointestinal Disorder

FD - Functional Dyspepsia

IBS - Irritable Bowel Syndrome

Figure 1. Transitions among symptom subgroups between the initial and final surveys.

Women with dysmenorrhea

FGID in 1996	Proportion of FGID in 2006 based on primary survey disorder				
	FD %	IBS %	Heartburn %	Frequent Abd. Pain %	No symptoms
FD (n=18)	44.4	27.8	16.7	5.6	5.6
IBS (n=29)	17.2	37.9	13.8	10.3	20.7
Heartburn (n=26)	7.7	15.4	42.3	11.5	23.1
Frequent Abdominal Pain (n=10)	0.0	30.0	10.0	10.0	50.0
No symptoms (n=80)	1.3	8.8	15.0	7.5	67.5



FGID - Functional Gastrointestinal Disorder
 FD - Functional Dyspepsia
 IBS - Irritable Bowel Syndrome

Figure 2. Transitions among symptom subgroups between the initial and final surveys. Women without dysmenorrhea.

Mortality data

For the 2006 survey we identified all deceased individuals with the assistance of the National Registry of Iceland.

Statistical Analysis

Tables were constructed for frequency and percentage. Categorical data were analysed using the χ^2 test (Chi square test). Type I error protection rate was set at 0.05. The exact p is listed in the tables and text. All the research data were imported into SPSS (Statistical Package of Social Science) software.

Ethics

The National Bioethics Committee of Iceland and The Icelandic Data Protection Authority gave their permission for the research.

RESULTS

Demographic Data of Involved Individuals

In 1996 the response rate was 66.8% (1336/2000). Of the 1336 individuals who participated in 1996, 81 were deceased by 2006, five subjects were unable to answer, mainly because of old age, and 70 could not be traced to a current address. This left 1180 individuals, out of which 799 responded in 2006 (Figure 3). Giving a response rate in 2006 was 68%. The mean age of the individuals in 1996 was 43 and in 2006 53, there was not a significant difference between those who responded 2006 and those who did not respond (NS). Women were more apt to respond than men in both years. A larger proportion of women responded again in 2006 (57.8%) than those who responded in 1996 but did not respond again 2006 (49.8%, $p<0.01$). The responders represented the population concerning sex and age distribution. The response rate was higher for older subjects than younger ones. There was no significant difference between those who responded or those who did not respond in the year 2006, whether they were diagnosed with IBS in the year 1996 or not. Age distribution and demographic details of the study cohort are presented in table II.

Dysmenorrhea (painful menstruation)

Of those women who responded 331 women reported menstruation 1996 and 205 in the year 2006. A total of 254/331 (76.7%) in 1996 and 152/205 (74.1%) in 2006 reported dysmenorrhea (table III). Half of those reported medium severity of dysmenorrhea. Slightly more reported minor dysmenorrhea in the year 1996 than 2006. Slightly more reported severe or very severe dysmenorrhea (figure 4).

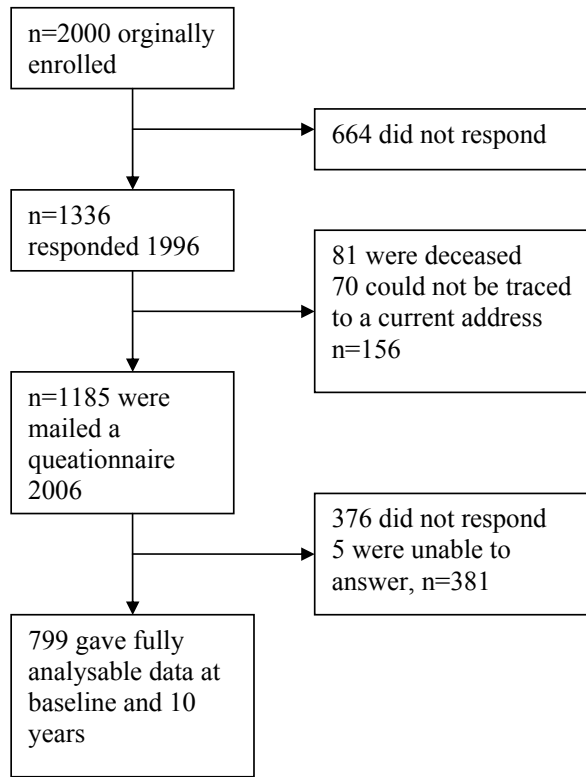


Figure 3. Flow of study participants.

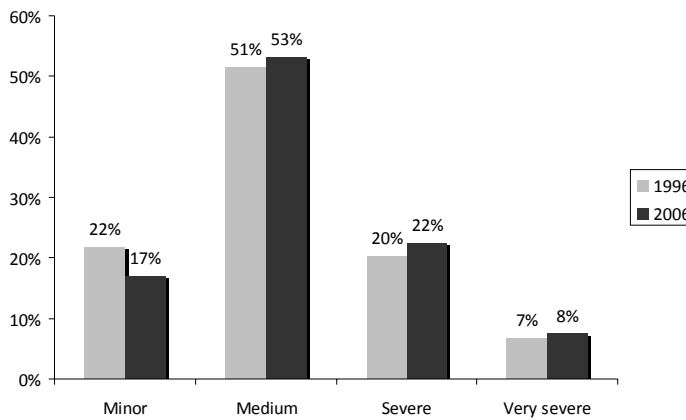


Figure 4. Distribution of dysmenorrhea severity.

Dysmenorrhea and irritable bowel syndrome

One out of ten women with dysmenorrhea had IBS according to Rome III criteria in the year 1996 and 5 % of women without dysmenorrhea had IBS ($p=0.170$) (table IV). A total of 39/152 (26 %) women with dysmenorrhea had IBS according to Rome III in the year 2006 and 14/152 9 % of women without dysmenorrhea had IBS ($p=0.013$). Overall 105/254 (42 %) of women with dysmenorrhea had IBS according to Manning criteria in the year 1996 and 25 % without dysmenorrhea had IBS ($p=0.014$). 49 % of the women in the year 2006 of women with dysmenorrhea had IBS according to Manning and 33 % of women without dysmenorrhea had IBS in the year 2006 ($p=0.063$).

Dysmenorrhea and other functional gastrointestinal disorders

A total of 45/57 (79 %) of those who had functional dyspepsia (FD) and 72/90 (80 %) heartburn had dysmenorrhea and 88% of those who had diarrhea and or constipation had dysmenorrhea (figure 5). Altogether 39% of those who had FD and 41% of those who had diarrhea and/or constipation had severe or very severe dysmenorrhea. There was a significant statistical difference ($p<0.01$) of dysmenorrhea between those who had FD and those who did not have FD. Those who had diarrhea and or constipation had proportionally higher prevalence of dysmenorrhea and those who did not have diarrhea and or constipation ($p<0.01$) , this can be seen in figure 5.

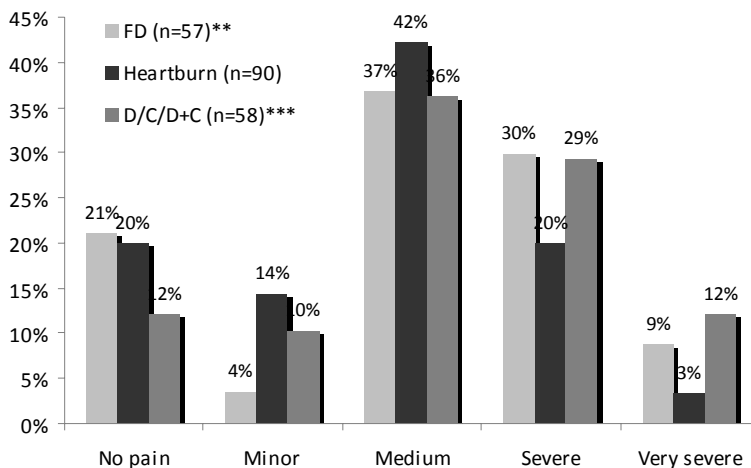


Figure 5. Functional gastrointestinal disorders and dysmenorrhea severity (2006).

Women with dysmenorrhea in 1996 and after menopause 2006, IBS and abdominal pain severity

In the year 1996, overall 64 women experienced dysmenorrhea but did not have periods in the year 2006. In the year 1996, 24/64 (38%) of those had IBS according to Manning criteria and 41% in the year 2006 altogether. 6 % experienced IBS according to Rome III criteria in the year 1996 and 13 % in the year 2006. Figure 6 shows the changes in abdominal pain severity in women with dysmenorrhea in the year 1996 and after menopause in the year 2006.

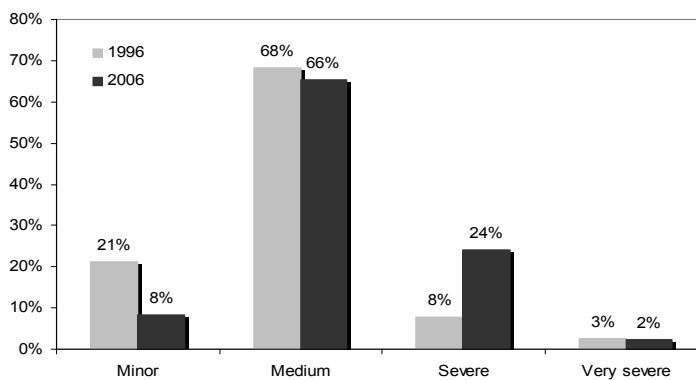


Figure 6. Abdominal pain in women with dysmenorrhea 1996 and after menopause 2006.

Transition between disorders from the 1996 and 2006 surveys

As described in the method section, the groups in this analysis were defined as mutually exclusive, using the symptom hierarchy so that each subject appears in only one category for both the 1996 and 2006 surveys. There was a “no symptoms” category for those who did not meet any of the criteria applied for FGID. Due to the hierarchical classification only a few participants occurred in some categories.

Transitions between disorders were explored in two ways; for women with dysmenorrhea (figure 1) and for women without dysmenorrhea (figure 2). There was a substantial change in proportions in all the categories between the two surveys. The group “no symptoms” was the most common in both transition models. For the women with

dysmenorrhea the FD was the most stable one. A total of 17% moved into the IBS group and 14% into the no symptom group. IBS was stable in 30% cases and the same number moved into the FD group. One fourth moved into the no symptom group. There were only 4 women in the heartburn group of women with dysmenorrhea. In women without dysmenorrhea the stability of symptoms was greater than for those who suffered from dysmenorrhea. A total of 44 % of the FD group was stable between the initial and final surveys. One out of four moved into the IBS group. The stability for the IBS group was 38 %. 5/29 (17 %) moved into the IBS group and 21 % into the no symptom group. The highest stability (42 %) was in the heartburn group.

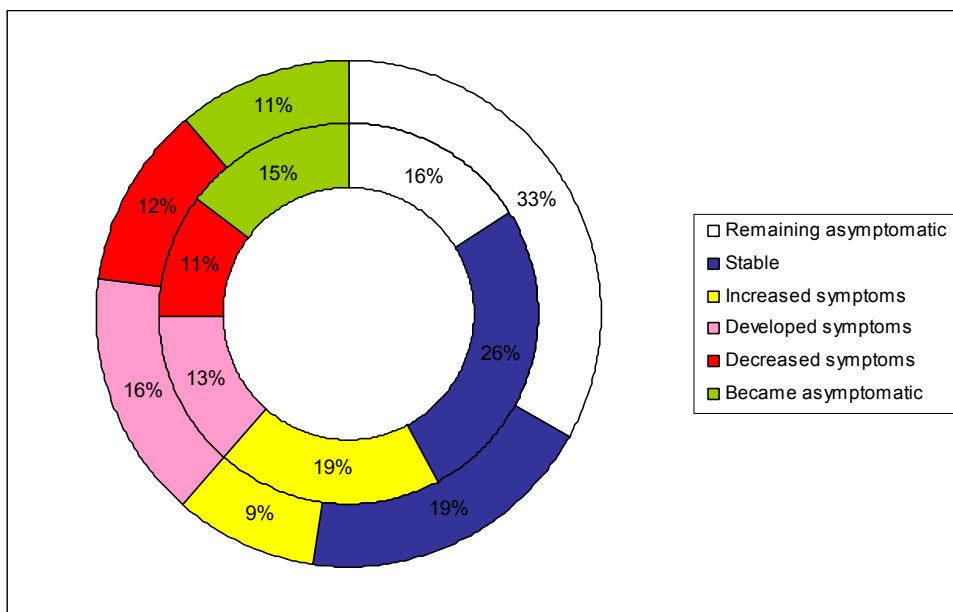


Figure 7. Six-group transition model, change from initial to the final survey. Women with dysmenorrhea (n=130) in the inner circle and Women without dysmenorrhea (n=163) in the outer circle.

The transitions were collected into six groups. Comparison of the differences between women with and without dysmenorrhea in those transition groups (figure 7) showed that the greatest difference was between the two groups of women who remained asymptomatic. The women without dysmenorrhea were twice as likely to remain

asymptomatic than the women with dysmenorrhea. The women with dysmenorrhea were also more likely to have stable symptoms at follow up than women without dysmenorrhea. The women with dysmenorrhea were two times more likely to have increased symptoms than women without symptoms.

Birth cohort effect of dysmenorrhea

There was no significant difference in prevalence between birth cohorts in women with dysmenorrhea nor in women without dysmenorrhea (fig. 8).

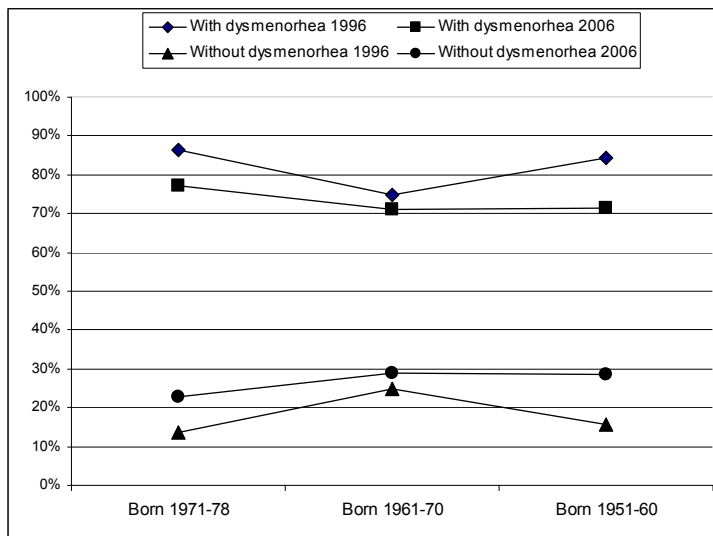


Figure 8. Birth cohort effect on the prevalence (%) in 10-years.

DISCUSSION

The current study makes it possible for the first time to follow up women with and without dysmenorrhea over a ten year period and to observe how the FGID symptoms are associated with the dysmenorrhea. Analysis of women with IBS, either based on the Rome III criteria and/or the Manning criteria, showed that they were more likely to have dysmenorrhea.

A meta-analysis based on a small number of studies compared gastrointestinal symptoms in pre- and post menopause women (Adeyemo MA, 2010). The authors concluded that there was insufficient evidence to determine the effect of menopausal status on IBS

symptoms. The current study demonstrated an increase in prevalence in women having IBS after menopause using both IBS criteria. Increase in gastrointestinal symptoms around the time of menses and early menopause occurs at times of declining or low ovarian hormones, suggesting that estrogen and progesterone withdrawal may contribute either directly or indirectly(Heitkemper MM, 2009). One study has shown that gastrointestinal symptoms burden were higher in postmenopausal women than in men, but these differences mostly disappeared when controlled for age(Cain KC, 2009).

Women with dysmenorrhea report more gastrointestinal symptoms prior to or concurrent with uterine cramping pain at menses than women who are nondysmenorrheic (Kane SV, 1998). Gastrointestinal symptoms tend to be increased across all cycle phases in women with IBS compared to healthy women, but both groups demonstrated a similar increase in severity immediately prior to or at the onset of menses(Heitkemper MM, 2003).

The current study compared the FGIDs and dysmenorrheal severity and demonstrated that the great majority of women with dysmeorrhea had other FGID symptoms than related to IBS. Women reported more severe abdominal pain after menopause than before. One study has shown that abdominal pain is the most disruptive IBS symptom(Cain KC, 2006).

The current study observed the transition between symptoms and revealed substantial difference between women with and without dysmenorrhea. Women without dysmenorrhea remained more often asymptomatic than women with dysmenorrhea. FGID symptoms were more stable in 10 years for women with dysmenorrhea and they also had more increase in symptoms than women without dysmenorrhea. This demonstrated a difference between those two groups of women. The prevalence of menstrually related symptoms has been shown to be high and appears to affect bowel patterns (Kane SV, 1998). A recent meta-analysis revealed a significant menstrual cycle effect for loose stools, bloating, abdominal pain, stool frequency and other changes in bowel habit(Adeyemo MA, 2010).

The strength of our study was the use of a stable and homogeneous population. The sample was randomly selected from the National Registry of Iceland and represented the nation as a whole in selected age groups. Only a minority of IBS patients seek medical care and population-based studies are therefore essential for studying IBS. The population of Iceland with approximately 300 thousand inhabitants represent 1% of the whole population from all around the country.

There are some limitations to our study. The subjects were not specifically interviewed or examined to evaluate the possibility of organic disease. However, the 10-year (postal) follow up went some way to making an organic cause of symptoms unlikely. Furthermore, since the response rate was 67 % in 1996 and 69 % in 2006, a dropout bias cannot be excluded. A similar mean age in the respondent group and the non-respondent group does not indicate an age dropout bias in the study.

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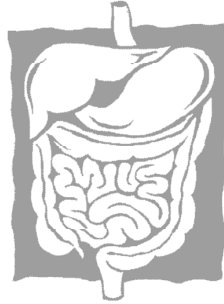
Competing interests: None.

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Appendix I: The Bowel Disease Questionnaire – The Icelandic version



Faraldsfræðileg könnun á meltingarfærakvillum hjá Íslendingum

Linda Björk Ólafsdóttir, lyfjafræðingur

*Hallgrímur Guðjónsson, sérfræðingur
í meltingarlækningum*

*Bjarni Þjóðleifsson, sérfræðingur
í meltingarlækningum*

*Jón Steinar Jónsson, sérfræðingur
í heilsugælsulækningum*



VINSAMLEGAST LESTU ÞETTA VANDLEGA ÁÐUR EN ÞÚ SVARAR SPURNINGUNUM

BRJÓSTSVIÐI er skilgreindur sem brunatilfinning sem á upptök í maga eða neðri hluta brjóstkassa.

NÁBÍTUR er skilgreindur sem súrt bragð sem kemur upp í munn eða kok.

Í byrjun viljum við spyrja þig nokkurra spurninga um verki í maga eða kvið á síðastliðnu ári.

S. 1 Hefur þú fundið fyrir verkjum í maga eða kvið á síðastliðnu ári?

1. ☐ Já
2. ☐ Nei

(Athugaðu að þetta á hvorki við um krampa eða verki tengda tíðablæðingum né verki í brjóstkassa)

Ef svarið er já, svaraðu þá
eftirfarandi spurningum:

Ef þú hefur ekki fundið fyrir verkjum,
vinsamlegast svaraðu næst spurningu 24 á bls. 4.

Erfitt getur verið að lýsa verkjum í maga eða kvið og eru þeir oft af fleiri en einni tegund. Reyndu að hugsa um vanalegan verk eða þann verk sem þú finnur oftast fyrir. Okkur langar til að spyrja þig aðeins um verki sem koma oft fyrir hjá þér og þú þekkir.

S. 2 Hefur þú fundið fyrir sama verknum oftár en sex sinnum á síðastliðnu ári?

1. ☐ Já
2. ☐ Nei

S. 3 Hversu mikill er verkurinn venjulega?

1. ☐ Lítill: Þú getur látið eins og hann sé ekki til staðar, ef þú hugsar ekki um hann.
2. ☐ Meðal: Hefur ekki áhrif á daglegt líf og störf.
3. ☐ Slæmur: Hefur áhrif á daglegt líf og störf.
4. ☐ Mjög slæmur: Hefur mikil áhrif á daglegt líf og störf.

S. 4 Verkir geta verið mismunandi staðsettir, fyrir neðan nafla, fyrir ofan nafla eða hvort tveggja, það er bæði fyrir ofan og neðan nafla.

Hefur verkurinn vanalega verið:

1. ☐ Fyrir ofan nafla, í efri hluta kviðarhols?
2. ☐ Fyrir neðan nafla, í neðri hluta kviðarhols?
3. ☐ Á mismunandi stöðum, bæði í efri og neðri hluta kviðarhols?

S. 5 Vaknar þú upp á nótunni við þennan verk?

1. ☐ Já
2. ☐ Nei

S. 6 Kemur verkurinn og fer yfir ákveðið tímabil? Þegar talað er um tímabil er átt við verki sem ekki eru til staðar í að minnsta kosti mánuð, en eru þess á milli til staðar samfellt í vikur eða mánuði.

1. ☐ Já
2. ☐ Nei

S. 7 Hversu oft fékkst þú verki í maga eða kvið?

1. ☐ Sjaldnar en einu sinni í mánuði
2. ☐ Um það bil einu sinni í mánuði
3. ☐ Um það bil einu sinni í viku
4. ☐ Oft í viku
5. ☐ Daglega

S. 8 Þegar þessi verkur er til staðar, hversu lengi varir hann?

1. ☐ Skemur en 30 mínútur
2. ☐ 30 mínútur til 2 klst.
3. ☐ 2 klst. til 6 klst.
4. ☐ Lengur en 6 klst.

S. 9 Hvenær fékkst þú fyrst þennan verk?

1. ☐ Á síðustu 6 mánuðum
2. ☐ Frá 7 til 12 mánuðum síðan
3. ☐ Lengra en 1 ár og skemur en 2 ár síðan
4. ☐ Lengra en 2 ár og skemur en 5 ár síðan
5. ☐ Lengra en 5 ár og skemur en 10 ár síðan
6. ☐ Lengra en 10 ár og skemur en 20 ár síðan
7. ☐ Lengra en 20 ár síðan

S. 10 Kemur þessi verkur fyrir máltíð eða þegar þú eru svangur/svöng?

1. ☐ Já
2. ☐ Nei

S. 11 Kemur verkurinn strax eftir máltíð (innan 30 mín.)?

1. ☐ Já
2. ☐ Nei

Vinsamlegast athugaðu að þegar við eigum við oft þá eigum við við meira en 25% tilvika.

S. 12 Kemur verkurinn oft fram eftir 30 mínútur en innan 2 klst. frá máltíð?

1. ☐ Já
2. ☐ Nei

S. 13 Minnkar verkurinn oft við það að ropa?

1. ☐ Já
2. ☐ Nei

S. 14 Minnkar verkurinn oft við það að hafa hægðir?

1. ☐ Já
2. ☐ Nei

S. 15 Minnkar verkurinn oft við það að borða?

1. ☐ Já
2. ☐ Nei

S. 16 Minnkar verkurinn oft við það að taka inn sýrubindandi lyf eða magamjólk (svo sem Alminox, Balancid, Natriumbikarbonat, Novalucid, Rennie)?

1. ☐ Já
2. ☐ Nei
3. ☐ Hef ekki tekið inn sýrubindandi lyf eða magamjólk

S. 17 Minnkar verkurinn oft við að taka inn histamínblokkandi lyf (svo sem Asýran, Gastran, Cytotec, Zantac)?

1. ☐ Já
2. ☐ Nei
3. ☐ Hef ekki tekið inn histamínblokkandi lyf

S. 18 Minnkar verkurinn ef þú tekur inn prótónupumpablokka (svo sem Lanser, Lanzo, Losec, Lómex, Nexíum, Pariet)?

1. ☐ Já
2. ☐ Nei
3. ☐ Hef ekki tekið inn prótónupumpablokka

S. 19 Eykst verkurinn oft ef þú drekkur bjór, vín eða annað áfengi?

1. ☐ Já
2. ☐ Nei

S. 20 Færist verkurinn oft á aðra staði fyrir utan kviðinn?

1. ☐ Já
2. ☐ Nei

S. 21 Hefur þú tíðar hægðir samfara verkjum í kvið eða maga?

1. ☐ Já
2. ☐ Nei

S. 22 Hefur þú linar hægðir (niðurgang) samfara kviðverkjum?

1. ☐ Já
2. ☐ Nei

S.23 Hefur þú tólf vikna sögu eða meir á seinustu 12 mánuðum um óþægindi í kviðarholi eða verki sem einkennast af eftirfarandi: (krossaðu við það sem á við um þig)

1. ☐ Lagast við að hafa hægðir
2. ☐ Tengist breytingum á tíðni hægða
3. ☐ Tengist breytingum á þéttleika hægða

Einn mikilvægur hluti þessa verkefnis er að kanna hægðavenjur almennings á síðastliðnu ári.

S. 24 Hafa hægðir þínar breyst á síðastliðnu ári?

1. ☐ Já
2. ☐ Nei

S. 25 Hvernig myndir þú lýsa hægðum þínum eins og þær voru á síðastliðnu ári?

1. ☐ Eðlilegar
2. ☐ Hægðatregða
3. ☐ Niðurgangur
4. ☐ Hægðatregða og niðurgangur til skiptis

S.26 Hversu oft hefur þú venjulega hægðir á einni viku?

1. ☐ 1 skipti eða sjaldnar
2. ☐ 2 skipti
3. ☐ 3-4 skipti
4. ☐ 5-8 skipti
5. ☐ 9-12 skipti
6. ☐ 13-16 skipti
7. ☐ 17-21 skipti
8. ☐ 22-26 skipti
9. ☐ Oftar en 26 skipti

S. 27 Tekur þú inn eitthvað (svo sem trefjar, hörfræ, laxerandi) vegna hægðatregðu?

1. ☐ Já
2. ☐ Nei

S. 28 Hefur þú orðið var/vör við slím í hægðum á síðastliðnu ári?

1. ☐ Já
2. ☐ Nei

S. 29 Hefur þú oft hægðir sjaldnar en þrisvar sinnum í viku?

1. ☐ Já
2. ☐ Nei

Vinsamlegast athugaðu að þegar við segjum oft þá eigum við við meira en 25% tilvika.

S. 30 Hefur þú oft hægðir oftari en þrisvar sinnum á dag?

1. ☐ Já
2. ☐ Nei

S. 31 Þarft þú oft að rembast mikið þegar þú hefur hægðir?

1. ☐ Já
2. ☐ Nei

S. 32 Eru hægðir þínar oft lausar eða vatnskenndar?

1. ☐ Já
2. ☐ Nei

S. 33 Eru hægðir þínar oft harðar?

1. ☐ Já
2. ☐ Nei

S. 34 Finnst þér þú hafa ófullkomna hægðalosun, þ.e. erfitt að tæma fullkomlega?

1. ☐ Já
2. ☐ Nei

S. 35 Upplifir þú oft skyndilega þörf til að hafa hægðir, þannig að þú þurfir að flýta þér á salernið?

1. ☐ Já
2. ☐ Nei

S. 36 Hefur þú orðið var/vör við blóð í hægðunum á síðastliðnu ári?

1. ☐ Já
2. ☐ Nei

**Ef S.36 er svarað játandi,
svaraðu þá S. 37 til S. 38**

Ef S. 36 er svarað neitandi svaraðu þá næst S. 40

S. 37 Umlykur blóðið hægðirnar?

1. ☐ Já
2. ☐ Nei

S. 38 Er blóðið dökkt og blandað hægðunum?

1. ☐ Já
2. ☐ Nei

S. 39 Er blóðið á salernispappírnum?

1. ☐ Já
2. ☐ Nei

Athugaðu hvort öllum spurningunum sem eiga við þig hafi verið svarað.

Næst viljum við spyrja þig um önnur einkenni.

S. 40 Hversu oft hefur þú fundið fyrir þörf til að kasta upp á síðastliðnu ári?

0. ☐ Aldrei
1. ☐ Sjaldnar en einu sinni í mánuði
2. ☐ Um það bil einu sinni í mánuði
3. ☐ Um það bil einu sinni í viku
4. ☐ Nokkrum sinnum í viku
5. ☐ Daglega

S. 41 Hversu oft hefur þú kastað upp á síðastliðnu ári?

0. ☐ Aldrei
1. ☐ Sjaldnar en einu sinni í mánuði
2. ☐ Um það bil einu sinni í mánuði
3. ☐ Um það bil einu sinni í viku
4. ☐ Nokkrum sinnum í viku
5. ☐ Daglega

S. 42 Færðu oft uppþembutilfinningu og sérðu kviðinn þenjast út?

1. ☐ Já
2. ☐ Nei

S. 43 Hefur þú átt erfitt með að kyngja á síðastliðnu ári?

1. ☐ Já
2. ☐ Nei

S. 44 Hefur þú fundið fyrir brjóstsviða (sviða eða hitatilfinningu undir bringubeini) á síðastliðnu ári?
(Á ekki við um hjartakveisu eða verki tengda hjartanu)

1. ☐ Já
2. ☐ Nei

S. 45 Hversu oft hefur þú fundið fyrir brjóstsviða á síðastliðnu ári?

0. ☐ Aldrei
1. ☐ Sjaldnar en einu sinni í mánuði
2. ☐ Um það bil einu sinni í mánuði
3. ☐ Um það bil einu sinni í viku
4. ☐ Nokkrum sinnum í viku
5. ☐ Daglega

S. 46 Lagast brjóstsviðinn ef þú tekur inn sýrubindandi lyf (svo sem Alminox, Balacid, Natriumbikarbonat, Novalucid, Rennie)?

1. ☐ Já
2. ☐ Nei
3. ☐ Hef ekki haft brjóstsviða
4. ☐ Hef ekki tekið inn sýrubindandi lyf

S. 47 Lagast brjóstsviðinn ef þú tekur inn histamínblokkandi lyf (svo sem Asýran, Gastran, Cytotec, Zantac)?

1. ☐ Já
2. ☐ Nei
3. ☐ Hef ekki haft brjóstsviða
4. ☐ Hef ekki tekið inn histamínblokkandi lyf

S. 48 Lagast brjóstsviðinn ef þú tekur inn prótónupumpablokka lyf (svo sem Lanser, Lanzo, Losec, Lómex, Nexíum, Pariet)?

1. ☐ Já
2. ☐ Nei
3. ☐ Hef ekki haft brjóstsviða
4. ☐ Hef ekki tekið inn prótónupumpablokka lyf

S. 49 Hefur þú fundið fyrir mjög súru eða sýrubragði aftarlega í kokinu (nábitur) á síðastliðnu ári?

0. ☐ Aldrei
1. ☐ Sjaldnar en einu sinni í mánuði
2. ☐ Um það bil einu sinni í mánuði
3. ☐ Um það bil einu sinni í viku
4. ☐ Nokkrum sinnum í viku
5. ☐ Daglega

S. 50 Hefur þú lést á síðastliðnu ári án þess að fara í megrun?

0. ☐ Nei
1. ☐ Minna en þrjú og hálf kíló
2. ☐ Þrjú og hálf kíló eða meira

S. 51 Er matarlyst þín sambærileg á þessu ári og áður?

0. ☐ Minni
1. ☐ Um það bil sú sama
2. ☐ Meiri

Annar mikilvægur tilgangur með könnun þessari er að fræðast um heilsu þína áður fyrr og heimsóknir til lækna.

S. 52 Fékkstu oft verki í kvið sem barn (fyrir 15 ára aldur)?

1. ☐ Já
2. ☐ Nei

S.53 Hefur botnlanginn verið fjarlægður?

1. ☐ Já
2. ☐ Nei

Ef já, hvenær? _____

S. 54 Hefur gallblaðran verið fjarlægð?

1. ☐ Já
2. ☐ Nei

Ef já, hvenær? _____

S. 55 Hefur þú nokkurn tímann fengið maga- eða skeifugarnarsár?

1. ☐ Já
2. ☐ Nei

Ef já, hvenær? _____

Hvernig var það greint?

- ☐ Röntgen
☐ Spegln
☐ Annað _____

S. 56 Hefur þú einhvern tímann gengist undir aðgerð á maga?

1. ☐ Já
2. ☐ Nei

Ef já, hvenær? _____

Hvers konar aðgerð? _____

S. 57 Hefur þú einhvern tímann gegnist undir aðgerð í kviðarholi?

1. ☐ Já
2. ☐ Nei

Ef já, hvenær? _____

Hvers konar aðgerð? _____

S. 58 Hversu oft leitaðir þú til læknis á síðastliðnum 12 mánuðum?

0. ☐ Aldrei
1. ☐ 1-2 sinnum
2. ☐ 3-5 sinnum
3. ☐ 6-10 sinnum
4. ☐ Oftar en 10 sinnum

S. 59 Leitaðirðu til læknis á síðastliðnum 12 mánuðum vegna verkja í kvið?

1. ☐ Já
2. ☐ Nei

Ef já við S. 59, vinsamlegast
svarið S. 60 til S. 62

Ef nei, svaraðu þá næst S. 63 á næstu síðu

S. 60 Ef þú fórst til læknis vegna verkja í kvið, var það vegna þess að einkennin voru slæm eða mjöslæm?

1. ☐ Já
2. ☐ Nei

S. 61 Ef þú leitaðir til læknis vegna verkja í kvið, var það vegna þess að einkennin ollu þér áhyggjum?

1. ☐ Já
2. ☐ Nei

S. 62 Ef þú leitaðir til læknis vegna verkja í kvið, var það vegna þess að þú hélst að um alvarlegan sjúkdóm væri að ræða?

1. ☐ Já
2. ☐ Nei

S. 63 Leitaðir þú til læknis á síðastliðnu ári vegna hægðavandamála?

1. ☐ Já
2. ☐ Nei

S. 64 Hversu oft fékkstu kvef eða flensu á síðastliðnu ári?

0. ☐ Aldrei
1. ☐ 1-2svar sinnum
2. ☐ 3-5 sinnum
3. ☐ 6-10 sinnum
4. ☐ Oftar en 10 sinnum

Vinsamlegast athugaðu hvort þú hafir svarað öllum spurningunum að framan sem eiga við þig?

Næstu tvær spurningar eru einungis ætlaðar konum.

S. 65 Finnur þú fyrir verkjum við upphaf tíðablæðinga (tíðaverki)?

1. ☐ Já
2. ☐ Nei
3. ☐ Hef ekki blæðingar

S. 66 Hversu mikill er verkurinn venjulega?

1. ☐ Lítill: Þú getur látið eins og hann sé ekki til staðar, ef þú hugsar ekki um hann.
2. ☐ Meðal: Hefur ekki áhrif á daglegt líf og störf.
3. ☐ Slæmur: Hefur áhrif á daglegt líf og störf.
4. ☐ Mjög slæmur: Hefur mikil áhrif á daglegt líf og störf.
5. ☐ Finn ekki fyrir verkjum.

Til að auðveldara sé að túlka niðurstöður rannsóknarinnar viljum við spyrja nokkurra spurninga um þínar athafnir, vinnu, menntun og bakgrunn. Farið verður með öll svör sem algjört trúnaðarmál.

S. 67 Hafa verkir í kvið haft áhrif á störf þín á síðastliðnu ári?

1. ☐ Já
2. ☐ Nei

S. 68 Hefur hægðavandamál haft áhrif á líf þitt á síðastliðnu ári?

1. ☐ Já
2. ☐ Nei

S. 69 Hafa önnur veikindi haft áhrif á líf þitt á síðastliðnu ári?

1. ☐ Já
2. ☐ Nei

Ef já, hvað veikindi? _____

S. 70 Hversu oft hefur þú verið frá vinnu á síðastliðnu ári?

0. ☐ Aldrei
1. ☐ 1-2svar sinnum
2. ☐ 3-5 sinnum
3. ☐ 6-10 sinnum
4. ☐ Oftar en 10 sinnum

S. 71 Reykir þú núna?

1. ☐ Já daglega
2. ☐ Já einstaka sinnum
3. ☐ Fyrrverandi reykingamaður
4. ☐ Aldrei reykt

S. 72 Hversu margar sígarettur reykir þú vanalega á dag?

0. ☐ Enga
1. ☐ Færri en 5
2. ☐ Milli 5 og 15
3. ☐ Fleiri en 15

S. 73 Hvert er kyn þitt?

1. ☐ Karl
2. ☐ Kona

S. 74 Hver er líkamshæð þín? _____

S. 75 Hver er líkamsþyngd þín? _____

S. 76 Hvert er fæðingarár þitt? _____

S. 77 Ert þú í launaðri vinnu núna?

- 0. ☐ Já
- 1. ☐ Nei

Ef já, hvaða starf stundar þú? _____

Hjá hvers konar fyrirtæki? _____

Næst verður spurt um áfenga drykki (svo sem bjór, léttvín eða aðra sterkari drykki eins og viski, vodka, gin eða koníak). Einn drykkur samsvarar einni bjórdós, einu glasi af léttvíni eða einum einföldum af sterku áfengi.

S. 78 Hversu marga drykki drekkur þú að meðaltali á viku?

- 0. ☐ Engan
- 1. ☐ 1-2 drykki
- 2. ☐ 3-6 drykki
- 3. ☐ 7-10 drykki
- 4. ☐ Fleiri en 10 drykki

S. 79 Hversu margar aspirintöflur tókst þú að meðaltali á viku á síðastliðnu ári (það eru töflur eins og Hjartamagnýl, Magnýl, Treo, Alka-Seltzer)

- 0. ☐ Enga
- 1. ☐ 1-2 töflur
- 2. ☐ 3-6 töflur
- 3. ☐ 7-10 töflur
- 4. ☐ Fleiri en 10 töflur

S. 80 Hversu margar parasetamóltöflur tókst þú að meðaltali á viku á síðastliðnu ári (það eru töflur eins og Norgesic, Panocod, Panodil, Paratabs, Parkósín, Somadril)

- 0. ☐ Enga
- 1. ☐ 1-2 töflur
- 2. ☐ 3-6 töflur
- 3. ☐ 7-10 töflur
- 4. ☐ Fleiri en 10 töflur

S. 81 Hvesu margar bólgueyðandi töflur tókst þú að meðaltali á viku á síðastliðnu ári (það eru töflur eins og Arthrotec, Íbúfen, Íbúkód, Naproxen, Voltaren, Vostar)

- 0. ☐ Enga
- 1. ☐ 1-2 töflur
- 2. ☐ 3-6 töflur
- 3. ☐ 7-10 töflur
- 4. ☐ Fleiri en 10 töflur

S. 82 Hver er núverandi hjúskaparstaða þín?

1. ☐ Gift(ur)
2. ☐ Einstæð(ur)
3. ☐ Ekkja/ekkill
4. ☐ Fráskilin(n)
5. ☐ Fráskilin(n) að borði og sæng
6. ☐ Sambúð
7. ☐ Annað

S. 83 Stundar maki þinn launaða vinnu núna?

1. ☐ Já
 2. ☐ Nei
 3. ☐ Einstæður
- Ef já, hvers konar starf? _____

S. 84 Vinsamlegast gefðu upp menntun þína?

1. ☐ Framhaldsmenntun eftir háskóla
2. ☐ Háskólapróf
3. ☐ Tækniskólanám
4. ☐ Tækniskólanám að hluta
5. ☐ Iðnskólanám
6. ☐ Sérskólanám
7. ☐ Stúdentspróf
8. ☐ 10-11 ára skólaganga, þar með talið hluti af mennt- og/eða fjölbrautarskóla
9. ☐ 7-19 ára skólaganga, grunnskólapróf
10. ☐ Minna en 7 ára skólaganga

Hluti rannsóknarinnar fer þannig fram að leitað verður eftir nánari upplýsingum hjá þátttakendum sem svara spurningalistanum og eru greindir með meltingafærakvilla. Til þess að það sé möguleg viljum við biðja þig um að skrá símanúmer þitt hér að neðan. Með því veitir þú leyfi þitt til að hringt verði í þig og nánari upplýsinga skráðar.

Símanúmer mitt er: _____

1. ☐ Ekki má hafa samband við mig

Vinsamlegast svaraðu öllum spurningunum eins samviskusamlega og þú getur, merktu við þann valmöguleika sem á best við varðandi líðan þína **UNDANFARNA VIKU**

S. 85 Hefur þú fundið fyrir brjóstsviða eða nábit á síðastliðinni viku?

1. ☐ Já
2. ☐ Nei

Ef já við S. 85, vinsamlegast svarið B. 1 til B. 24

Ef nei, svaraðu þá næst einkennalista á baksíðu

B. 1 Tekur þú lyf við brjóstsviða eða nábit.

1. ☐ Já
2. ☐ Nei

Ef svarið er já:

Hvaða lyf (settu kross við þau lyf sem við á)?

- ☐ Asýran
- ☐ Lanzo
- ☐ Losec
- ☐ Nexiun
- ☐ Pariet
- ☐ Annað

B. 2 Tekur þú lyfin að staðaldri eða eingöngu þegar þú hefur einkenni?

1. ☐ Já
2. ☐ Nei

B. 3 Hefur þú farið í aðgerð vegna vélindabakflæðis

1. ☐ Já
2. ☐ Nei

B. 4 Hversu oft undanfarna viku hefur þú fundið fyrir þreytu eða kraftleysis vegna brjóstsviða eða nábits?

1. ☐ Alltaf
2. ☐ Oftast
3. ☐ Talsvert oft
4. ☐ Stundum
5. ☐ Sjaldan
6. ☐ Svo til aldrei
7. ☐ Aldrei

B. 5 Síðastliðna viku, hve mikinn bróstsviða eða nábit hefur þú haft vegna matar eða drykkjar?

1. ☐ Mikinn
2. ☐ Talsverðann
3. ☐ Allnokkurn
4. ☐ Einhvern
5. ☐ Líttinn
6. ☐ Varla nokkurn
7. ☐ Engann

B. 6 Hve oft síðastliðna viku hefur þér liðið illa almennt vegna brjóstsviða eða nábits?

1. ☐ Alltaf
2. ☐ Oftast
3. ☐ Talsvert oft
4. ☐ Stundum
5. ☐ Sjaldan
6. ☐ Svo til aldrei
7. ☐ Aldrei

B. 7 Hversu oft undanfarna viku hefur þér fundist þú þurfa að borða minna en venjulega vegna brjóstsviða eða nábits?

1. ☐ Alltaf
2. ☐ Oftast
3. ☐ Talsvert oft
4. ☐ Stundum
5. ☐ Sjaldan
6. ☐ Svo til aldrei
7. ☐ Aldrei

B. 8 Hversu oft undanfarna viku hafa brjóstsviði eða nábitur komið í veg fyrir að þú gerðir eitthvað með fjölskyldu eða vinum?

1. ☐ Alltaf
2. ☐ Oftast
3. ☐ Talsvert oft
4. ☐ Stundum
5. ☐ Sjaldan
6. ☐ Svo til aldrei
7. ☐ Aldrei

B. 9 Hversu oft undanfarna viku áttir þú í erfiðleikum með að ná góðum nætursvefni vegna brjóstsviða eða nábits?

1. ☐ Alltaf
2. ☐ Oftast
3. ☐ Talsvert oft
4. ☐ Stundum
5. ☐ Sjaldan
6. ☐ Svo til aldrei
7. ☐ Aldrei

B. 10 Hversu oft undanfarna viku hefur þú fundið fyrir vonleysi, kvíða eða óþolinmæði vegna brjóstsviða eða nábits?

1. ☐ Alltaf
2. ☐ Oftast
3. ☐ Talsvert oft
4. ☐ Stundum
5. ☐ Sjaldan
6. ☐ Svo til aldrei
7. ☐ Aldrei

B. 11 Undanfarna viku, hve mikinn brjóstsviða eða nábit hefur þú fengið vegna matar sem þú hefur ekki þolað?

1. ☐ Mikinn
2. ☐ Talsverðann
3. ☐ Allnokkurn
4. ☐ Einhvern
5. ☐ Lítilinn
6. ☐ Varla nokkurn
7. ☐ Engann

B.12 Hversu oft undanfarna viku hefur þú fundið fyrir áhyggjum eða hræðslu varðandi heilsu þína vegna brjósviða eða nábits?

1. ☐ Alltaf
2. ☐ Oftast
3. ☐ Talsvert oft
4. ☐ Stundum
5. ☐ Sjaldan
6. ☐ Svo til aldrei
7. ☐ Aldrei

B.13 Hversu mikinn pírning upplifðir þú vegna brjósviða eða nábits undanfarna viku?

1. ☐ Mikinn
2. ☐ Talsverðan
3. ☐ Allnokkurn
4. ☐ Einhvern
5. ☐ Lítinn
6. ☐ Varla nokkurn
7. ☐ Engan

B.14 Hversu oft undanfarna viku forðaðist þú ákveðnar fæðutegundir, áfengi eða drykki vegna brjósviða eða nábits?

1. ☐ Alltaf
2. ☐ Oftast
3. ☐ Talsvert oft
4. ☐ Stundum
5. ☐ Sjaldan
6. ☐ Svo til aldrei
7. ☐ Aldrei

B.15 Hversu oft undanfarna viku gast þú ekki sinnt daglegum störfum þínum (bæði innan heimilis og utan) vegna brjósviða eða nábits?

1. ☐ Alltaf
2. ☐ Oftast
3. ☐ Talsvert oft
4. ☐ Stundum
5. ☐ Sjaldan
6. ☐ Svo til aldrei
7. ☐ Aldrei

B.16 Hversu oft undanfarna viku gast þú ekki hreyft þig (þar með talið íþróttir, tómstundir og hreyfing utan heimilis) vegna brjóstsviða eða nábits?

1. ☐ Alltaf
2. ☐ Oftast
3. ☐ Talsvert oft
4. ☐ Stundum
5. ☐ Sjaldan
6. ☐ Svo til aldrei
7. ☐ Aldrei

Að lokum viljum við biðja þig um að fylla út eftirfarandi einkennalista.

Athugaðu að svara fyrir hvert og eitt einkenni, bæði hversu oft það kom fyrir og hversu slæmt það var á síðastlinu ári.

(Skrifaðu númer frá 0 til 4 fyrir allar spurningarnar 17 hér að neðan)

• Hversu oft

- 0 Ekki vandamál
- 1 kemur fyrir um það bil einu sinni í mánuði
- 2 kemur fyrir um það bil einu sinni í viku
- 3 kemur fyrir oft í viku
- 4 Kemur daglega fyrir

• Hversu slæmt

- 0 Ekki vandamál
- 1 Finnur lítið fyrir því
- 2 Finnur fyrir því í meðallagi
- 3 Er slæmt
- 4 Er mjög slæmt

	Hversu oft	Hversu slæmt
1 Höfuðverkur	_____	_____
2 Bakverkur	_____	_____
3 Maga- eða skeifugarnarsár	_____	_____
4 Magaverkir	_____	_____
5 Astmi	_____	_____
6 Iðraólga (ristilkrampar)	_____	_____
7 Svefnleysi	_____	_____
8 Hár blóðþrýstingur	_____	_____
9 Þreyta	_____	_____
10 Þunglyndi	_____	_____
11 Ógleði, flökurleiki	_____	_____
12 Almennur stífleiki	_____	_____
13 Aukaslög í hjarta, óeðlilega hraður hjartsláttur	_____	_____
14 Sársauki í augum í tengslum við lestur	_____	_____
15 Niðurgangur/hægðatregða	_____	_____
16 Svimi	_____	_____
17 Slappleiki	_____	_____

Appendix II: The telephone survey

Þátttakandi (númer): _____

Finnur þú fyrir iðraólgu (ristilkrömpum)?

- ☐ Já
- ☐ Nei

S. 2 Hefur þú fengið greininguna iðraólga?

- ☐ Já
- ☐ Nei

S. 2.1 Hvenær? _____

S. 2.2 Hver greindi þig með iðraólgu?

S. 2.3 Hvaða einkenni leiddu til greiningar á iðraólgu?

S. 2.4 Hvaða meðferð fékkstu við iðraólgunni?

S. 3 Þekkirðu iðraólgu /ristilkrampa

- ☐ Já
- ☐ Nei

S. 4 Hefurðu leitað til læknis vegna einkenna?

- ☐ Já
- ☐ Nei

Ef nei, hvers vegna?

- ☐ Einkenni ekki nógu alvarleg
- ☐ Hef lært að lifa með einkennunum
- ☐ Of mikið að gera – of upptekin(n)
- ☐ Vil ekki fara til læknis
- ☐ Annað

S. 5 Telurðu þú hafir fengið fullnægjandi meðferð við iðraólgunni?

- ☐ Já
- ☐ Nei

S. 6 Hefur iðraólgan áhrif á daglegt líf og störf þín í dag?

- ☐ Já
- ☐ Nei

Hve mikil áhrif?

- ☐ Mjög mikil áhrif
- ☐ Töluvert mikil áhrif
- ☐ Mikil áhrif
- ☐ Lítil áhrif
- ☐ Engin áhrif

S. 7 Telurðu að þú munir lækna af iðraólgu?

- ☐ Já
- ☐ Nei

S. 8 Telurðu að þú munir alltaf þjást af iðraólgu?

- ☐ Já
- ☐ Nei

S. 9 Tekurðu lyf við iðraólgu?

- ☐ Já
- ☐ Nei

Ef já, hvaða lyf?

S. 10 Notar þú óhefðbundnar lækningar til að meðhöndla einkenni iðraólgu?

- ☐ Já
- ☐ Nei

Ef já, hvaða?

S. 11 Telurðu að mataræði skipti máli í meðhöndlun á iðraólgu?

- ☐ Já
- ☐ Nei

S. 12 Ertu ánægð(ur) með þau úrræði sem eru við iðraólgu?

- ☐ Ánægð(ur)
- ☐ Frekar ánægð(ur)
- ☐ Frekar óánægð(ur)

☐ Óánægð(ur)

S. 13 Hvaða kyn:

☐ Karl

☐ Kona

S. 17 Hvað ár ertu fædd(ur)?

Appendix III: The physician questionnaire

Rannsókn á meltingarfærakvillum

Spurt er um starfræna meltingarfærakvilla.

1. Hvaða meltingarfærakvillar eru algengastir hjá þeim skjólstæðingum sem til þín leita?

2. Hversu margir fá að jafnaði greininguna iðraólga (irritable bowel syndrone, ristilkrampar) í hverjum mánuði?

3. Hvernig greinir þú iðraólgu?

4. Eru til greiningarviðmið til að greina iðraólgu?

☐ Já

☐ Nei

☐ Þekki þau ekki

Ef já; Hvaða greiningarviðmið?

5. Hvaða greiningaraðferð notar þú við greiningu á iðraólgu?

Framhald á næstu síðu.

2.

6. Þekkir þú greiningarviðmiðin?:

Manning criteria ☐ Já

☐ Nei

Rome criteria

☐ Já

☐ Nei

Rome II criteria ☐ Já

☐ Nei

7. Hvaða einkenni eru algengust hjá skjólstaðingum með iðraólgu?

8. Hvaða meðferð beitir þú í meðhöndlun á einkennum iðraólgu?

9. Telurðu að mataræði skipti máli í meðhöndlun á iðraólgu?

Nú verður spurt um bakgrunn þinn.

10. Hvenær laukst þú læknaprófi? _____

11. Við hvaða grein læknisfræðinnar starfar þú? _____

12. Hvaða kyn?: ☐ Karl

13. Hvað ár ertu fædd(ur)? _____

☐ Kona

Kærar þakkir fyrir þátttökuna

