Functional Gastrointestinal Disorders and the Joint Hypermobility Syndrome

Asma Fikree BMBCh, MA, MRCP

St Bartholomew's and the Royal London
School of Medicine and Dentistry

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Abstract

Despite the fact that functional gastrointestinal disorders (FGID), such as irritable bowel syndrome, are common, our understanding of them is limited. The Joint Hypermobility Syndrome (JHS) is a common non-inflammatory connective tissue disorder which is thought to be associated with FGID although this has never been proven. Thus, further understanding of the link between JHS and GI symptoms is warranted.

Our aim was to fully characterise the gastrointestinal (GI) manifestations of JHS, to determine if there is a true association between GI symptoms in JHS and FGID, and to determine the factors that are involved in this association.

Using a cross-sectional design I demonstrate in the first study that patients with a known diagnosis of JHS who are referred from rheumatologists to gastroenterologists have significantly increased gastro-oesophageal symptoms, alternating bowel habit, bloating and abdominal pain compared to other patients referred to the GI clinics. Autonomic factors, and to a lesser extent, somatic hypersensitivity factors appear to mediate the association between JHS and gastro-oesophageal symptoms.

In the second study, I demonstrate that healthy university students with JHS are more likely to experience postprandial dyspeptic symptoms compared to those without JHS. Although autonomic and somatic symptoms are increased in JHS their presence does not seem to confound the association with GI symptoms in this group of healthy individuals.

In a case-control study of patients attending secondary care GI clinics, I demonstrate that JHS is overrepresented in patients with FGID and reflux disease but not in those with organic disease. Furthermore, the association with FGID is specifically with postprandial distress syndrome and this association is dependent on autonomic factors.

In the final chapter, I confirm that abnormalities in GI physiology are common in JHS patients with GI symptoms attending a physiology unit. 60% of JHS patients with reflux symptoms have non-erosive pathological acid reflux, 56% with dysphagia have oesophageal hypomotility, and 87% with dyspeptic symptoms have gastroparesis.

My studies suggest that there is overlap between JHS, gastro-oeosphageal symptoms, FGID and GI dysmotility. Understanding the mechanisms underlying GI involvement in JHS may further our understanding of FGID.

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Declaration

This work was carried out during my tenure as a research fellow in the Wingate Institute of Neurogastroenterology, Barts and the London School of Medicine and Dentistry between April 2009 and December 2012.

I designed and wrote the ethics applications for all the studies. All the studies were performed and analysed by myself except as stated below:

The skin stretch tests were performed by my research assistant, Miss Rubina Aktar.
The GI physiology studies in non-JHS patients presented in Chapter 5 were performed collectively by all the fellows working in the upper GI physiology unit, but the data was collated and analysed by myself.
The gastric emptying breath tests were performed by Dr Jafari, Dr Shaub, and Dr Yu Tien, all research fellows in the upper GI physiology unit.
The endoflip data for healthy volunteers was obtained and analysed by Dr W Rohof in the Netherlands.
The administrative tasks including the transcription of data to electronic format, and contacting patients were performed jointly by myself and by my research assistant, Miss Rubina Aktar.

I believe that this work represents a new contribution to medical knowledge. The work in this thesis has not already been accepted in substance for any degree and is not being concurrently submitted in candidature for any degree.

Dr Asma Fikree BMBCh, MA, MRCP

To my late father,
who was fond of asking questions
and even fonder of finding answers

Table of contents

List of tables

List of Figures

List of Abbreviations

AD:	Autosomal dominant
AR:	Autosomal recessive
BMI:	Body Mass Index
BDQ:	Bowel Disease Questionnaire
CI:	Confidence interval
COL1:	Collagen 1
COL3:	Collagen 3
COL5:	Collagen 5
CRPS:	Complex regional pain syndrome
CSA:	Cross-sectional area
CSES:	Corrected skin extensibility score
CWP:	Chronic widespread pain
DCI:	Distal contractile integral
EDS:	Ehlers-Danlos Syndrome
EDS-HT:	Ehlers-Danlos Syndrome – Hypermobility Type
FGID:	Functional Gastrointestinal Disorders
FODMAPS:	Fermentable oligo- di- monosaccharides and polyols.
FM:	Fibromyalgia
GERD:	Erosive gastro-oesophageal reflux disease
GI:	Gastrointestinal
GOJ:	Gastro-oesophageal junction
GJH:	Generalised Joint Hypermobility
GORD:	Gastro-oesophageal reflux disease

GP:	General practitioner
HADS:	Hospital Anxiety and Depression Scale
HRM:	High Resolution Manometry
IBD:	Inflammatory bowel disease
IBS:	Irritable bowel syndrome
IBS-C:	Irritable bowel syndrome, constipation predominant
IBS-D:	Irritable bowel syndrome, diarrhoea predominant
IBS-M:	Irritable bowel syndrome, mixed bowel habit
IQR:	Interquartile range
IRP:	Integrated relaxation pressure
JHM:	Joint Hypermobility
LOS:	Lower oesophageal sphincter
MII:	Multichannel Intraluminal Impedance Testing
MRS:	Multiple rapid swallow
NERD:	Non-erosive reflux disease
NSAIDS:	Non-steroidal anti-inflammatory drugs
PDS:	Postprandial distress syndrome
PHQ15:	Patient Health Questionnaire 15 – somatic symptom questionnaire
PI-IBS:	Post-infectious Irritable Bowel Syndrome
POTS:	Postural Orthostatic Tachycardia Syndrome
PPI:	Proton pump inhibitor
QOL:	Quality of life
SCL90:	Symptom Checklist 90 – psychopathology questionnaire
SF36:	Quality of Life questionnaire
TMJ:	Tempero-mandibular joint
TNX:	Tenascin X

TNF: Tumour Necrosis Factor

UC: Ulcerative Colitis

UOS: Upper oesophageal sphincter

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Chapter 1

Introduction, literature review and aims

1.1 Functional Gastrointestinal Disorders

Functional Gastrointestinal Disorders (FGID) are a common group of disorders causing chronic or recurrent gastrointestinal (GI) symptoms in the absence of any biochemical, anatomical, metabolic, radiological or histological abnormalities on conventional testing. They are often characterised by abnormal sensori-motor functioning of the GI tract. As a diagnostic biomarker for FGID does not exist, diagnosis is based on clinical criteria and recognition of a pattern of symptoms in the absence of structural or organic abnormalities that may account for those symptoms. The most widely recognised classification system for FGIDs is the ROME symptom-based classification system. The most recent version of this, ROME III, divides FGIDs into 45 subcategories (28 adult, 17 paediatric). The adult subcategories are shown in Table 1.1.

Table 1.1: ROME III classification of Functional Gastrointestinal Disorders in Adults (Drossman 2006)

A. Functional Oesophageal Disorders:
A1. Functional heartburn
A2. Functional chest pain of presumed oesophageal origin
A3. Functional dysphagia
A4. Globus

B. Functional Gastroduodenal Disorders:
B1.Functional dyspepsia
- B1a: Postprandial distress syndrome
- B1b: Epigastric pain syndrome

B2. Belching disorders
- B2a: Aerophagia
- B2b: Unspecified excessive belching

B3. Nausea and Vomiting disorders
- B3a: Chronic Idiopathic nausea
- B3b: Functional vomiting
- B3c: Cyclical vomiting syndrome

B4. Rumination syndrome in adults

C. Functional Bowel Disorders:
C1. Irritable Bowel Syndrome
C2. Functional Bloating
C3. Functional Constipation
C4. Functional Diarrhoea
C5. Unspecified functional bowel disorder

D. Functional abdominal pain syndrome

E. Functional gallbladder and Sphincter of Oddi disorders:
E1. Functional gallbladder disorder
E2. Functional biliary Sphincter of Oddi disorder
E3. Functional pancreatic Sphincter of Oddi disorder

F. Functional anorectal disorders:
F1. Functional faecal incontinence
F2. Functional anorectal pain
- F2a. Chronic proctalgia
  - F2a1. Levator Ani Syndrome
  - F2a2. Unspecified functional anorectal pain
- F2b. Proctalgia fugax

F3. Functional defecation disorders
- F3a. Dyssynergic defecation
- F3b. Inadequate defecatory propulsion

1.1.1 Epidemiology of Functional Gastrointestinal Disorders

FGIDs are very common with a prevalence of up to 36% in the general population (Chang 2004). They are present worldwide, and show no geographical distribution. They are more commonly reported in females, and their prevalence decreases with age (Drossman, Li et al. 1993; Hungin, Whorwell et al. 2003). FGIDs tend to cluster in families (Whorwell, McCallum et al. 1986), and it is common for patients with IBS to have a similarly affected parent or sibling.

1.1.2 The burden of FGID

FGIDs carry a substantial socio-economic burden to healthcare, the economy, and most importantly to patients.

1.1.2.1 Healthcare burden

These disorders generate a substantial workload in both primary care and secondary care. Up to 50% of patients in the community experiencing GI symptoms will consult their general practitioner (GP) (Wilson, Roberts et al. 2004) and half the patients seen by GP's for gut complaints end up with a diagnosis of a FGID (Thompson, Heaton et al. 2000). 17-30% of these will be referred to a secondary care gastroenterologist (Harvey, Salih et al. 1983; Wilson, Roberts et al. 2004). This equates to FGIDs accounting for 12% of the GP workload in primary care (Jones, Crowell et al. 2007) and 40% of the workload in secondary care gastroenterology clinics (Harvey, Salih et al. 1983).

1.1.2.2 Patient morbidity and quality of life

FGIDs are chronic disorders - 8% of patients experience symptoms for more than 21 days a month (Hungin, Whorwell et al. 2003), and 95% of patients with IBS have persistent symptoms 5 years after initial symptom presentation (Kay, Jorgensen et al. 1994). 62% of patients do not respond completely to prescribed medication (Hungin, Whorwell et al. 2003), and in a proportion of patients, the unrelenting symptoms result in repeated outpatient visits and hospitalisations (Brun-Strang, Dapoigny et al. 2007). All these factors contribute to the significant decrements in quality of life in patients with FGID (Hungin, Whorwell et al. 2003; Brun-Strang, Dapoigny et al. 2007). IBS restricts, or negatively affects, many aspects of patients' lives including diet, leisure, travel, intimacy, with 50% of patients feeling unable to lead a normal life (Hungin, Whorwell et al. 2003). The quality of life (QOL) in IBS sufferers is worse when compared to patients with other GI disorders such as gastro-oesophageal reflux disease, inflammatory bowel disease and peptic ulcer disease, and compared to patients with chronic medical conditions such as Grade III congestive cardiac failure, chronic obstructive airways disease and osteoarthritis (Frank, Kleinman et al. 2002; Amouretti, Le Pen et al. 2006; Spiegel, Harris et al. 2009).

1.1.2.3 Economic burden

As a consequence of the above, IBS is associated with significant direct costs (use of health care resources) and indirect costs (work productivity). In the United States, an average of $1.7 billion to $10 billion (GBP 1 billion - 6 billion) is spent on IBS annually (Martin Mdel and Barron 2001; Martin, Barron et al. 2001; Sandler, Everhart et al. 2002). In the US in 2002, estimates of the total

annual direct cost per patient for IBS ranged from US$348 (GBP 215) to US$8750 (GBP 5423) (Maxion-Bergemann, Thielecke et al. 2006). In Europe, the annual cost of an IBS patient was 756 Euros (GBP 625), and most of this was accounted for by investigations and hospitalizations, with the highest costs reported in patients with severe IBS symptoms, particularly those with abdominal pain (Brun-Strang, Dapoigny et al. 2007). Lack of response to IBS treatment also adds to the costs, and in a cross-sectional study from the UK, patients who did not respond to conventional treatments incurred annual costs of up to GBP 1400 (Creed, Ratcliffe et al. 2001).

The average total number of days taken off work in the US due to IBS-related problems ranges from 8 to 21 (Jones, Crowell et al. 2007), and absence at work due to IBS is equivalent to that due to the common cold (Camilleri and Williams 2000). The total annual indirect cost per patient, attributable to both absenteeism (missed days of work) and presenteeism (impairment while at work) ranged from US$355 (GBP 220) to US$334,479 (GBP 207,332) (Fortea and Prior), with total costs to the economy reaching US$ 20 billion (GBP 12.4 billion) (Martin Mdel and Barron 2001; Sandler, Everhart et al. 2002).

These disorders are clearly a burden not only to patients, but also to healthcare systems and to the economy. Treatment of IBS symptoms improves quality of life, productivity, and reduces national healthcare expenditure (Akehurst, Brazier et al. 2002). However, this is not as easy in practice, as some of the symptoms associated with IBS are extra-intestinal and many are ‘unexplained’.

1.1.3 Associated features and disorders in FGID

1.1.3.1 Extra-intestinal features of FGID

Studies that have investigated the non-GI associations of FGID have predominantly been performed in patients with IBS. These patients have a significantly increased prevalence of lethargy, back pain, bad breath, menstrual disturbances, sleep disturbances and dyspareunia, compared to patients with organic GI disorders (Whorwell, McCallum et al. 1986; Maxton, Morris et al. 1991; Hershfield 2005). IBS patients are also more likely to have urinary frequency, bladder dysfunction and detrusor instability compared to age and sex-matched controls (Whorwell, McCallum et al. 1986).

There is an association between IBS and atopy. Patients with atopy are 3.1 times more likely to satisfy criteria for IBS compared to a non-atopic control group, and patients with asthma have an increased prevalence of IBS compared to non-asthmatic controls (Panicker, Arifhodzic et al. 2010).

IBS patients also have significant psychopathology. When compared with Inflammatory Bowel Disease (IBD) patients, IBS patients have significantly more lifetime diagnoses of major depression, somatisation disorder, generalized anxiety disorder, panic disorder, and phobic disorder (Walker, Roy-Byrne et al. 1990).

1.1.3.2 Association with medically unexplained disorders

Considerable overlap is seen between FGID and medically ‘unexplained’ disorders, also known as functional somatic syndromes (White 2012). IBS is associated with migraines, tempero-mandibular joint (TMJ) disorder, interstitial

cystitis, painful bladder syndrome, chronic pelvic pain, vulvodynia, fibromyalgia (FM) and chronic fatigue syndrome (Schur, Afari et al. 2007).

Fibromyalgia and IBS

Fibromyalgia (FM) is a rheumatological condition characterized by chronic widespread pain and multiple tender points over the body. It is associated with somatic and psychological conditions, and is strongly associated with IBS. A third of patients with FM have IBS and a third of patients with IBS have FM, and those with both disorders have a lower quality of life (Sperber, Atzmon et al. 1999). Broadening this to FGIDs in general, the association is even stronger with 98% of FM patients satisfying criteria for an FGID, with IBS being the most common subtype (Almansa, Rey et al. 2009).

IBS and unexplained urological conditions

In a systematic review of 1038 publications investigating the association of various medically unexplained disorders, the most robust evidence for an overlap was between IBS and unexplained urological conditions such as interstitial cystitis, irritable bladder, and chronic pelvic pain, with up to 79% overlap between the two (Rodriguez, Afari et al. 2012).

1.1.3.3 Common features in FGID and other functional somatic syndromes

Functional somatic syndromes, such as IBS, FM and chronic pelvic pain (Creed, Guthrie et al. 2009), share common features such as pain, fatigue, disability out of proportion to physical examination findings, inconsistent laboratory abnormalities, and an association with stress and psychosocial

factors (Rodriguez, Afari et al. 2012) . Recent studies suggest that they all share a common patho-aetiology, which probably involves autonomic dysfunction, disturbances of the hypothalamic-pituitary adrenal axis, abnormal central processing of pain, immune mechanisms or a combination of these (Scully, McKernan et al. 2010; White 2012). All of these factors have been researched thoroughly for FGID, albeit with no conclusive results.

All the extra-intestinal and unexplained disorders associated with FGID contribute to the increasing healthcare utilisation and worsening quality of life of affected patients (Kindt, Van Oudenhove et al. 2011). Understanding the aetiology of these disorders is thus crucial not only to improve quality of life for its sufferers, but also to reduce the financial burden on the health system.

1.1.4 Aetiology of FGID

Over the past two decades, an increasing amount of research has been done to shed further light on our understanding of FGID and to discover an aetiology for these GI disorders. No single factor has been found to cause FGIDs but instead, various factors have been found to be associated with these functional disorders and they are thought to play an aetiological role.

1.1.4.1 Psychopathology

The old-fashioned view of FGIDs were that they were more a nuisance than a disorder, and that the symptoms were all ‘in the mind’, suggesting that they were more psychiatric in nature. FGIDs are not psychiatric conditions although stress and coexistent psychological morbidity can exacerbate the symptoms experienced (Drossman, Creed et al. 1999). FGID are associated with

psychopathology, such as anxiety and depression, and the somatisation disorder (Wessely, Nimnuan et al. 1999; Palsson and Drossman 2005). This refers to the presence of multiple vague and recurring somatic complaints that cannot be fully explained by any known general medical condition or the direct effect of a chemical substance, but which are not intentionally feigned or produced.

'Somatisation' is the hallmark of the medically unexplained disorders, including FGID, and is increasingly thought to arise due to processes involving altered pain processing or autonomic dysfunction (White 2012).

1.1.4.2 Autonomic dysfunction

Dysfunction of the autonomic nervous system is associated with FGID (Farmer and Aziz 2009). The specific type of central nervous system dysregulation has not yet been elucidated with respect to individual FGIDs, however increased sympathetic and decreased parasympathetic function have been associated with various functional GI disorders (Farmer and Aziz 2009). In IBS patients increased sympathetic drive is associated with dysmotility in the upper GI tract (Mazur, Furgala et al. 2007), and vagal dysfunction has been demonstrated in response to rectal distension (Spaziani, Bayati et al. 2008). In functional dyspepsia, vagal dysfunction is thought to contribute to antral hypomotility and impaired gastric accommodation (Oustamanolakis and Tack 2012). Autonomic dysfunction is considered to be one mechanism by which visceral hypersensitivity arises (Farmer and Aziz 2009), though clear evidence for this is still lacking.

1.1.4.3 Visceral hypersensitivity

Patients with IBS have visceral hypersensitivity, which refers to the fact that they have lower thresholds for visceral pain (Mertz, Naliboff et al. 1995). Clinically, this is manifest as reduced pain tolerance to endoscopic or digital rectal examinations. Visceral hypersensitivity is thought to occur due to sensitisation at both a peripheral and central level (Zhou and Verne 2011).

Peripheral sensitisation

Peripheral sensitisation occurs due to sensitisation of primary afferent nerves. It is unclear exactly why peripheral sensitisation occurs but recent work suggests that a variety of factors including low grade immune mechanisms, increased intestinal permeability or altered microbiota may be responsible (Piche, Barbara et al. 2009; Barbara, Cremon et al. 2011; Zhou and Verne 2011).

Central sensitisation / hypervigilance

Central sensitisation is due to altered pain processing at the level of spinal dorsal horn neurones and brain. It is exacerbated by stress and abnormal mood states due to descending pathways from the brain to the spinal cord and is considered aetiologically important in the development of visceral hypersensitivity in FGID (Palsson and Drossman 2005). It has been documented using brain imaging techniques and is manifest as altered central nervous system activation to stimuli in IBS patients compared to controls (Tillisch and Labus 2010).

1.1.4.4 Immune mechanisms

Half of IBS patients have increased numbers of activated T lymphocytes and mast cells in the GI tract (Chadwick, Chen et al. 2002; Walker, Warwick et al. 2011). IBS patients also have altered plasma cytokine profiles (Scully, McKernan et al. 2010), and altered expression of pathogen recognition receptors (toll-like receptors) compared to controls (Brint, MacSharry et al. 2010; McKernan, Gaszner et al. 2011). All this points towards the presence of low-grade immune mechanisms in IBS. Further evidence for immune involvement comes from the fact that IBS can develop after an enteric infection i.e. post infectious IBS (PI-IBS) (Villani, Lemire et al. 2010).

1.1.4.5 Increased intestinal permeability

IBS patients have altered intestinal integrity and increased intestinal permeability (Dunlop, Hebden et al. 2006) and this is in part thought to be due to alterations in tight junction proteins (Piche, Barbara et al. 2009).

1.1.4.6 Altered microbiota

In IBS, small bowel bacterial overgrowth is associated with GI symptoms in at least a subset of patients (Pimentel, Chow et al. 2000; Stoicescu, Andrei et al. 2013), and altered composition and biodiversity of the intestinal microbiota is also present (Carroll, Ringel-Kulka et al. 2011). When either of these is altered e.g. by the use of probiotics or antibiotics, IBS symptoms improve (Moayyedi, Ford et al. 2008; Pimentel, Lembo et al. 2011; Pimentel, Morales et al. 2011; Simren, Barbara et al. 2013).

1.1.4.7 Gastrointestinal dysmotility

Dysmotility in the fore, mid and hindgut is associated with FGID. Gastroparesis is present in functional dyspepsia and contributes to postprandial symptoms (Sarnelli, Caenepeel et al. 2003; Haag, Talley et al. 2004). Small bowel dysmotility has been documented in patients with FGID, particularly those with more severe presentation and associated malnourishment (Cogliandro, Antonucci et al. 2011). Delayed colonic transit is present in about a third of patients with lower FGID (Manabe, Wong et al. 2010) and appears to be related to stool form and frequency, but not to symptoms of IBS (Deiteren, Camilleri et al. 2010; Tornblom, Van Oudenhove et al. 2012). In general, the presence of dysmotility in FGID is associated with poor nutritional status, and decrements to QOL (Cogliandro, Antonucci et al. 2011).

1.1.4.8 Alterations in the Brain-Gut axis

Evidence from brain imaging, pharmacology and neuroscience point towards the involvement of the brain-gut axis in the development of FGID (Fichna and Storr 2012). The brain-gut axis consists of the enteric nervous system, the central nervous system, and the bi-directional interaction between the two, also involving the hypothalamic-pituitary axis. Dysfunction in the brain-gut axis, is thought to be responsible for the sensori-motor aspects of FGID i.e. visceral hypersensitivity and dysmotility (Fichna and Storr 2012), though the exact nature by which this occurs is still not clear.

1.1.4.9 Diet

Although true food allergies are uncommon in IBS, there is an increase in self-reporting of food intolerances compared to the general population, and there is

a growing body of evidence that certain dietary constituents can exacerbate symptoms in IBS (Niec, Frankum et al. 1998; Eswaran, Tack et al. 2011). : Fermentable oligo- di- monosaccharides and polyols (FODMAPS) are short chain carbohydrates that are poorly absorbed in the intestine. Ingestion of FODMAPS leads to altered fluid content and bacterial fermentation in the colon, resulting in GI symptoms, particularly bloating, abdominal pain and altered bowel habit in susceptible individuals with FGID (Barrett and Gibson 2012). Lactose intolerance is increased in patients with IBS-D compared to controls (Yang, Deng et al. 2012). There is also an increasing body of work to suggest that non-coeliac gluten sensitivity is more common in IBS, particularly in patients with atopic symptoms (Aziz and Sanders 2012). In support of the concept that food intolerance is responsible for symptoms, elimination diets e.g. FODMAP diet, gluten-free and lactose-free diets, have been shown to improve symptoms in FGID (Eswaran, Tack et al. 2011).

1.1.4.10 Genetics

Twin studies have demonstrated that genes are important in the aetiology of IBS but that environmental factors have an even greater effect, which suggests that both nature and nurture are important (Levy, Jones et al. 2001). So far, studies suggest that polymorphisms in genes that encode proteins involved in neurohumoral mechanisms, epithelial cell barrier function and the innate immune response to enteric bacteria are associated with development of IBS (Camilleri, Atanasova et al. 2002; Kim, Camilleri et al. 2004; Villani, Lemire et al. 2010; Zucchelli, Camilleri et al. 2011).

Neurohumoral genes

IBS is associated with polymorphisms in the serotonin transporter gene (Camilleri and Katzka 2012) which leads to alterations in the concentration and signalling of serotonin (5-HT), a protein responsible for GI secretion, motility and visceral perception (Gershon and Tack 2007). In particular, the association appears to be between the homozygous short genotype (SS) of the serotonin reuptake transporter and IBS-D (Yeo, Boyd et al. 2004; Park, Choi et al. 2006). Polymorphisms in the Alpha-2-Adrenoceptor, which are involved in the maintenance of colonic tone and in sensation (Viramontes, Malcolm et al. 2001) are associated with IBS-C and with high somatic symptom scores (Kim, Camilleri et al. 2004), though the contribution of the genotype to the IBS phenotype is still unclear at this stage.

Inflammatory / immune genes

Polymorphisms in genes encoding IL-10, IL23, TNF-α and TNF superfamily 15 (TNFSF15) have been associated with IBS, though the results are not always reproducible (Camilleri and Katzka 2012). Polymorphisms associated with Toll-like receptor 9 (TLR-9) and IL-6 have been reported in association with PI-IBS (Villani, Lemire et al. 2010).

Epithelial cell barrier function genes

The cadherins are a group of transmembrane proteins that are involved in cell adhesion and barrier function. Polymorphisms in E-Cadherin 1 genes are associated with PI-IBS (Villani, Lemire et al. 2010).

Association with Crohn's and Coeliac disease susceptibility genes

It is of interest that several of the above-mentioned gene polymorphisms, which are associated with IBS, are also associated with susceptibility to Crohn's Disease or Coeliac Disease. This includes polymorphisms in TLR-9, IL-6, E-Cadherin 1, and TNSF-15, and suggests a possible genetic overlap between IBS and these organic disorders (Wouters 2011).

Although several genetic polymorphisms have been linked to FGID and these support molecular findings in FGID, no clear pattern of inheritance has emerged, so the exact role of genetics in IBS is unclear. It seems however, that a combination of genetic and environmental factors are important and that the genes confer susceptibility, whereas the environment influences the development or progression of FGID in a genetically susceptible individual, through any of the mechanisms described above.

1.1.5 Biopsychosocial model for FGID

The biopsychosocial model tries to combine all the above-mentioned associations into a single explanatory model (Drossman, Creed et al. 1999). It theorises that FGIDs are due to dysregulation of the brain-gut neuroenteric axis, which leads to altered sensory processing in the gut (hypersensitivity) and abnormal motility (dysmotility), both of which lead to the symptoms of FGID. According to the model, psychosocial factors such as early life events, coping strategies, life stresses and psychological states can influence this interaction between the brain and the gut and thus exacerbate symptoms. The model also recognises the influence of genetics on the presence of FGID namely that some

people are genetically predisposed to these disorders, and FGIDs tend to cluster in families (Drossman, Creed et al. 1999).

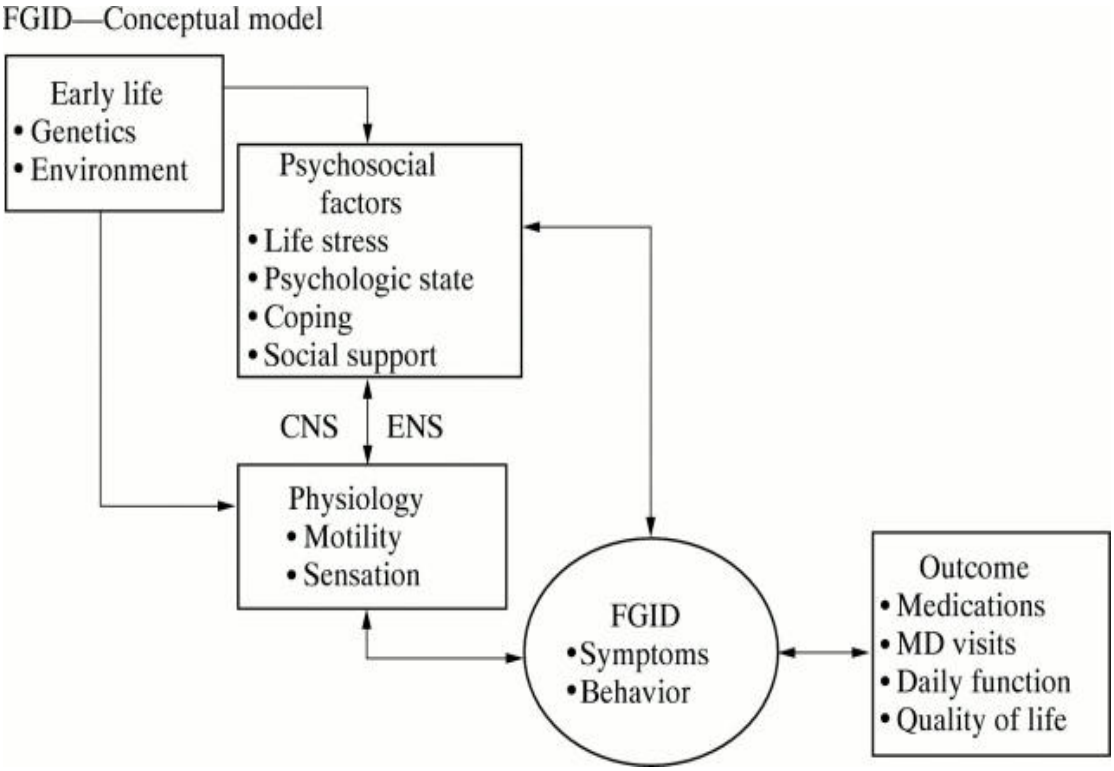


Figure 1.1: Biopsychosocial model of IBS.
This demonstrates the relationship between psychosocial and physiological factors, FGID symptoms and clinical outcome (Drossman, Creed et al. 1999). CNS: Central nervous system, ENS: Enteric nervous system

This model is an effective framework to use when treating FGID as it focuses on the multimodal nature of the functional disorders and tackles all the different aspects. However, it is fairly generalised, it cannot explain why FGIDs develop in the first place, nor can it predict which individuals, or groups of individuals will develop FGIDs. Furthermore, none of these associative factors can fully explain the range of GI symptoms present in these heterogeneous conditions, nor why

individuals with FGID have an increased prevalence of other 'unexplained' disorders such as chronic fatigue syndrome, fibromyalgia and food intolerances, as described above.

1.1.6 Limitations of FGID research

Slow progress is being made in our understanding of the aetiology of FGID. This was initially thought to be due to the fact that the GI conditions being investigated were a heterogeneous group of conditions all lumped under the umbrella term 'FGID', not all of which may have identical aetiologies. Therefore, in orde to maintain homogeneity, the more recent studies have used the ROME classification systems to divide FGIDs into separate entities, and have tried to focus research on particular entities, mainly IBS and functional dyspepsia. However, once again this research has continued to yield solely associations with no all-encompassing aetiological explanation. This may be due to a general misguided approach to FGID and the erroneous categorisation of FGID into symptom-based subtypes.

The problem with looking at individual ROME subtypes is that the classification provides a very arbitrary categorisation of these disorders. Patients who fulfil criteria for one subtype of FGID frequently fulfil criteria for several others (Talley 2007) i.e. patients do not fall neatly into only one FGID subtype. Dividing FGIDs into these symptom-based subtypes may be hampering our research into these disorders, and what may be needed is a more holistic view of these conditions and of their associated 'unexplained' multi-systemic phenomena. This may be achieved by looking at a potential aetiological factor that is ubiquitous throughout the body, including the GI tract, and which, when

abnormal, can lead to pathology that is associated with FGID and other disorders. The most obvious candidates are the major tissue types i.e. epithelium, muscle, nerves and connective tissue. Although research is ongoing into the first three potential aetiological candidates, almost none has looked at connective tissue. This is surprising because not only is connective tissue ubiquitous throughout the GI tract, but also GI symptoms are inextricably linked to connective tissue disorders.

1.2 Connective tissue

Connective tissue is one of the four major tissue types and functions to connect, support, bind and enclose the structures of the body, much like scaffolding. It is present in all parts of the body, including the skin, joints, internal organs and GI tract, albeit in different forms and quantities.

1.2.1 Connective tissue components

Connective tissue is made up of 3 main components: fibres, ground substance and cells. Abnormalities in any of the components can lead to disease.

1) Fibres: Collagen is the main fibre and the main component of connective tissue. 29 different subtypes of collagen exist, but the most common is collagen I. Collagen is mostly found in fibrous tissues such as tendon, ligament and skin, but is also abundant in cornea, cartilage, blood vessels, intervertebral discs and the GI tract. Elastin and fibrillin are other fibres that provide flexibility and stretch.

2) Ground substance *:* This consists of glycoproteins and proteoglycans that form an amorphous gel-like material in which the connective tissue fibres are

contained. Tenascin is an important family of glycoproteins, and consists of 6 members: Tenascin C, X, W, R, N and Y (Jakovcevski, Miljkovic et al. 2012). They have different distributions and functions, and as an example, Tenascin X (TNX) is expressed by neurones and glia, associates with collagen I, and interacts with the elastogenic pathways and matrix remodelling enzymes (Bristow, Carey et al. 2005). It is important in cell signalling, cell adhesion and the regulation of collagen deposition (Chiquet-Ehrismann and Tucker 2011).

3) Cells: This includes fibroblasts, which synthesise the fibres and ground substance.

Connective tissue is ubiquitous throughout the gastrointestinal (GI) tract, and alterations in connective tissue are associated with GI disease.

1.2.2 Connective tissue and the GI tract in health

In healthy individuals, connective tissue is present in all layers of the gut, albeit to different degrees (Figure 1.2). In the lamina propria and serosa it is most abundant and supports all the blood vessels and glands that are found in those layers. In the muscularis propria it forms connective tissue scaffolds which traverse the muscle layers and then enclose the myenteric plexi (Figure 1.3). Of the collagen subtypes, I, III, IV and V are the most common in the GI tract. Type IV is present in the subepithelial basement membrane and in the basement membrane surrounding smooth muscle cells. I III and V are mainly in the stomach and small intestine, so are thought to play a role in regulating permeability (Seki, Naito et al. 1998; Sato, Naito et al. 2007). As can be seen from the figures below (Figure 1.2, Figure 1.3) most of the connective tissue is in the deeper layers of the intestinal wall, which makes it difficult to study unless

full thickness specimens of bowel are obtained, which can only be done surgically or during post mortem. Consequently, very little research has examined the importance, functions and distribution of connective tissue in the GI tract in health, and even less so in disease.

1.2.3 Connective tissue and the GI tract in GI disease

Localised abnormalities in connective tissue have been described in association with GI pathology. In diverticular disease, there is increased elastin deposition in the taenia of the colon, and structural changes in the collagen of the smooth muscle (Whiteway and Morson 1985). Patients with hiatus hernias have fragmentation and distortion of elastin in their gastro-hepatic and phreno-oesophageal ligaments (Curci, Melman et al. 2008). Children with megacolon have atrophy of collagen in the tendinous connective tissue membrane of the myenteric plexus and muscularis propria (Figure 1.4), referred to as 'atrophic desmosis' (Meier-Ruge 1998).

Thus it is clear that localised connective tissue abnormalities are associated with GI pathology. In addition, evidence exists for the association between generalised connective tissue disorders, both inflammatory and non-inflammatory, and GI pathology.

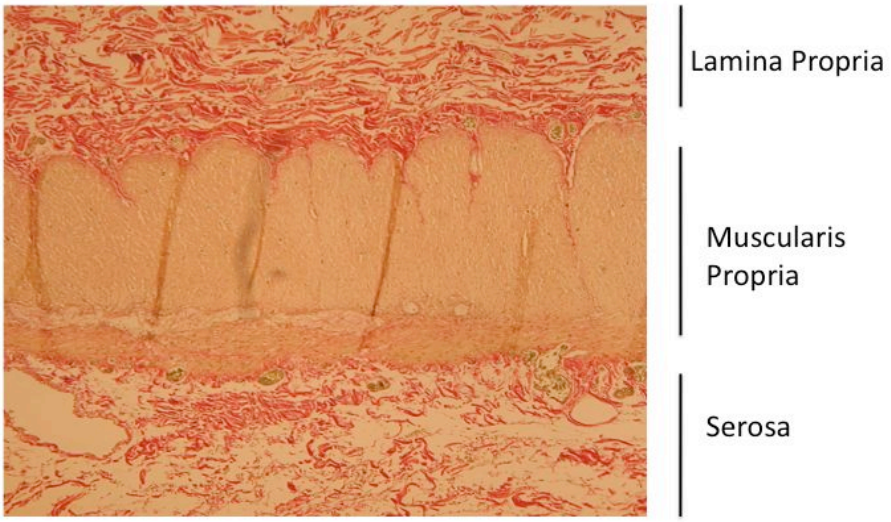


Figure 1.2: Full thickness colon specimen, stained with Millers Elastic Vangieson.
Collagen in red, muscle in yellow. Different layers of bowel annotated to right of vertical bars.

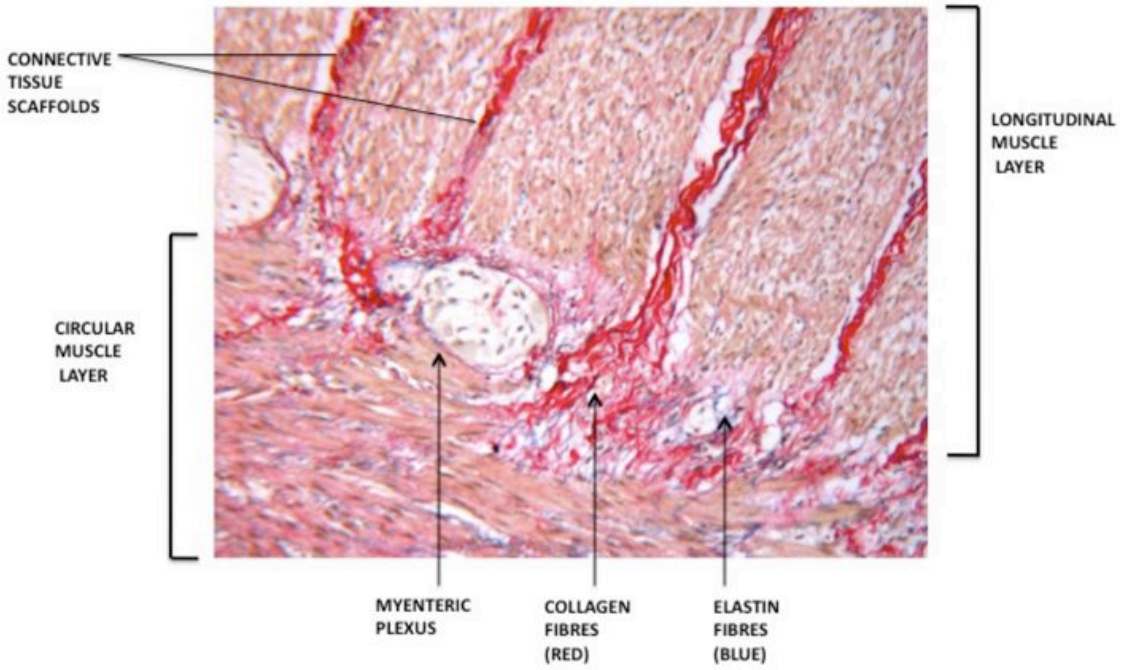


Figure 1.3 Millers Elastic Vangieson staining of the colonic muscularis propria.
Collagen scaffolds can be seen traversing the muscularis propria and then encapsulating the myenteric plexus.

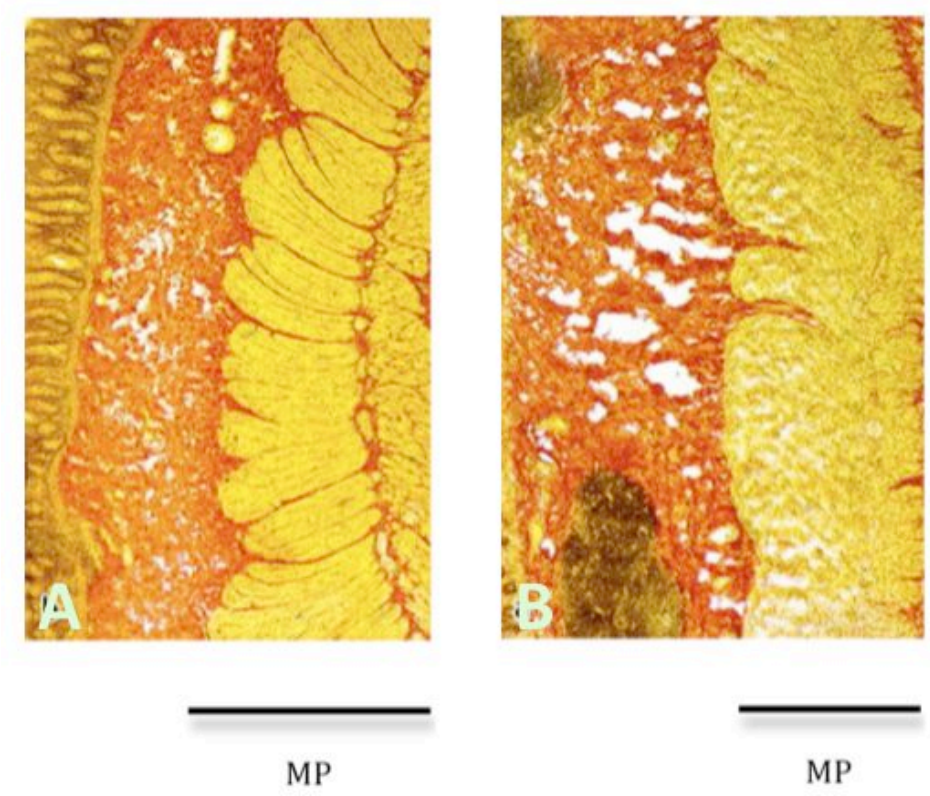


Figure 1.4: Atrophic desmosis of the colon.
Full thickness colonic tissue, collagen stained in red, horizontal bar identifying muscularis propria (MP) layer. a- Normal colonic tissue, with collagen bands seen running through the muscularis propria. b-Tissue from megacolon. Absence of collagen scaffolds in the muscularis propria compared to normal colon - 'atrophic desmosis'.

1.2.3.1 GI pathology in inflammatory connective tissue disorders

Scleroderma is an inflammatory connective tissue disorder characterised by autoimmune-mediated fibrosis in various organs. 90% of scleroderma patients have gastrointestinal involvement but only half are symptomatic. Typical symptoms include reflux, regurgitation, bloating and constipation (Figure 1.5) (Akesson and Wollheim 1989; Sallam, McNearney et al. 2006). GI symptoms are associated with pan-GI dysmotility – oesophageal hypomotility, gastroparesis, small bowel and anorectal dysmotility are all common in

scleroderma (Sallam, McNearney et al. 2006; Domsic, Fasanella et al. 2008; Gao, Liao et al. 2009).

Gastrointestinal involvement is thought to occur in two stages – a neuropathic process followed by a myopathic one, and both are thought to be, in part, a consequence of fibrosis (Ebert 2008). Evidence for this comes from animal studies whereby increased collagen deposition and fibrosis in the gut was associated with diminished colonic contractility (Thoua, Derrett-Smith et al. 2012).

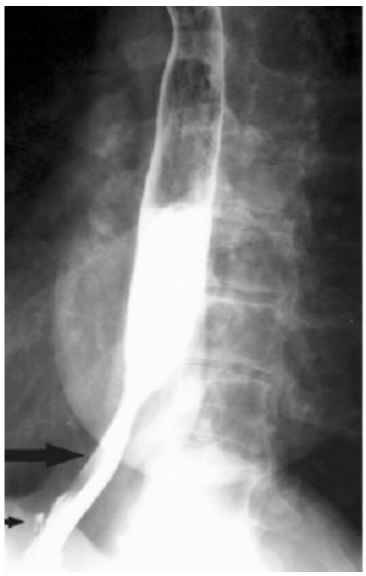


Figure 1.5: Barium swallow of scleroderma patient.
A long oesophageal peptic stricture (arrow) is visible.

1.2.3.2 GI pathology in non-inflammatory connective tissue disorders

Non-inflammatory connective tissue disorders are generally rare, and so most evidence comes from small case series and individual case reports. Mega-oesophagus, hernias and diverticular disease have been described in the Marfan Syndrome (Figure 1.6) (Eliashar, Sichel et al. 1998), and intestinal perforation and ruptured viscera in Ehlers Danlos Syndrome (EDS) vascular

type (Solomon, Abrams et al. 1996). The latter is part of the Ehlers-Danlos Group of disorders, which are characterised by tissue fragility, musculoskeletal symptoms and joint hypermobility.

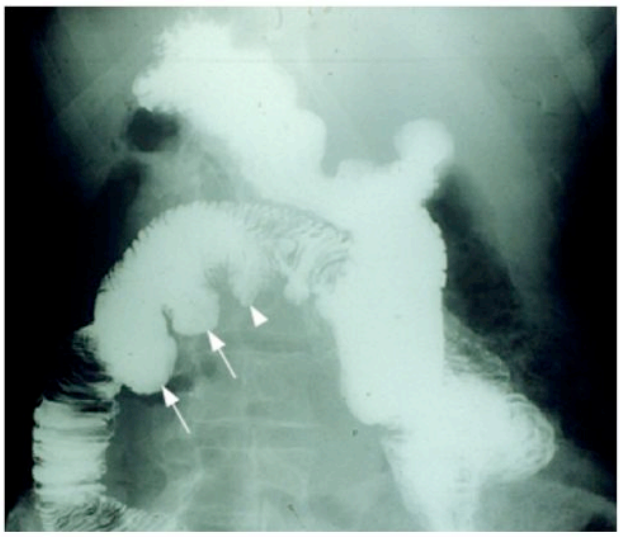


Figure 1.6: Barium enema of patient with the Marfan Syndrome, demonstrating large colonic diverticulae

1.3 Joint hypermobility

Joint hypermobility refers to the increased passive or active movement of a joint beyond its normal range (Figure 1.7). It can be localised to one or few joints, or generalised, the latter referred to as generalised joint hypermobility (GJH). Artistic depictions of GJH date as far back as the 15th century, as can be seen in Figure 1.8. It is a relatively common finding, with a prevalence of 5-17% (Bulbena, Duro et al. 1992). This varies geographically and with gender and age - it is more common in youth, in females and in non-whites (Rikken-Bultman, Wellink et al. 1997; Ishaq, Sheikh et al. 2010; Castori, Sperduti et al. 2012). It is a phenotypic trait or sign, and on its own does not signify the presence of disease i.e. it is not pathological. In fact, in some individuals e.g. ballerinas, gymnasts, musicians, it is considered an asset, and several studies

have confirmed a high prevalence of GJH in such populations (Kujala, Salminen et al. 1992; Decoster, Vailas et al. 1997; Day, Koutedakis et al. 2011).

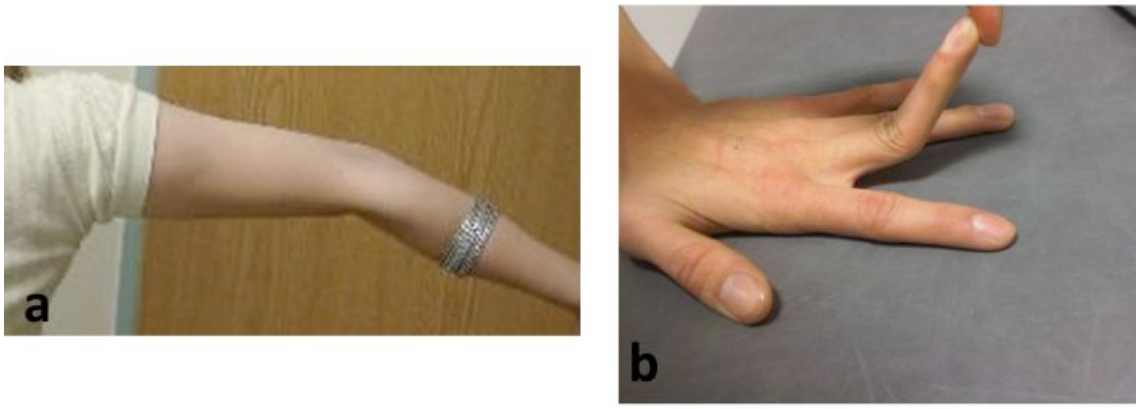


Figure 1.7: Joint hypermobility in the elbows (a), and fingers (b)

Figure 1.8: 'Saint Cyriaque' by Matthias Grunewald (1460-1628). Hypermobility of the fingers can be seen.

1.3.1 Assessment of Generalised Joint Hypermobility

1.3.1.1 Beighton score

The Beighton score is the gold standard technique for diagnosing GJH. This scores the flexibility of 9 joints (back, elbows, little fingers, thumbs and knees) as shown in Figure 1.9 (Beighton 1988). The maximum score is 9 out of 9; higher scores represent greater degrees of joint hypermobility. A score of 4 or more out of 9 is considered diagnostic of GJH (Beighton, Solomon et al. 1973).

1.3.1.2 5 point hypermobility questionnaire

GJH can also be diagnosed using a validated 5-point questionnaire, which has 84% sensitivity and 80% specificity when 2 or more questions are answered in the affirmative (Hakim and Grahame 2003) - Table 1.2. This questionnaire is particularly useful as a screening tool as it is easy and quick to complete.

Table 1.2: Validated questionnaire for generalised joint hypermobility. Answering YES to 2 or more out of the 5 questions is 84% sensitive and 80% specific for diagnosing GJH (Hakim and Grahame 2003).

1. Can you now [or could you ever] place your hands flat on the floor without bending your knees?
2. Can you now [or could you ever] bend your thumb to touch your forearm?
3. As a child, did you amuse your friends by contorting your body into strange shapes or could you do the splits?
4. As a child or teenager, did your kneecap or shoulder dislocate on more than one occasion?
5. Do you consider yourself ‘‘double-jointed’’?

Figure 1.9: **Calculation of the Beighton score.**

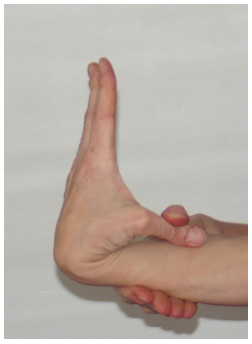
A score of 4 or more is diagnostic of joint hypermobility (GJH).

Ability to place hands flat on the floor without bending the knees – score 1

Hyperextension of elbow beyond 10 °

Score 1 for each elbow

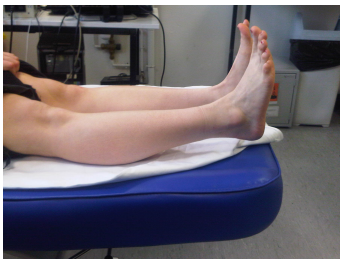
Maximum score: 2



Passive extension of thumb to the forearm

Score 1 for each thumb

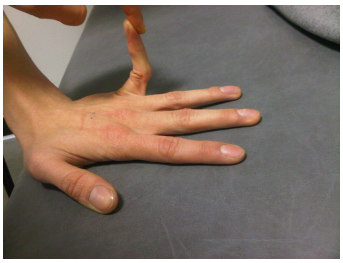
Maximum score: 2



Hyperextension of knee by at least 10° -

Score 1 for each knee

Maximum score: 2



Passive dorsiflexion of the little finger beyond 90°

Score 1 for each little finger

Maximum score: 2

1.3.2 Generalised Joint Hypermobility and connective tissue disorders

On its own, GJH is only a sign and not pathological. However, it is the hallmark of several connective tissue disorders that are pathological. These are the hereditary disorders of connective tissue, a group of inherited disorders characterised by abnormalities in connective tissue matrix proteins. Ehlers Danlos Syndrome and the Joint Hypermobility Syndrome are two examples of this.

1.4 Ehlers-Danlos Syndrome

The Ehlers Danlos Syndromes (EDS) are a heterogeneous group of inherited non-inflammatory connective tissue disorders which are thought to arise secondary to abnormalities in the synthesis and structure of collagen (Byers, Barsh et al. 1981). The current Villefranche classification divides EDS into 6 subtypes, based on the clinical phenotype and on the genetic and protein defect present, as shown in Table 1.3. All of the subtypes are characterised by varying degrees of tissue fragility, widespread musculoskeletal symptoms and joint hypermobility (Beighton, De Paepe et al. 1998) as shown in Figure 1.10 .

Table 1.3: Villefranche classification of Ehlers Danlos Syndromes (Beighton, De Paepe et al. 1998).

AD: autosomal dominant, AR: autosomal recessive, COL5: collagen 5, COL3: collagen 3, COL1: collagen 1, TNX: Tenascin X. ADAMTS: metalloproteinase genes

Villefranche nosology	Number	Prevalence	Features	Mode of inheritance	Aetiology	Genes implicated
Classical	Type 1 and 2	1 in 20,000 to 50,000	Hyperelasticity of skin, severe scarring	AD	Defect in collagen 5 synthesis	COL5A1, COL5A2, COL1A1
Hypermobility	Type 3	Unclear: thought to be 1 in 10,000	Extreme joint hypermobility	AD Or AR	Defect in tenascin X, a glycoprotein is responsible in 5% of cases	TNXB and COL3A1 in some cases
Vascular	Type 4	1 in 100,000 to 250,000	Rupture of blood vessels and organs	AD	Defect in collagen 3 synthesis	COL3A1
Kyphoscoliosis	Type 6	Fewer than 60 reported cases	Scoliosis, fragile eyes, severe muscle weakness	AR	Defects in lysyl hydroxylase enzyme	PLOD1
Arthrochlasis	Types 7A and B	Fewer than 30 reported cases	Joint hypermobility and congenital dislocation of both hips	AD	Defects in collagen 1	COL1A1, COL1A2
Dermatospraxis	Type 7C	Fewer than 10 reported cases	Extremely fragile and saggy skin	AR	Procollagenl N-terminal peptidase	ADAMTS2

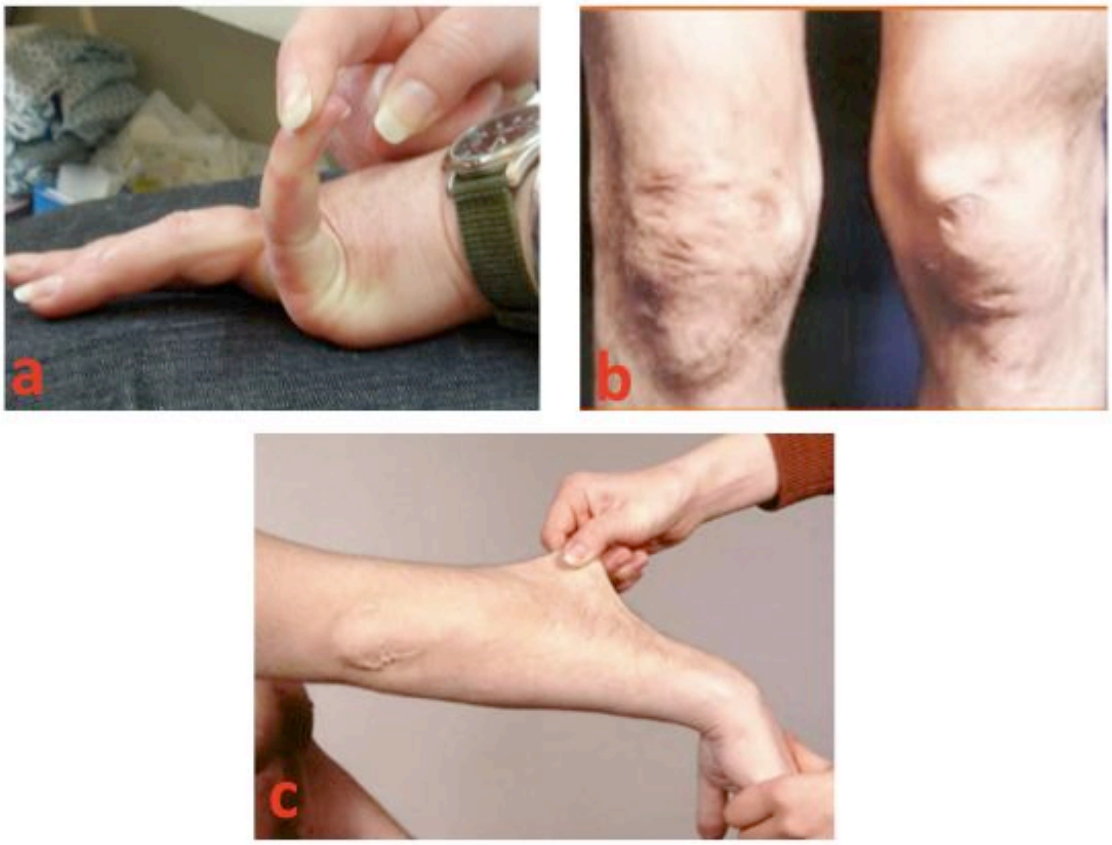


Figure 1.10: Common features of Ehlers Danlos Syndrome.
a- Hypermobility of the finger joints , b- Atrophic papyraceous scarring over the knees, c- Hyperelasticity of the skin.

1.4.1 Ehlers-Danlos Syndrome Hypermobility Type (EDS-HT)

1.4.1.1 Characteristic features

EDS Hypermobility Subtype (EDS-HT), formerly known as EDS Type III, is characterised by generalised joint hypermobility, easy bruising, poor wound healing and widespread musculoskeletal symptoms, predominantly pain (Beighton, De Paepe et al. 1998; Castori 2012). It is the most common of all the EDS subtypes, with a prevalence of around 1-5/10,000, and is more common in women than in men (De Paepe and Malfait 2012). It is present worldwide and cases have been documented in every continent (Beighton, Solomon et al.

1973; Bravo and Wolff 2006; Stoler and Oaklander 2006; Tofts, Elliott et al. 2009; Castori, Camerota et al. 2010; Liu, Fuh et al. 2011; De Wandele, Rombaut et al. 2013).

1.4.1.2 Aetiology

EDS-HT is an inherited disorder, and displays an autosomal dominant pattern of inheritance (De Paepe and Malfait 2012). Unlike the other forms of EDS, the causative gene has not been located, and so its aetiology is as yet unknown. Light microscopic and ultrastructural examinations of skin from affected individuals reveal non-specific changes in collagen and elastin, which are non-pathognomonic (Hausser and Anton-Lamprecht 1994; Hermanns-Le and Pierard 2007; Carlesimo, Cortesi et al. 2011; Hermanns-Le, Reginster et al. 2012).

Tenascin X deficiency

An autosomal recessive form of EDS-HT also exists, and this is associated with haploinsufficiency of Tenascin X (TNX), a glycoprotein involved in cell adhesion and the regulation of collagen deposition (Burch, Gong et al. 1997). This defect is thought to be present in no more than 5% of patients with EDS-HT (Zweers, Hakim et al. 2004). Affected individuals have a similar phenotype with generalised joint hypermobility, joint dislocations, poor wound healing, easy bruising, and muscle weakness. They do not, however, have atrophic scarring (Lindor and Bristow 2005; Voermans, Altenburg et al. 2007; Hendriks, Voermans et al. 2011; Merke, Chen et al. 2013). In these individuals, ultrastructural changes in the elastic fibres of the skin have been described (Zweers, Dean et al. 2005). In TNX-deficient patients with muscle weakness,

myopathic features are present in muscle biopsies. Tenascin-X null knockout mice recapitulate the skin and muscular findings of the human disease (Zweers, Schalkwijk et al. 2005; Voermans, Verrijp et al. 2011), confirming that TNX deficiency is responsible for the phenotype seen.

1.4.1.3 Diagnosis

As the aetiology of EDS-HT has not been characterised, there are no molecular, genetic or biochemical test available to diagnose it. Consequently, diagnosis is made using clinical criteria – the Villefranche diagnostic criteria for EDS-HT (Beighton, De Paepe et al. 1998) (Table 1.4). The presence of at least 2 major criteria is required for diagnosis.

As the clinical features of EDS-HT overlap substantially with the other subtypes (Table 1.3), diagnosis can be extremely difficult, and it is considered to be grossly underdiagnosed (Grahame 2008) .

Table 1.4: **Villefranche diagnostic criteria for the hypermobility type of Ehlers-Danlos Syndrome (Beighton 1988)**

Major criteria:
1-Beighton score of ≥ 5
2-Skin involvement: hyperextensibility or smooth velvety skin
Minor criteria:
1-Recurrent joint dislocations
2-Chronic limb/joint pain
3-Positive family history

1.4.1.4 Comparison of EDS-HT to other subtypes

It is clear that EDS-HT is quite different to the other subtypes for a number of reasons. It is more common than the other subtypes (De Paepe and Malfait 2012) (Table 1.3) , its aetiology has not been characterised, no diagnostic tests are available, and it is considered more benign. In fact, it seems to share more features in common with another hereditary disorder of connective tissue – the Joint Hypermobility Syndrome.

1.5 Joint Hypermobility Syndrome

The Joint hypermobility Syndrome (JHS) is an inherited non-inflammatory connective tissue disorder which was first described in 1967 (Kirk, Ansell et al. 1967). It is defined as the presence of widespread musculoskeletal symptoms in patients with GJH, in the absence of systemic rheumatological disease (e.g. rheumatoid arthritis, scleroderma) or life-threatening complications (e.g. bowel perforations and cardiac valvular abnormalities) (Hakim and Grahame 2003). It is pathological, unlike isolated GJH.

1.5.1 Epidemiology

The exact prevalence of JHS has not been determined, partly as most individuals with JHS are undiagnosed (Adib, Davies et al. 2005), and therefore population studies underestimate its prevalence. Consequently, quoted prevalences in the literature are either mathematical estimates, or obtained from observational studies of JHS in specific populations. Mathematical estimates propose a prevalence of 0.75-2% (Hakim and Sahota 2006). Prevalences of 5% (Biro, Gewanter et al. 1983), 15% (Garcia Campayo, Asso et al. 2010), 30% (Baeza-Velasco, Gely-Nargeot et al. 2011), 34% (Liu, Fuh et

al. 2011) and 39% (Bravo and Wolff 2006; Baeza-Velasco, Gely-Nargeot et al. 2011) , have been published in studies performed in USA, Spain, France, Taiwan and Chile respectively. The differences in prevalence reflect differences in the sampling population, and may not accurately reflect the true population prevalence. It does however, seem that the prevalence is geographically dependent. JHS is more frequently reported in females (Hakim and Grahame 2003) and tends to cluster in families (Finsterbush and Pogrund 1982).

1.5.2 Classical features in JHS

JHS is characterised by GJH, skin hyperelasticity and musculoskeletal symptoms. Skin tends to be thin and almost transluscent with visible capillaries and a bruising tendency (Castori, Camerota et al. 2010). Papyraceous scarring is common, as are excessive striae (Hakim and Sahota 2006) – Fig 1.11. The most common musculoskeletal complaint is arthralgia, but also includes recurrent dislocations, subluxations, and soft tissue injuries, all of which are thought to arise secondary to joint instability (Castori, Camerota et al. 2010).

Patients also exhibit non-musculoskeletal features, probably a consequence of fragility and laxity in other organs and tissues. Uterine and rectal prolapses, varicose veins, abdominal and inguinal hernias and myopia, and skeletal deformities such as scoliosis and the presence of a Marfanoid habitus (i.e. tall thin stature, long arms and fingers, high arched palate), have all been described in JHS and form part of the diagnostic criteria (Grahame, Bird et al. 2000).

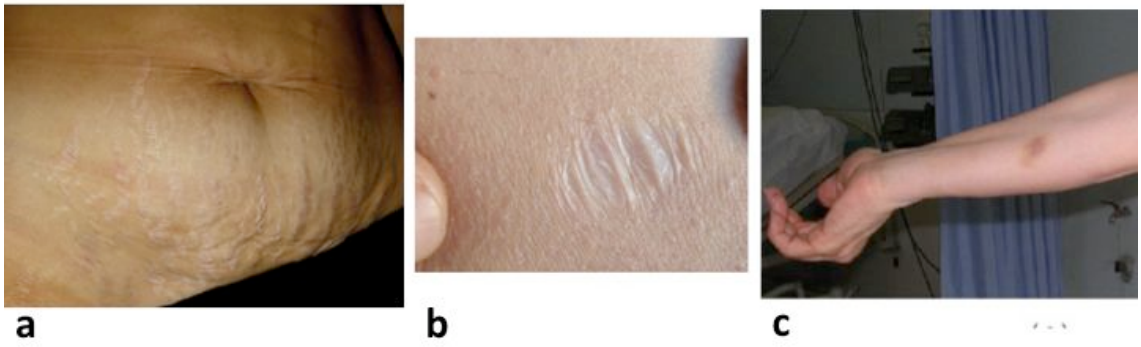


Figure 1.11: Cutaneous features of JHS
a – excessive striae , b – papyraceous scarring , c - bruising

Although JHS shares several features to the EDS disorders, namely the presence of GJH and skin abnormalities, presentation is not necessarily as pronounced, and life-threatening features are not present. As such it was previously known as the *benign* joint hypermobility syndrome. Recently, it has been recognised that the intensity and the burden of multiple different symptoms in JHS can, in fact, be quite debilitating to the patient (Adib, Davies et al. 2005). Studies confirm that quality of life is severely reduced in these patients (Rombaut, Malfait et al. ; Rombaut, Malfait et al. 2010) and pain seems to be an important predictor of poor quality of life (Castori, Camerota et al. 2010). As such, the use of the prefix 'benign' from the Joint Hypermobility Syndrome is now omitted (Tofts, Elliott et al. 2009).

1.5.3 Aetiology

JHS is a hereditary disorder, and inheritance follows an autosomal dominant pattern (Hakim, Cherkas et al. 2004; Malfait, Hakim et al. 2006). The exact aetiology of JHS, and the causative gene, is however, undiscovered. As the phenotype is very similar to the other EDS disorders, the aetiology is thought to involve abnormal connective tissue which then causes multi-system

involvement. However, genetic studies to date have been unsuccessful at identifying a gene responsible for JHS. This probably reflects the heterogeneity of the disorder.

Increased urinary excretion of collagen type I and III metabolites has been associated with the presence of JHS in patients with pelvic organ prolapses (Knuuti, Kauppila et al. 2010). However histological examination of skin from affected individuals do not reveal any pathognomonic abnormalities in connective tissue which can account for the disease (Hausser and Anton-Lamprecht 1994). Interestingly, a recent family study of JHS and EDS patients has demonstrated that non-specific ultrastructural collagen and elastin abnormalities are present in skin from patients with JHS and in those with EDS-HT. These changes seemed to be preserved in families, regardless of whether the family members had the hypermobility phenotype, suggesting some genetic linkage. More importantly however, flower-like collagen fibrils were seen in all affected patients, regardless of whether they were diagnosed with JHS or EDS-HT, and these changes were seen in a third of unaffected family members (Hermanns-Le, Reginster et al. 2012). This suggests that subtle collagen abnormalities are probably present in these individuals, but also that other (non-collagen) factors must be involved, in order to explain how relatives with the same abnormalities did not have a hypermobile phenotype.

1.5.4 Diagnosis

As no biomarker exists for JHS, diagnosis is made using clinical criteria. The 1998 Brighton classification system is the gold standard (Grahame, Bird et al.

2000) and incorporates most of the typical features of JHS described above (Table 1.5)

Table 1.5: The 1998 Brighton classification—diagnostic criteria for the Joint Hypermobility Syndrome (Grahame, Bird et al. 2000)

Major criteria

1. A Beighton score of 4/9 or greater (either currently or historically) .

2. Arthralgia for longer than 3 months in four or more joints.

Minor criteria

1. A Beighton score of 1,2, or 3/9 (0,1,2,or 3 if aged 50+).

2. Arthralgia (for 3 months or longer) in one to 3 joints or back pain for (for 3 months or longer), or spondylosis, sponylolysis/spondylolisthesis.

3. Dislocation/subluxation in more than one joint, or in one joint on more than one occasion.

4. Soft tissue rheumatism: three or more lesions (e.g. epicondylitis, tenosynovitis, bursitis).

5. Marfanoid habitus (tall, slim, span/height ratio>1.03 upper: lower segment ratio <0.89, arachnodactyly).

6. Abnormal skin: striae, hyperextensibility, thin skin, papyraceous scarring.

7. Eye signs: drooping eyelids or myopia or antimongoloid slant.

8. Varicose veins or hernia or uterine/rectal prolapse.

A diagnosis of JHS requires the presence of either:

- 2 major criteria,
- 1 major and 2 minor criteria
- 4 minor criteria, or
- 2 minor criteria and the presence of an unequivocally affected first-degree relative.

JHS is excluded by the presence of the Marfan Syndrome or EDS, other than EDS-HT.

As can be seen from Table 1.5 the diagnostic criteria incorporate the Beighton score. For major criteria a Beighton Score of 4 or more is required while for minor criteria, Beighton scores of less than 4 are acceptable. This may seem surprising, as this would suggest that individuals who are not hyperflexible may still satisfy criteria for JHS. The rationale behind such a design was to account for aging – older patients are less likely to have GJH, and so Beighton scores will decrease with age (Finsterbush and Pogrund 1982). However, in parallel with this, other complications such as soft tissue injuries and hernias (other minor criteria) will become more important (Castori, Sperduti et al. 2012). Thus the Brighton criteria are considered to take account of age and allow diagnosis of JHS independent of age (Grahame, Bird et al. 2000).

Diagnosis of skin changes

Skin changes in JHS appear under the minor criteria (Table 1.5), and include skin hyperextensibility, and papyraceous scarring (Figure 1.11). This requires an examination of the skin, and in particular a test of its ‘elasticity’. Historically

this was done by retracting the skin from the back of the hand or forearm, and performing a visual estimation of the degree of stretch. This is clearly subjective, so attempts to develop a more objective marker have been made. One technique uses a suction or cupping device, but this has not shown much reproducibility or validity (Remvig, Duhn et al. 2009; Remvig, Duhn et al. 2010). In a novel method called the skin stretch test, a lateral force is applied to the skin on the back of the hand to calculate the percentage increase in stretch. This is then divided by the thickness of the skin to give a corrected skin extensibility score (CSES) (Farmer, Douthwaite et al. 2010) (Figure 1.12).The CSES was shown to correlate very well with the Beighton score in healthy individuals, and a cut-off of 18 percent per mm, had a 72% sensitivity and 75% specificity for predicting GJH in healthy individuals (Farmer, Douthwaite et al. 2010). This test has been validated in healthy volunteers but not in individuals with JHS.

Most of the Brighton criteria are subtle and relatively subjective and so it is unsurprising that the exact prevalence of JHS has not been well documented, nor indeed that the condition is grossly underdiagnosed and patients can seek help for their symptoms for over a decade before a diagnosis is reached (Simpson 2006). The Brighton classification exemplifies the fact that JHS phenotypes can be heterogeneous as a diagnosis of JHS can be achieved by differing combinations of the Brighton criteria. For example, a young patient with a Beighton score of 8 out of 9, a Marfanoid habitus and multiple spontaneous dislocations, fulfils the criteria for JHS, as does an older patient with a Beighton score of 2 out of 9, varicose veins, multiple soft tissue injuries and the presence of generalised arthralgia, despite the fact that their presentations are quite

different (Table 1.5). This is a consequence of the Brighton classification which was designed as such to account for the multisystem nature of the disorder and the changing presentation with increasing age.

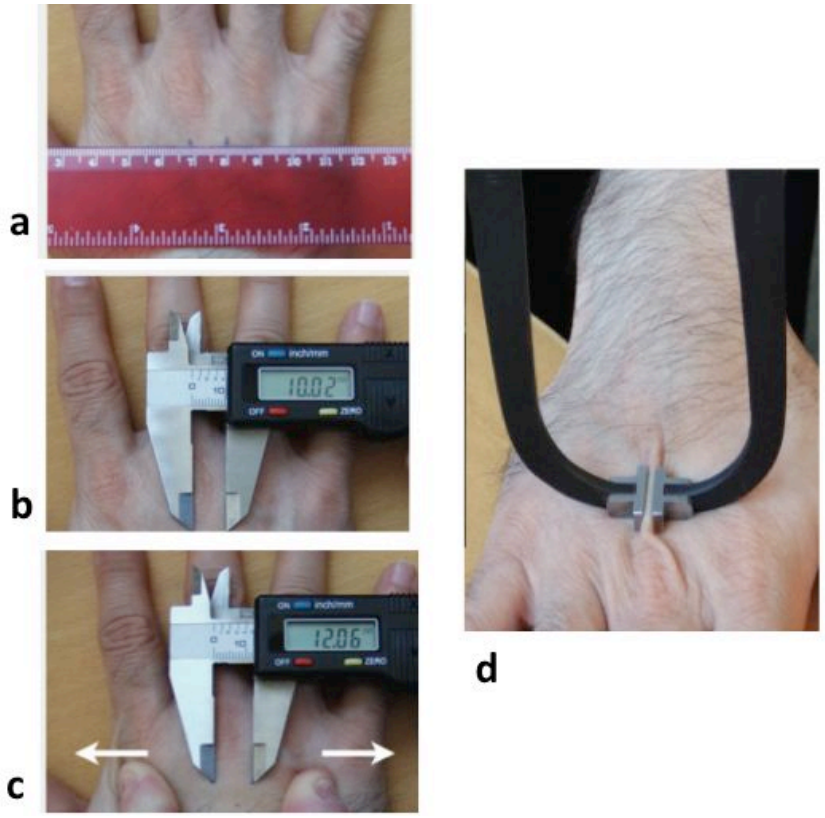


Figure 1.12: Skin stretch test

a) 2 dots are placed on the back of the hand, 1cm apart b) the distance between the dots is measured c) a lateral force is applied to the skin and the percentage increase in stretch is measured; d) this is then divided by the thickness of the skin to give a corrected skin extensibility score (CSES) (Farmer, Douthwaite et al. 2010)

From Table 1.4 and Table 1.5, it can be seen that the Brighton classification for JHS is very similar to the Villefranche classification for EDS-HT. In fact both EDS-HT and JHS are thought to be part of the same disorder and the two terms are now used interchangeably (Tinkle, Bird et al. 2009) . For the purpose of this thesis, the term JHS will be used to describe both JHS and EDS-HT. The term

'hypermobility' will be used to describe any disorder which is characterised by joint hypermobility, and will therefore include GJH, EDS-HT and JHS.

1.5.5 Extra-articular associations of JHS

Since the Brighton classification was formulated over 14 years ago, it has become apparent that the effect of JHS is much more widespread than originally suspected. Epidemiology studies have revealed that several disorders and extra-articular symptoms are associated with JHS, all of which contribute to morbidity and further decrease quality of life in affected patients (Verbraecken, Declerck et al. 2001; Hakim and Grahame 2004; Voermans, Knoop et al. 2009).

1.5.5.1 Neurological

Autonomic dysfunction –Postural Orthostatic Tachycardia Syndrome

The association between JHS and autonomic dysfunction was recognised over 10 years ago. Up to 78% of patients with JHS have autonomic symptoms (Rombaut, Malfait et al. 2011), particularly orthostatic symptoms (Gazit, Nahir et al. 2003) and these are associated with demonstrable changes in autonomic parameters (Gazit, Nahir et al. 2003). More recently, this association has been refined and it appears that most JHS patients with autonomic dysfunction suffer with the Postural Orthostatic Tachycardia Syndrome (PoTS) (Bohora 2010; Kanjwal, Saeed et al. 2010). Patients with PoTS have symptoms of dizziness, palpitations, pre-syncope and syncope, and these symptoms can be exacerbated by prolonged standing, exertion, alcohol, heat and sometimes ingestion of carbohydrates (Mathias, Low et al. 2011). It is present in a large proportion of patients with JHS and is diagnosed by the presence of a rise in pulse rate by more than 30, or an increase in pulse to greater than 120 bpm ,

within 10 minutes of moving from a recumbent to a standing position, without accompanying orthostatic hypotension. It is often accompanied by visible venous pooling in the lower limbs or blotching of the skin. It is not considered an autonomic failure, as specific sympathetic and parasympathetic tests appear to be normal. In PoTS, a rise in noradrenaline levels (NA) is common but baseline catecholamine levels are normal. The exact mechanism by which this occurs in unknown, but it is thought to involve a failure of normal vasoregulatory mechanisms and therefore an uneven redistribution of circulatory blood volume, with various precipitants (Mathias, Low et al. 2011).

Neuromuscular

Muscle weakness can be a major cause of disability in JHS (Rombaut, Malfait et al. 2010), and several patients have severe limitations in their mobility, to the point at which they are wheelchair-bound. Muscle weakness in JHS is due to impaired muscle function rather than a reduction in muscle mass (Rombaut, Malfait et al. 2012). Affected individuals appear to have proprioceptive problems mainly involving the large joints and this seems to improve with training (Eyigor, Ozdedeli et al. 2008; Rombaut, De Paepe et al. 2009). They also have increased passive muscle tension and stiffness (Rombaut, Malfait et al. 2012), confirming that hypermobility extends beyond the joints, and also affects the muscles and tendons (Voermans, van Alfen et al. 2009).

Fatigue

Fatigue is a frequent JHS symptom and significantly contributes to disability (Voermans, Knoop et al. 2009). Fatigue is strongly correlated with both the self-report of muscle weakness and objective assessment of weakness (Voermans,

Knoop et al. 2011). Both pain and fatigue are important predictors of muscle weakness, suggesting that they co-occur. This is typical for presentation of the chronic fatigue syndrome, and in fact studies have documented a strong association between hypermobility conditions and chronic fatigue syndrome in both children and adults (Barron, Cohen et al. 2002; Nijs, Aerts et al. 2006).

Migraine

Females with JHS have an increased prevalence of migraines (Bendik, Tinkle et al. 2011).

1.5.5.2 Uro-gynaecological

Urological

Urinary symptoms are common in JHS. Even in nulliparous women and children, urinary stress incontinence, detrusor instability and recurrent urinary tract infections occur more frequently compared to controls (de Kort, Verhulst et al. 2003; Manning, Korda et al. 2003; Arunkalaivanan, Morrison et al. 2009).

Gynaecological

There is an increased prevalence of obstetric complications with a higher risk of premature rupture of the membranes, early delivery, bleeding and perineal trauma (Dutta, Wilson et al. 2011; Molloholli 2011). Later complications include poor wound healing, urine and faecal incontinence and uterine prolapse (Molloholli 2011). Prolapse appears to be the most clinically relevant complication and is associated with episiotomy (Castori, Morlino et al. 2012).

Dysmenorrhoea and menorrhagia is present in over half of patients with established JHS; irregular menses and vulvodynia is present in over a third (Castori, Morlino et al. 2012).

1.5.5.3 Chronic pain

Pain is a common finding in JHS (Voermans and Knoop 2010; Voermans, Knoop et al. 2011), and in fact, joint pain is an important component of the Brighton classification (Table 1.5). However, in addition to arthralgia, individuals with JHS experience widespread pain, which is often recurrent, chronic, and significantly impairs quality of life (Castori, Morlino et al. 2012). As testament to this, opiates and antidepressants are common prescriptions in these individuals. In a recent study of JHS patients in a genetics clinic setting, 37% were on opiates, and 20% were on antidepressants (Rombaut, Malfait et al. 2011). Interestingly, it has been observed that patients with JHS (or EDS-HT) have far more pain than those with classical EDS despite the fact that the latter subtypes have far more dramatic joint involvement (Castori 2012). This would suggest that pain is not solely due to joint damage, but rather that altered pain mechanisms are involved. This is supported by the fact that these patients suffer with chronic pain syndromes, such as fibromyalgia and chronic regional pain syndrome (Ofluoglu, Gunduz et al. 2006; Stoler and Oaklander 2006), and that neuropathic pain is common (Voermans, Knoop et al. 2011).

Fibromyalgia (FM)

The prevalence of FM in JHS is high and is present in almost 50% of adults with JHS (Sendur, Gurer et al. 2007) . Equally, the prevalence of JHS in FM is also high. 64% of adults with FM have JHS (Ofluoglu, Gunduz et al. 2006), and in

children with FM the prevalence of JHS ranges from 40% (Siegel, Janeway et al. 1998) to 81% (Gedalia, Press et al. 1993). Adolescents with JHS and FM have significantly more pain sensitivity i.e. more tender points and lower threshold for pain, but no differences in the self reporting of pain (Ting, Hashkes et al. 2012). This supports the notion that pain processing may be altered in JHS.

Complex regional pain syndrome

Complex regional pain syndrome (CRPS), formerly known as reflex sympathetic dystrophy , is a chronic systemic disorder characterised by limb pain, swelling, and vasoregulatory changes, often visible in the skin. Dysregulation of the autonomic and central nervous system, causing central and peripheral sensitisation, is thought to be involved, as are immune mechanisms (Goebel). Interestingly, recent literature has found a possible association between both JHS and EDS (including classical EDS), and CRPS, although the exact mechanism is still unknown (Stoler and Oaklander 2006).

It would thus appear that a significant proportion of patients with JHS have a chronic pain syndrome which probably includes different types of pain including nociceptive pain (arthralgias), neuropathic pain (e.g. chronic regional pain syndrome), and functional somatic pain (e.g. fibromyalgia), and is accompanied by fatigue . A clear explanation for several of these pain syndromes, and for the accompanying fatigue, is not available, although it is thought that both peripheral and central hypersensitivity are likely to be involved (Castori, Morlino et al. 2012). The lack of understanding of the cause of pain adds to the difficulty

in treatment, thus causing further disability and impairing quality of life (Voermans and Knoop 2010).

1.5.5.4 Psychopathology

JHS individuals have high levels of emotional and psychological distress, and a higher number of somatic symptoms. Individuals with JHS are almost 16 times over-represented in those with panic disorders (Garcia Campayo, Asso et al. 2010). JHS patients who are pain-free have a higher frequency and intensity of somatic symptoms (somatosensory amplification), and higher anxiety scores compared to a control group (Ercolani, Galvani et al. 2008; Garcia-Campayo, Asso et al. 2010), suggesting that the psychopathology is not secondary to pain. Population studies have demonstrated that in previously undiagnosed JHS (i.e. non-patients), high levels of somatosensory amplification and anxiety are present in both males and females, and that females had higher levels of depression compared to controls (Baeza-Velasco, Gely-Nargeot et al. 2011).

The association between JHS and anxiety is robust - it has been replicated, it is present in non-patients and the prevalence of anxiety has been shown to increase with time (Garcia-Campayo, Asso et al. 2010). In a longitudinal study with a 15 year follow up, the relative risk of developing anxiety in patients with, compared to without, JHS was 22.3 (Bulbena, Gago et al. 2011) , suggesting that JHS is a risk factor for anxiety disorders. The mechanism for this is unknown but is thought to be either due to alterations in linked genes which predispose to both GJH and anxiety disorders (Gratacos, Nadal et al. 2001) , or due to altered autonomic processing centrally (Gazit, Nahir et al. 2003). One MRI study has reported increased amygdala volumes in patients with JHS – this

brain region is responsible for emotional processing of pain (Eccles, Beacher et al. 2012). This has not been replicated so firm conclusions cannot yet be drawn from this.

From the evidence it is clear that higher levels of psychological distress are present in JHS, both in patients and in healthy non-patients.

1.5.5.5 Cardio-respiratory

Individuals with JHS tend to suffer with palpitations (Gazit, Nahir et al. 2003), and there is an increased incidence of JHS in individuals with mitral valve prolapse (Yazici, Ataoglu et al. 2004).

There is an increased prevalence of asthma and atopy in JHS and this is associated with physiological evidence of increased lung volumes, impaired gas exchange and an increased tendency of both the lower and upper airways to collapse (Morgan, Pearson et al. 2007) .

1.5.5.6 Orthopaedic

Early osteoarthritis is frequently encountered in JHS, and is thought to be a consequence of the excessive and unusual strain put on the joints while they are hyperextended (Dolan, Hart et al. 2003). JHS is also associated with osteopenia and osteoporosis, though the exact mechanism by which this occurs is not clear (Dolan, Arden et al. 1998; Gulbahar, Sahin et al. 2006).

1.5.5.7 Dental

Tempero-mandibular joint dysfunction is present in over 70% of JHS patients (Hirsch, John et al. 2008) which results in repeated jaw clicking, locking, and pain and is thought to be due to increased tempero-mandibular joint mobility.

1.5.5.8 Bleeding disorders

Clinically, patients with JHS tend to have a bleeding or bruising tendency, but clotting parameters are generally normal. In a haematology 'bleeding disorder' clinic, the prevalence of JHM in patients with a bleeding disorder was 23% compared to a prevalence of 2% in a control population with no bleeding disorder. 77% of the patients with JHM also had JHS (Jackson, Odiaman et al. 2012).

1.5.5.9 Ocular

Ocular features in JHS include xerophthalmia, steeper corneas, pathologic myopia, and vitreous abnormalities, as well as a higher rate of minor lens opacities (Gharbiya, Moramarco et al. 2012). Blue sclera, are also relatively common and are thought to be due to the visible uveal vessels through the thinner sclera (Bravo and Wolff 2006).

1.5.6 Functional somatic symptoms, JHS and FGID

It is clear that JHS is a systemic disease with widespread organ involvement. Furthermore, it is associated with several medically unexplained disorders, the so called functional somatic syndromes e.g. FM, chronic fatigue syndrome, chronic regional pain syndrome, TMJ dysfunction and migraines (Castori, Celletti et al. 2011), all of which are also linked with FGID.

Several of these somatic symptoms were described in a study investigating possible autonomic-induced symptoms in JHS. It was found that apart from joint pain and fatigue, the most common symptoms in JHS patients were insomnia, syncope, migraines, psychopathology and gastrointestinal symptoms (Hakim and Grahame 2004). From the link between functional somatic symptoms and both JHS and FGID independently, it would be assumed that an association exists between FGID and JHS. As yet, there is no direct evidence for this. However, there is an increasing body of work that supports an association between joint hypermobility, anatomical and physiological GI abnormalities and GI symptoms.

1.6 Joint Hypermobility and the GI tract

1.6.1 Joint Hypermobility and abnormal GI anatomy

Joint Hypermobility is associated with several anatomical abnormalities in both the upper and lower GI tract. In a study of 100 patients attending an endoscopy unit, the prevalence of GJH in patients with hiatus hernias (22%) was significantly increased compared to age and sex-matched controls without hernias (6%, $p<0.001$) (Al-Rawi, Al-Dubaikel et al. 2004).

In patients with constipation and symptoms of rectal evacuatory dysfunction those with GJH had an increased prevalence of rectal morphological anomalies compared to those without GJH (Mohammed, Lunniss et al. 2010), most commonly large functional rectoceles (24%) and external compression of the anterior rectal wall (11%). Lower GI symptoms frequently overlap with urinary symptoms, and a study of patients with lower urinary tract dysfunction similarly

demonstrated that patients with JHS were significantly more likely to have symptoms of rectal evacuatory dysfunction and evidence of rectal morphological anomalies e.g. rectal prolapses, compared to those without JHS (Manning, Korda et al. 2003) .

Case reports of patients with JHS or EDS-HT describe further anatomical abnormalities in small numbers of patients, including diverticular disease (Lindor and Bristow 2005), and viscerotopsis of the bowel (Reinstein, Pimentel et al. 2012). The latter is rare and refers to the downward displacement of abdominal organs below their natural position. It can cause kinking of blood vessels and nerves and thereby cause symptoms, which can be severe. In one case described, the patient presented with a 4 year history of abdominal distension and bloating that interfered with her eating and activities of daily living.

1.6.2 Joint hypermobility and abnormal GI physiology

Physiologically, there is an association between GJH and constipation (Reilly, Chase et al. 2008; Manning, Korda et al. 2003; Al-Rawi, Al-Dubaikel et al. 2004) In young boys, a higher prevalence of GJH was demonstrated in those with slow transit constipation compared to those without (Reilly, Chase et al. 2008) . Adults appear to have a different pattern of constipation, and in a study of adults referred for lower GI physiology testing for functional constipation, those with GJH had more severe constipation, greater abdominal pain, increased laxative use and need for manual evacuation. However, there was no increase in slow transit constipation, but instead a higher prevalence of rectal evacuatory dysfunction was observed in these patients (Mohammed, Lunniss et al. 2010).

1.6.3 Association between JHS and GI symptoms

The association between JHS and GI symptoms was first described 8 years ago by Hakim and Grahame (Hakim and Grahame 2004). They found that JHS patients attending a hypermobility clinic had significantly more GI symptoms compared to age and sex matched controls (37% vs 11%) (Figure 1.13). The most common GI symptoms were nausea, abdominal pain, constipation and diarrhoea. It was felt that dysautonomia was one mechanism by which this may occur (Gazit, Nahir et al. 2003; Hakim and Grahame 2004), and since then it has been shown that POTS is associated with GI symptoms such as nausea, reflux, bloating, constipation and diarrhoea (Mathias, Low et al. 2011). Thus it would appear that JHS, autonomic symptoms and GI symptoms are indeed linked, though the exact mechanism for the association is unknown.

Since that landmark study, other studies worldwide in specialist hospital settings have confirmed that GI symptoms are common in patients with an existing diagnosis of JHS. In a study of 21 JHS patients attending a genetics clinic in Italy, 87% of patients were found to have GI symptoms, most commonly dyspepsia (67%), gastro-oesophageal reflux (57%), recurrent abdominal pain (62%), alternating constipation and diarrhoea (33%) and abdominal hernias (5%) (Castori, Camerota et al. 2010). Furthermore, it was observed that the incidence of GI symptoms increased with age, and that older JHS patients were more likely to have GI symptoms than their younger counterparts (Castori, Sperduti et al. 2012).

Another study demonstrated not only that GI symptoms such as constipation, diarrhoea, bloating and swallowing problems are present in JHS, but that these

GI symptoms are also associated with clusters of other extra-articular symptoms, in particular cognitive problems, insomnia, postural dizziness and syncope (Rombaut, Malfait et al. 2011), supporting previous findings. Furthermore, there was large heterogeneity in presentation and with cluster analysis it was demonstrated that 2 main clusters of symptoms, and therefore patients, were present. Musculoskeletal symptoms were prominent in both clusters but GI symptoms were particularly prominent in the group which also had high levels of fatigue, cutaneous changes, orthostatic, immune, urogynecologic, visual and respiratory problems (De Wandele, Rombaut et al. 2013).

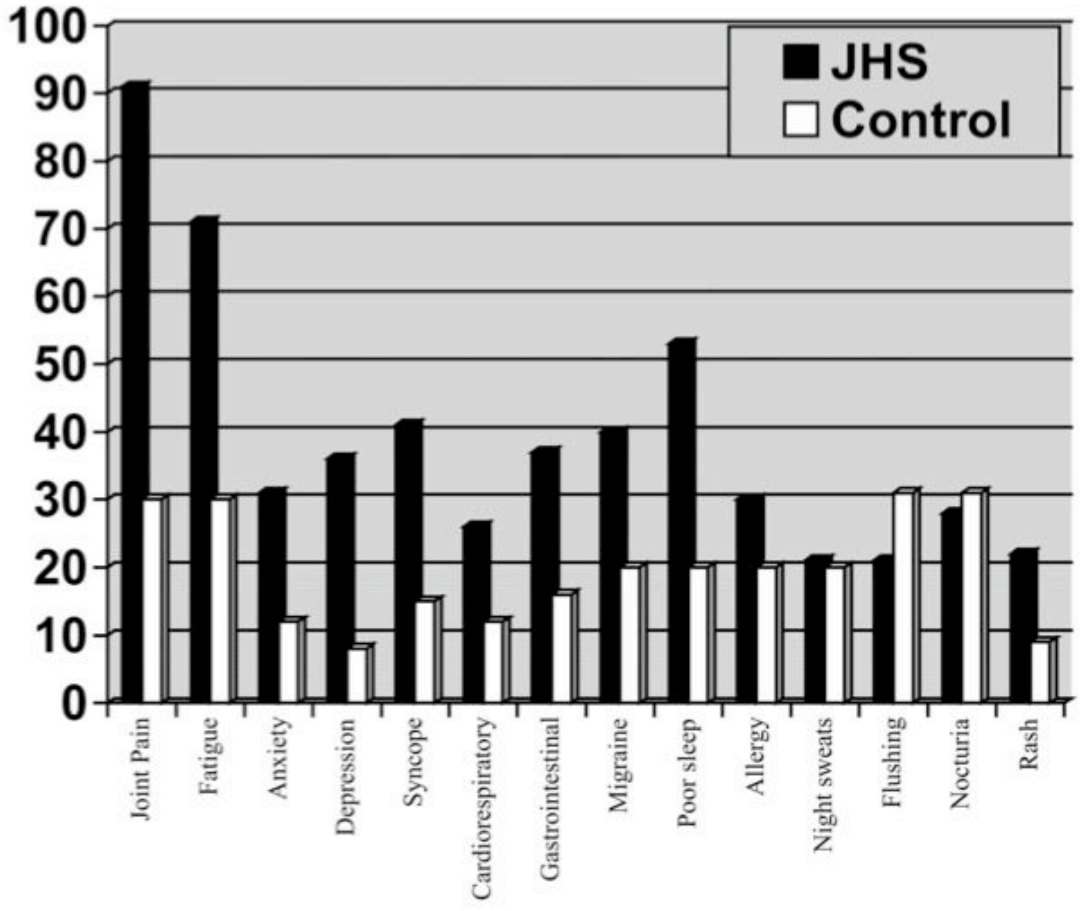


Figure 1.13: Extra-articular symptoms in JHS
(Hakim and Grahame 2004)

Thus the association between GI symptoms and JHS in specialist hospital settings seems to be consistent. Furthermore there appears to be clustering of JHS and GI symptoms with several other symptoms, including musculoskeletal pain, fatigue, autonomic symptoms and urological symptoms, to varying degrees.

From a gastroenterology point of view, GI symptoms can be due to organic disorders or functional disorders. There is literature, albeit limited, that associates JHS with both types of disorder.

1.6.4 Joint hypermobility and organic GI disorders

Only 2 published studies exist which demonstrate a possible association between hypermobility and organic disorders, and these were done in patients with inflammatory bowel disease (IBD) and coeliac disease. The first compared 69 patients with IBD to 67 age and sex-matched controls. A significantly higher prevalence of GJH was found in patients with Crohn's disease (70%) compared to controls (25%) and to patients with Ulcerative colitis (36%), (Vounotrypidis, Efremidou et al. 2009), suggesting a possible association between GJH and Crohn's Disease though this has not yet been replicated. Additionally, only GJH was assessed, so it is questionable whether the findings can be generalised to JHS.

The other study assessed 31 JHS patients for celiac disease. 5 (16%) had a confirmed diagnosis based on both serological and histological testing (Danese, Castori et al. 2011), which was significantly higher than the estimated population prevalence (1%). However, the patients were a highly selected

group of patients attending specialist clinics and therefore these findings are not necessarily generalisable to the majority of patients with JHS, most of whom remain undiagnosed.

1.6.5 Joint hypermobility and functional GI disorders

The only direct evidence for an association between FGID and hypermobility comes from a single retrospective observational study in tertiary gastroenterology setting (Zarate, Farmer et al. 2009). In this study, the validated 5-point hypermobility questionnaire was used to screen for GJH in 129 consecutive patients attending a neurogastroenterology clinic. The prevalence of GJH in these clinic patients was 49%, three times higher than the prevalence in healthy controls (17%). Those with GJH were more likely to have GI symptoms without a known underlying structural, biochemical, metabolic or autoimmune cause compared to those without GJH i.e. the symptoms were more likely to be unexplained. A subgroup of these patients were assessed further by a rheumatologist, and found to have JHS. The patients with JHS tended to have motility problems in their gut on physiological testing, e.g. small bowel dysmotility, delayed gastric emptying and delayed colonic transit. This study confirmed that in a tertiary neurogastroenterology setting, GJH was strongly associated with unexplained GI symptoms, or FGID, and that GI dysmotility was common in patients with GI symptoms and JHS, suggesting that these patients may have a neuromuscular basis for their symptoms.

These may represent a unique group of patients in FGID clinics, who are more likely to have unexplained symptoms and underlying dysmotility. Abnormal connective tissue may be contribute to GI pathology in this group,

Although no large observational studies have been published that definitely confirm an association between JHS and FGID, smaller studies have demonstrated not only that IBS symptoms are common in JHS (Hakim and Grahame 2004; Castori, Camerota et al. 2010; De Wandele, Rombaut et al. 2013), but that JHS patients with GI symptoms often have a pre-existing diagnosis of IBS (Manning, Korda et al. 2003; Castori, Camerota et al. 2010).

Further support for the association between JHS and FGID comes from the fact that both disorders share several features, in particular an association with several medically-unexplained disorders, also known as functional somatic syndromes – Table 1.6. In fact, it has been speculated that that the same underlying process, involving a combination of somatic hypersensitivity, chronic pain, and dysautonomia, underlies all the functional somatic syndromes and that JHS is the common link (Castori, Celletti et al. 2011).

Table 1.6: Similarities between JHS and FGID.
Asterisks mark disorders that are considered functional somatic syndromes.

	JHS	FGID
DEMOGRAPHICS		
Population prevalence	5-17%	2.5-13%
Gender	More common in females	More common in females
Age	Incidence decreases with age	Incidence decreases with age
SYMPTOMS		
Chronic pain	Yes	Yes
Hypersensitivity	Somatic	Visceral
DIAGNOSIS		
Validated biomarker	No	No
Criteria based diagnosis	Yes	Yes
DISEASE ASSOCIATIONS		
Fibromyalgia*	Yes	Yes
Chronic fatigue syndrome*	Yes	Yes
Anxiety	Yes	Yes
Depression	Yes	Yes
Migraine*	Yes	Yes
TMJ disorder*	Yes	Yes
Pelvic/bladder pain*	Yes	Yes
Insomnia	Yes	Yes
Allergies/Atopy	Yes	Yes
Autonomic dysfunction	Yes	Yes

1.7 Limitations and Knowledge gaps

Despite the lack of direct evidence, the existence of this growing body of work is suggestive of an association between JHS and GI symptoms. Moreover, it leads us to think that there might be an overlap between FGID and JHS, and that they share a common aetiology which may explain a subgroup of patients with FGID. This would have important prognostic and aetiological implications, and could potentially lead to a paradigm shift in the way we approach FGID. However, before such a novel concept is proposed, and a detailed analysis of connective tissue in the GI tract of these individuals is begun, it is imperative to conclusively confirm that an association between GI symptoms, FGID and JHS exists, to characterise it fully, and to tease out the various factors which might be involved in this association. This has not yet been done, and the studies described above all have their limitations which restricts the conclusions that can be drawn from them.

1.7.1 Limitations of currently performed research studies

The main limitation of the above studies is the selection bias. The JHS patients studied were those seeking specialist care in rheumatology or genetics clinics, which are often tertiary care settings (Hakim and Grahame 2004; Castori, Camerota et al. 2010; Rombaut, Malfait et al. 2011; De Wandele, Rombaut et al. 2013). Given that JHS is underdiagnosed, this population is unlikely to represent the majority of JHS patients, but instead more likely to represent the most severe cases at the tip of the iceberg with refractory symptoms. Secondly, several of the studies were small, with not more than 40 JHS patients (Reilly, Chase et al. 2008; Castori, Camerota et al. 2010). In view of the fact that JHS is

actually quite common and heterogeneous, this is a very limited sample, and again may not reflect the general population of JHS patients. Thirdly, there is huge variation in the type of controls used in the study – in the majority of studies these were healthy patients (Hakim and Grahame 2004), but in some studies, there were no controls at all (Castori, Camerota et al. 2010; Rombaut, Malfait et al. 2011; De Wandele, Rombaut et al. 2013). GI symptoms are very common in the general population, therefore it is difficult, in the absence of a suitable control group, to comment on whether the prevalence of GI symptoms is disproportionately high. Furthermore, it is interesting that no studies of GI symptoms in JHS have been performed in a gastroenterology setting. In view of the high incidence of GI symptoms reported in JHS, it would be expected that some of these patients would end up in a gastroenterology clinic, yet this has not been reported, nor has a comparison of symptoms in JHS been made with a GI control population. The only studies that have been performed in a GI setting were those relating to GI physiology and anatomy (Al-Rawi, Al-Dubaikel et al. 2004; Zarate, Farmer et al. 2009; Mohammed, Lunniss et al. 2010), but these looked at patients with GJH rather than JHS. Even with the GJH patients, methods of diagnosing hypermobility varied amongst the studies – some used the Beighton score (Al-Rawi, Al-Dubaikel et al. 2004; Reilly, Chase et al. 2008) which is the gold standard, and others used the hypermobility questionnaire, which is just a screening tool (Zarate, Farmer et al. 2009; Mohammed, Lunniss et al. 2010). Thus the definitions for hypermobility and the methods for diagnosing it were not standardised, making comparisons, and conclusions, difficult. Lastly, and very importantly, GI symptoms are influenced by a number of factors including, psychopathology, hypersensitivity, opiates and autonomic dysfunction, all of which are common in JHS. None of the studies controlled for

these variables and so it is impossible to know whether these were confounding the association seen between GI symptoms and JHS.

1.7.2 Knowledge gaps

Data on the relationship between JHS and both GI symptoms and GI disorders in patients not referred to tertiary centres are lacking and similarly, no population based data in JHS non-patients is available. In addition, the comparison of GI symptom prevalence with a GI control group and the effect of confounding factors such as psychopathology, autonomic dysfunction and hypersensitivity has not been ascertained. Lastly, the physiological mechanisms for the increased symptoms in these individuals is unknown.

1.8 Aims

The general aim of the studies is to address the above knowledge gaps - to fully characterise the range and prevalence of GI symptoms in patients and non-patients with JHS , to determine the influence of various confounding factors on these symptoms, to investigate the physiological mechanisms for the most common symptoms and to determine if a true association exists between JHS and FGID.

1.8.1 Specific aims

1. To characterise the GI presentation in patients with an established diagnosis of JHS and known GI symptoms, and to compare this to patients without JHS attending GI clinics. Specifically:
    a. To determine the range and prevalence of GI symptoms in patients referred to gastroenterology clinics with a known diagnosis of JHS.
    b. To compare the prevalence of individual GI symptoms to that in patients without JHS, also attending GI clinics.
    c. To determine whether there is a high prevalence of FGID in JHS patients.
    d. To determine what associated extra-intestinal factors are confounders, and the effect of these on GI symptoms in JHS.
    e. To determine the increased burden of GI symptoms on quality of life in JHS patients.

2. To determine if there is an association between JHS and GI symptoms in a population based sample of non-patients. Specifically:
    a. To determine and compare the range and prevalence of GI symptoms in university students with and without JHS.
    b. To determine which associated factors confound the association between JHS and GI symptoms, and whether these are the same as those present in patients
    c. To determine the effect of JHS on quality of life in non-patients.

3. To determine if there is an association between JHS and GI disorders in secondary care. Specifically:
    a. To determine and compare the prevalence of JHS in GI patients with organic GI disorders, FGID and in a non-GI control group, and therefore to determine if JHS is associated with FGID.
    b. To determine whether JHS is associated with particular subtypes of FGID or organic disease.
    c. To determine whether the association between JHS and GI disorders is dependent on autonomic, somatisation, psychological, or chronic pain factors.
    d. To determine if the added presence of JHS is clinically significant in patients with GI disorders and whether it is associated with altered quality of life or comorbidity.

4. To determine whether physiological abnormalities are present in JHS patients with upper GI symptoms. Specifically:
    a. To determine whether dysphagia is associated with oesophageal dysmotility.
    b. To determine whether reflux symptoms are caused by true reflux, or functional heartburn.
    c. To determine whether gastroparesis is present in patients with dyspepsia.
    d. To determine whether gastro-oesophageal compliance is increased in JHS patients.

1.9 Hypothesis

Individuals with JHS have a generalised connective tissue disorder which not only affects the skin and joints leading to musculoskeletal features, but also affects the GI tract and everything within it including the sensory and autonomic nerves. This will lead to altered compliance and altered autonomic and sensory function. Autonomic dysfunction will lead to altered motility, sensory dysfunction will lead to hypersensitivity and both these will contribute to the generation of GI symptoms and disorders. Thus it is expected that JHS patients with GI symptoms will have increase autonomic symptoms and hypersensitivity, and altered compliance of the GI tract. All these abnormalities are genetically determined and therefore will be present at an early age, even before individuals present as patients. Hence the following is expected:

1. JHS patients will have a high prevalence of GI symptoms as well as autonomic and somatic symptoms. Autonomic and somatic factors will be involved in the association between JHS and GI symptoms.
2. A high prevalence of GI symptoms will be present in young JHS non-patients, and again this will be associated with the presence of autonomic and somatic symptoms.
3. There will be an association between JHS and FGID but not with organic GI disorders. In particular, ROME III categories of FGID which are characterised by hypersensitivity will be most associated with JHS.
4. Physiological abnormalities, particularly altered sensori-motor function, will be present in symptomatic JHS patients. JHS patients will also have altered compliance of GI tissue, and this will contribute to symptom presentation.

Chapter 2

Characterisation of Gastrointestinal Symptoms in the Joint Hypermobility Syndrome

2.1 Introduction

As described in the introduction, several preliminary studies have demonstrated that GI symptoms occur in patients with JHS (Castori, Camerota et al. 2010) and that symptoms such as constipation, diarrhoea abdominal pain and nausea are more common than in the general population (Hakim and Grahame 2004). However, a GI control group was not used in any of these studies, therefore it is not known if the prevalence and range of GI symptoms in JHS patients is any different from patients with other GI disorders. In addition, it is unknown whether GI symptoms in JHS patients are due to primarily an organic or functional cause. Furthermore, several factors known to be associated with GI symptoms such as autonomic dysfunction and psychopathology are also present in JHS patients (Table 1.5) but it is not yet known whether these factors are responsible for the association between JHS and GI symptoms. Lastly, it has been demonstrated that in patients with JHS, the presence of musculoskeletal symptoms, particularly pain, is associated with decreased QOL. The added effect of GI symptoms on QOL has never been studied in these patients.

2.2 Aims

The primary aims of the study were (1) To determine the range and prevalence of GI symptoms in patients referred to gastroenterology clinics with a known diagnosis of JHS in comparison to patients referred with GI symptoms, but

without JHS; (2) to compare the prevalence of FGID in patients with JHS compared to those without JHS; (3) to determine what associated extra-intestinal factors are confounders of the association between GI symptoms and JHS; and (4) to compare the quality of life in patients with a combination of both JHS and GI symptoms to those with GI symptoms but without JHS.

2.3 Hypothesis

It was hypothesised that in a GI clinic, patients with JHS compared to patients without JHS will have a higher prevalence of GI symptoms, extra-intestinal symptoms, and FGID, and a reduced quality of life. Furthermore, GI symptoms in JHS patients would be influenced by psychopathology, opiate use, autonomic and hypersensitivity factors i.e. those were confounding factors.

2.4 Materials and Methods

2.4.1 Study design

This study was part of a much larger study that was designed to address the aims in this Chapter as well those in Chapter 4 – see Figure 2.1 for details. Consecutive 'new' patients attending general gastroenterology clinics for their first visit between April 2010 and April 2012 participated in studies described in Chapter 2 and 4. All patients completed a set of validated questionnaires, and were assessed for hypermobility and fibromyalgia status (see below) before their initial clinical consult with the attending gastroenterologist. The GI diagnosis that the patients were eventually given could be obtained from the medical notes.

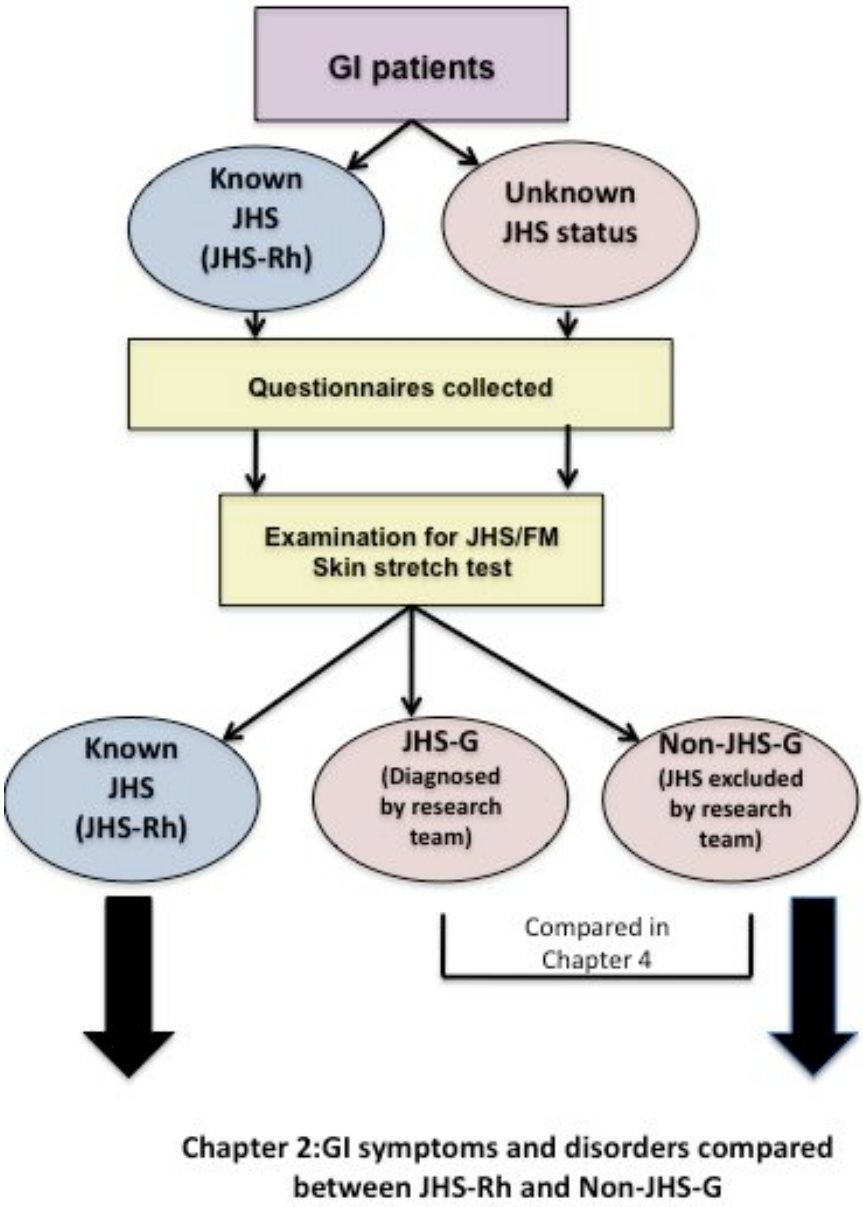


Figure 2.1 Overall study design for Chapter 2.
GI symptoms were compared in patients with a pre-existing diagnosis of JHS (JHS-Rh) and those in whom JHS had been excluded (Non-JHS-G).

For the study described in this Chapter, two groups of patients were selected and compared: those with a previous rheumatology diagnosis of JHS (JHS-Rh), and those in whom JHS was excluded (Non-JHS-G) - Figure 2.1. These two groups were compared with respect to the presence of GI and extra-articular symptoms and disorders, and quality of life.

2.4.2 Patients

Eligibility criteria

Consecutive patients aged 16-70, who had GI symptoms and were newly referred to gastroenterology clinics at Barts and the London NHS Trust and Mile End Hospital between April 2010 and April 2012 were eligible to take part. Patients who were illiterate or who could not speak English were excluded as the study relied heavily on questionnaires. Patients who were asymptomatic e.g. those attending for routine bowel cancer screening, and patients with predominantly hepatology problems were also excluded.

Patients were assessed for eligibility and recruited after informed written consent. Patients who had previously seen a rheumatologist and had an established diagnosis of JHS formed the JHS-Rh group. Patients who did not fulfill the Brighton diagnostic criteria for JHS formed the Non-JHS-G group.

2.4.3 Questionnaires

Subjects completed validated questionnaires to systematically assess for GI symptoms, psychopathology, autonomic symptoms, somatic symptoms and quality of life. Demographic information and medication histories were also collected via standardized case report forms. Questionnaires once completed were placed in a sealed envelope to ensure blinding of the researchers to questionnaire responses.

GI symptom assessment: The Bowel Disease Questionnaire (BDQ) (Talley, Phillips et al. 1990) is a validated instrument used to obtain a detailed assessment of the frequency and severity of both functional and organic GI symptoms experienced over the past 6 months and to collect medical history

data. For this study, GI symptoms were considered to be present if they occurred at least once a week.

Autonomic symptom assessment: The Composite Autonomic Symptom Scale (COMPASS questionnaire) is a validated questionnaire that provides a score of autonomic dysfunction, with higher scores representing a higher number of autonomic symptoms. Scores correlate well with objective measures of autonomic dysfunction (Suarez, Opfer-Gehrking et al. 1999). Scores are provided for various autonomic domains; for this study, scores relating to orthostatic, urinary, vasomotor and syncope domains were used. The scores are converted into a percentage of the maximum possible score for each domain where higher scores represent greater autonomic dysfunction. The maximum score is 100% (Suarez, Opfer-Gehrking et al. 1999).

Psychological assessment: The psychological profile of each patient was assessed using the validated SCL-90 questionnaire (Derogatis, Rickels et al. 1976). This is a 90-item self-report questionnaire that provides an assessment of the psychological symptom pattern and severity in various dimensions including anxiety and depression. The individual raw scores for anxiety and depression were used. Scores range from 0.005-4.05 with higher scores representing increased severity of symptoms.

Somatic symptoms: The validated Patient Health Questionnaire 15 (PHQ 15) assesses the presence, type and severity of somatic symptoms and serves as a screening tool for somatosensory amplification (Kroenke, Spitzer et al. 2002). It consists of 15 symptoms, each of which can be scored 0 (not bothered by

symptom), 1 (bothered a little by symptom) or 2 (bothered a lot by symptom). A total score is calculated which can range from 0 to 30, with higher scores indicating a higher number of somatic symptoms. Three of the questions relate to GI symptoms: 1 relates to indigestion type symptoms, 1 related to bowel disturbance and 1 relates to abdominal pain. As we were interested in the non-GI somatic symptoms, The PHQ15 score was recalculated (PHQ15 adj) without these three questions resulting in a score ranging from 0 to 24.

Quality of life assessment: Health-related quality of life (QOL) was evaluated using the SF-36, a generic QOL tool that includes eight multi-item scales. The SF-36 evaluates the extent to which an individual's health limits their physical, emotional, or social functioning (McHorney, Ware et al. 1993). Each scale is scored from 0 to 100, with higher scores indicating better health-related QOL.

2.4.4 Examination and structured interview

Structured interviews and examinations were performed by me, following a period of formal training from hypermobility specialists. All assessments were conducted blind to the results of the questionnaires.

2.4.4.1 Assessment for JHS

Diagnosis of JHS was made using the Brighton criteria (Grahame, Bird et al. 2000), which requires the presence of a combination of major and minor features as described in the introduction (Table 1.5). This was assessed using a combination of structured interview and examination. Examination was required to calculate the Beighton score (Figure 1.9) and to assess for scoliosis, skin signs and Marfanoid habitus.

Beighton score:

This is an established measure of generalised joint hypermobility based on the flexibility of 9 joints - back, thumbs, little fingers, knees, elbows. This was calculated as described in the introduction (Figure 1.9). A score of 4 or more out of 9 is considered indicative of generalised joint hypermobility and is a major criteria, whereas a score of 1-3 out of 9 satisfies a minor criteria (Table 1.5).

Assessment of scoliosis

A scoliometer was used to assess for the presence of scoliosis. The subject was asked to flex their back forward and the scoliometer (Figure 2.2) was placed at 3 different points on the back (upper, mid and lower). The angle of the spine was measured at each of the points and the difference between the largest and smallest values was calculated to give the angle of scoliosis. A scoliosis > 5 degrees was considered pathological.

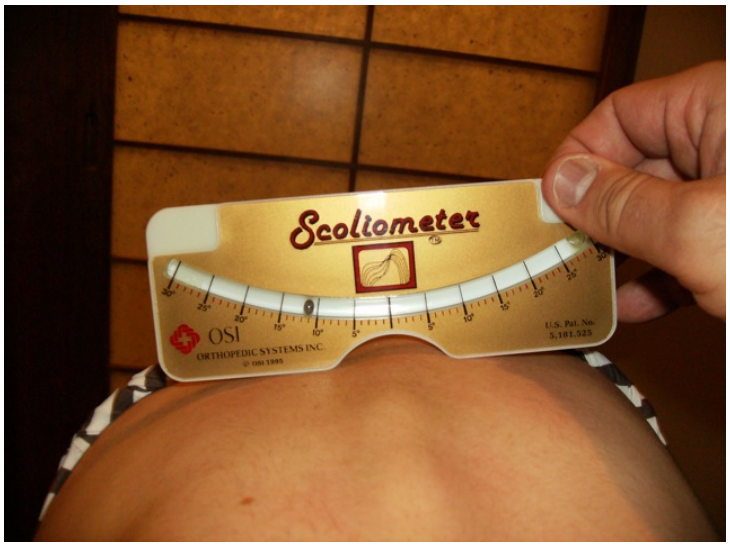


Figure 2.2: Assessment of scoliosis using a scoliometer.

Assessment of Marfanoid Habitus

A Marfanoid Habitus was confirmed if the student had an arm span/height ratio >1.03 or if they had arachnodactyly. The latter was assessed using the wrist sign and the Steinberg sign as shown in Figure 2.3.

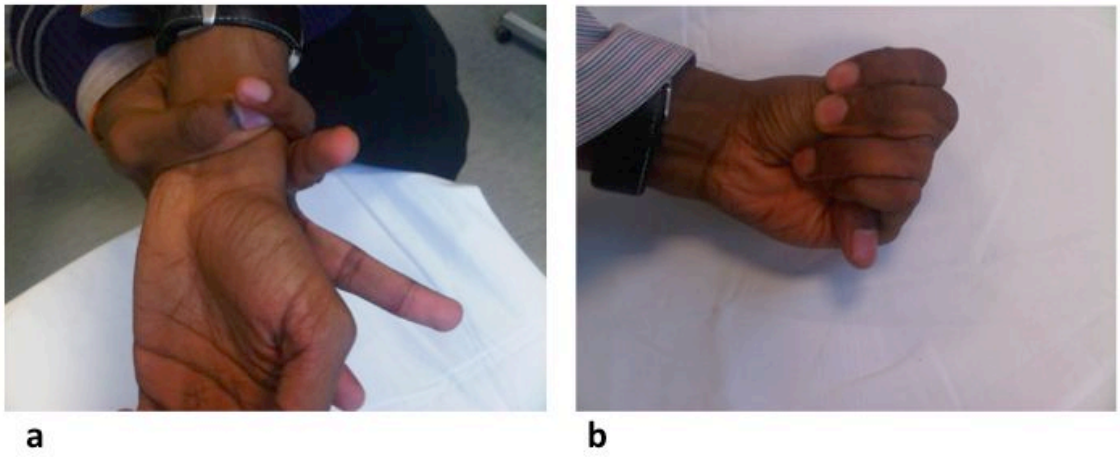


Figure 2.3: Features of arachnodactyly.
A- Wrist sign: the ability of the thumb and little finger to overlap while encircling the contralateral wrist. B-Steinberg sign: the ability of the thumb to protrude beyond the lateral aspect of the ipsilateral palm when the remaining 4 digits are clenched over it

Assessment of skin

Skin was examined for the presence of papyraceous or keloid scars, for soft velvety texture and for the degree of stretchiness of the skin, all of which are associated with hypermobility. Assessment of skin stretchiness was first performed on the medial aspect of the forearm by pinching and stretching the skin (Figure 2.4).

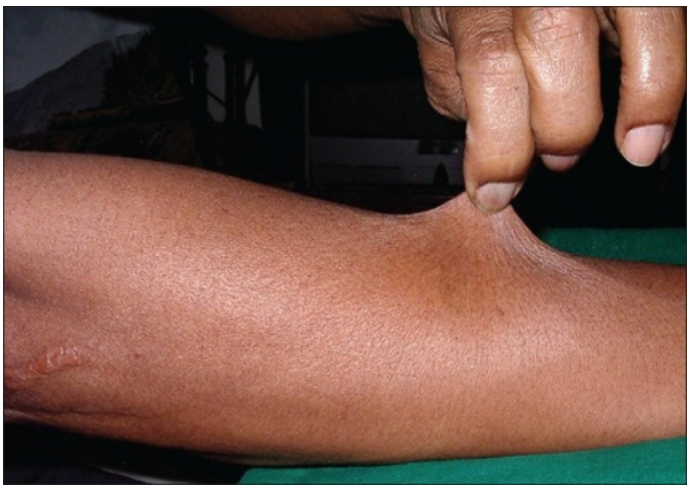


Figure 2.4: Assessment of skin hyperextensibility.
Skin is pinched and pulled at the medial aspect of the forearm.

2.4.4.2 Skin stretch test

A skin stretch test, which gave a corrected skin extensibility score (CSES), was also performed to provide an objective measure of skin stretch (Farmer, Douthwaite et al. 2010), as illustrated in the introduction (Figure 1.12) . Skin extensibility was measured by placing 2 dots on the dorsum of the left hand between the 2nd and 3rd metacarpals, approximately 10mm apart, and the distance between them was measured using an electronic caliper (+/- 0.01mm) A lateral force was applied to the dots, perpendicular to the metacarpals, until the skin was fully taut and the increase in distance between the dots was noted and transformed into a percentage increment. Skin fold thickness was measured using a Harpenden calliper. A corrected skin extensibility score (CSES) was calculated by dividing the percentage increment by skin thickness in mm (skin fold/2).

2.4.4.3 Assessment for fibromyalgia

Assessment of fibromyalgia was made using both the 1990 Wolfe criteria, which are considered the gold standard (Wolfe, Smythe et al. 1990), and the revised

2010 ACR criteria (Wolfe 2010). The 1990 criteria requires the presence of more than 11 tender points out of a total 18 tested, in the presence of chronic widespread pain - Figure 2.5. The revised (2010) criteria requires the presence of insomnia and memory changes in addition to the presence of chronic widespread pain, and does not require a tender point assessment. Patients were considered to have fibromyalgia if they satisfied the 1990 or 2010 criteria.

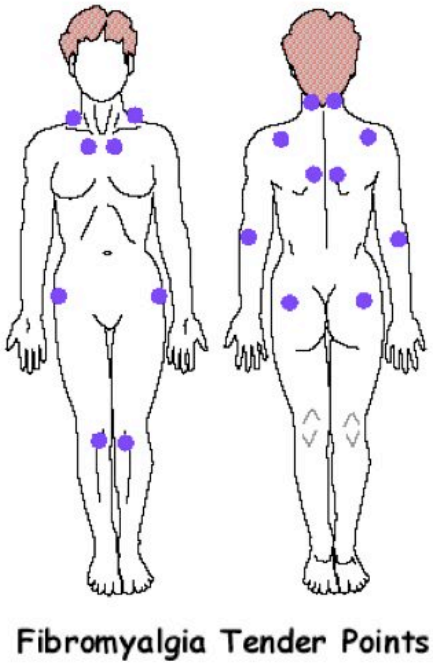


Figure 2.5: Location of 18 fibromyalgia tender points

2.4.5 Data analysis and Statistics

Data were described in terms of means and confidence intervals (normal ordinal data), medians and IQR (non-normal ordinal data) and proportions and confidence intervals (categorical data). Comparisons between patients with and without JHS were performed using the t-test (normal ordinal data), Mann Whitney U-test (non-normal ordinal data) and chi-squared test (categorical data). The associations of particular GI symptoms with JHS were investigated

using odds ratios adjusted for age and gender. Multivariate logistic regression analyses, adjusting for other factors which were significantly different in the groups (possible confounders) were performed to further investigate the effect of these factors on the association between GI symptoms and JHS. Due to multiple comparisons, only results of univariate comparisons with a p value < 0.01 were interpreted as being significant. Stata IC/12.0 (StataCorp, College Station, Texas, USA) was used to carry out data management and statistical analysis in this chapter and in the other three results chapters in this thesis.

The study was approved by the East London and City Research Ethic Committee: REC Ref: 09/H0704/72.

2.5 Results

2.5.1 Patients

2445 new patients scheduled to attend GI clinics were sent letters a few weeks prior to their appointment, inviting them to participate - Figure 2.6. 273 cancelled their appointments or did not attend, and 304 could not speak English, leaving 1868 potential subjects. Of these, 778 patients consented to take part, giving a response rate of 42%. Out of the 778, 146 did not complete their questionnaires, 21 did not undergo a full examination and 15 did not meet the inclusion criteria, leaving 596 patients who were included in the study. Of these 596, 44 were referred from rheumatology clinics with a known diagnosis of JHS (JHS-Rh), and 372 did not have JHS (Non-JHS-G). To simplify the group labels in the remainder of the chapter, the JHS-Rh patients will be referred to as JHS patients, and the Non-JHS-G will be referred to as Non-JHS patients.

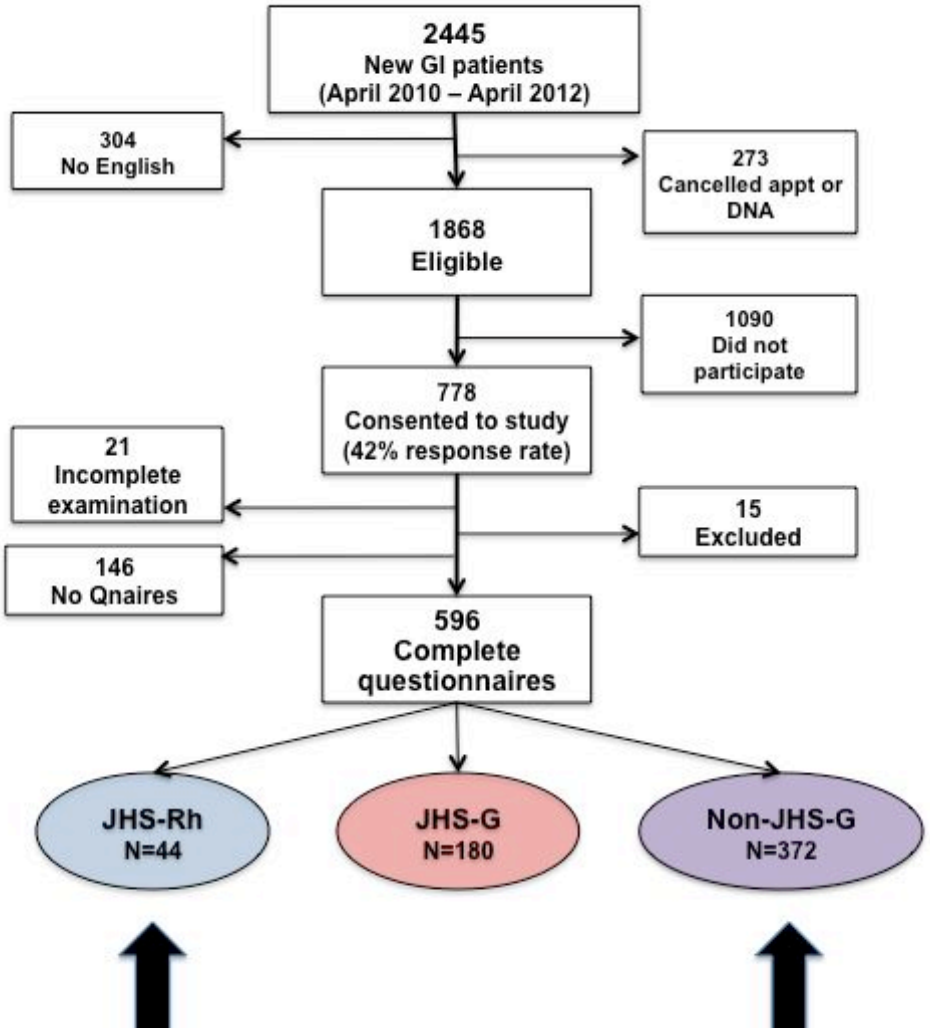


Figure 2.6: Flowchart of patients recruited.
JHS-Rh: patients referred from rheumatology clinics with an established diagnosis of JHS. JHS-G: patients who had been diagnosed with JHS by the research team. Non-JHS-G: patients in whom JHS had been excluded. In this study, only JHS-Rh and Non-JHS-G (bold arrows) were included.

2.5.2 Demographics and hypermobility features

JHS patients were significantly younger (34.7 ± 10.9 vs 44.2 ± 13.6, $p<0.001$) and more likely to be female (95.5% vs 54.6%, $p<0.001$). The JHS group had significantly more hypermobility features including a higher median Beighton score, and a higher incidence of polyarthralgia, dislocations, soft tissue injuries,

Marfanoid habitus, skin signs, varicose veins and organ prolapses (all p<0.001) -

Table 2.1.

2.5.3 Gastrointestinal symptoms in JHS vs Non-JHS

The most common symptoms experienced weekly in JHS were bloating (89%), early satiety (79%), abdominal pain (66%), alternating bowel habit (66%) and postprandial fullness (61%). The prevalence of individual GI symptoms experienced at least weekly were compared in JHS and non-JHS, and adjusted for age and gender using an adjusted odds ratio (ORadj). The only lower GI symptoms which were significantly more common in JHS than in Non-JHS was alternating bowel habit (ORadj: 4.3, CI: 2.08-8.92) and faecal urgency (ORadj:2.2, CI: 1.09-4.20) - Table 2.2.

Several upper GI symptoms were significantly more prevalent in JHS including abdominal pain (ORadj:4.7, CI: 2.3-9.6), globus (ORadj:3.6, CI: 1.8-7.2), dysphagia (ORadj: 3.8, CI: 1.7-8.4), regurgitation (ORadj: 3.0, CI: 1.4-6.6), postprandial fullness (ORadj: 3.1, CI: 1.5-6.1), early satiety (ORadj: 4.1, CI: 1.8-9.0) and bloating (ORadj:6.0, CI: 2.3-16.0) - Table 2.3.

2.5.4 Functional gastrointestinal disorders in JHS and non-JHS patients

40 out of the 44 JHS patients (91%) were given a diagnosis of FGID, and this was significantly higher than in Non-JHS patients (45%, OR: 2.9, CI: 1.7-4.9, p<0.001).

Table 2.1: Comparison of features of Brighton criteria between patients with and without JHS.

Values represent proportion of patients with each features. Interquartile ranges/confidence intervals are given in brackets. All features, apart from back pain, scoliosis, eye problems and hernias were significantly more common in JHS patients.

	NON - JHS (n=372)	JHS (n=44)	p
Median beighton score (IQR)	1 (0-2)	5.5 (4-6)	<0.001
Arthralgia> 4 joints (CI)	15.0 (11.6-19.1)	95.5 (84.5-99.4)	<0.001
Back pain (CI)	27.7 (23.2-32.5)	20.5 (9.8-35.3)	0.31
Spondylosis etc (CI)	9.1 (6.4-12.5)	18.2 (8.2-13.7)	0.06
Dislocations/subluxations (CI)	10.8 (7.8-14.3)	77.3 (62.2-88.5)	<0.001
Soft tissue injury (CI)	14.2 (10.9-18.2)	65.9 (50.1-79.5)	<0.001
Marfanoid habitus (CI)	1.3 (0.4-3.1)	13.6 (51.7-27.4)	<0.001
Skin signs (CI)	27.7 (23.2-32.5)	81.8 (67.3-91.8)	<0.001
Eye signs (CI)	11.3 (8.3-15.0)	18.2 (8.2-32.7)	0.18
Varicose veins (CI)	10.5 (7.6-14.0)	31.8 (18.6-47.6)	<0.001
Hernias (CI)	7.5 (5.1-10.7)	6.8 (1.4-18.7)	0.87
Organ prolapse (CI)	1.9 (0.8-13.8)	13.6 (5.2-27.3)	<0.001

Table 2.2: Comparison of Lower GI symptoms in JHS and Non-JHS patients.

Values in first 2 columns represent the percentage of patients who experience symptoms at least once a week. The third column represents the odds ratio for an association between JHS and each symptom, adjusted for age and gender. Confidence intervals are in brackets.

	Non-JHS (n=372)	JHS (n=44)	ORadj(age,gender) (CI)	p
Alternating bowel habit	30.4 (25.6-35.6)	65.8 (49.4-79.9)	4.30 (2.08-8.92)	<0.001
Less than 3 bowel movements/week	16.9 (13.2-21.2)	36.4 (22.4-52.2)	1.77 (0.86-3.60)	0.12
More than 3 bowel movements/day	34.3 (29.3-39.5)	31.8 (18.6-47.6)	0.92 (0.45-1.87)	0.82
Faecal urgency	28.5 (23.9-33.5)	50 (34.6-65.4)	2.15 (1.09-4.20)	0.03
Straining	29.6 (24.9-34.7)	44.2 (29.1-60.1)	1.53 (0.77-3.02)	0.22
Incomplete evacuation	41.2 (36.0-46.5)	61.4 (45.5-75.6)	1.67 (0.85-3.29)	0.14
Blocked sensation	22.7 (18.4-27.4)	34.9 (21.0-50.9)	1.58 (0.77-3.24)	0.21
Digitation	11.3 (8.2-15.0)	22.7 (11.5-37.8)	1.75 (0.76-4.0)	0.19

Table 2.3: Comparison of Upper GI symptoms in JHS and Non-JHS patients.

Values given are percentage of patients who experience symptoms at least once a week.

	Non-JHS (n=372)	JHS (n=44)	ORadj(age,gender) (CI)	p
Abdominal pain > 5 years	31.4 (26.2-37.0)	65.9 (50.1-79.5)	4.69 (2.29-9.58)	<0.001
Globus	19.1 (15.1-23.6)	47.7 (32.5-63.3)	3.57 (1.78-7.17)	<0.001
Retrosternal chest pain	24.2 (19.8-28.9)	40.9 (26.3-56.8)	1.91 (0.96-3.80)	0.06
Heartburn	23.5 (19.2-28.3)	25 (13.2-40.3)	1.18 (0.55-2.55)	0.67
Waterbrash	18.5 (14.5-22.9)	29.5 (16.8-45.2)	1.95 (0.92-4.14)	0.08
Dysphagia	10.6 (7.5-14.3)	31.8 (18.6-47.6)	3.82 (1.73-8.4)	0.001
Early satiety	42.8 (37.7-48.0)	79.1 (64.0-90.0)	3.06 (1.84-8.96)	0.001
Postprandial fullness	27.1 (22.6-32.1)	61.4 (45.5-75.6)	2.14 (1.54-6.07)	0.001
Epigastric pain	28.4 (23.9-33.4)	51.2 (35.5-66.7)	2.14 (1.09-4.22)	0.03
Nausea	22.4 (18.2-27.0)	46.5 (31.2-62.3)	2.00 (1.01-3.97)	0.05
Vomiting	9.6 (6.7-13.2)	14.0 (5.3-27.9)	1.14 (0.43-3.05)	0.79
Regurgitation	11.4 (8.3-15.2)	33.3 (19.6-49.5)	3.05 (1.4-6.6)	0.005
Belching	33.2 (28.3-38.4)	46.3 (30.6-62.6)	1.80 (0.90-3.61)	0.10
Bloating	47.9 (42.6-53.2)	88.6 (75.4-96.2)	6.03 (2.27-16.0)	<0.001

2.5.5 Extra-intestinal factors in JHS and non-JHS patients - Table 2.4

Psychopathology

Anxiety and depression scores were significantly higher in JHS compared to Non-JHS ($p<0.001$).

Autonomic symptoms

JHS patients had significantly higher autonomic scores for urinary symptoms (30 vs 0, $p<0.001$), orthostatic intolerance (68.75 vs 25, $p<0.001$), and vasomotor symptoms (56.7 vs 0, $p<0.001$) but not for reflex syncope (0 vs 0, $p=0.19$). The highest scores were in the orthostatic domain.

Somatic symptoms

JHS patients had significantly more somatic symptoms than did the Non-JHS patients as evidenced by higher median PHQ15adj scores (13.5 vs 6, $p<0.001$).

Fibromyalgia

57% of JHS patients satisfied either the 1990 or 2010 ACR fibromyalgia criteria, compared to 5% of the Non-JHS patients ($p<0.001$). In line with this, the JHS patients had significantly more chronic widespread pain (59% vs 10%, $p<0.001$), memory problems (50% vs 15%, $p<0.001$), insomnia (67% vs 28%, $p<0.001$) and a higher median number of tender points (8.5 vs 0, $p<0.001$).

Table 2.4: Autonomic scores, somatic symptoms scores and fibromyalgia features in JHS and Non-JHS patients.

CWP: Chronic widespread pain. Values given are medians and interquartile ranges, or proportions and 95% confidence intervals

	NON-JHS (n=372)	JHS (n=44)	p
PSYCHOPATHOLOGY- SCL90			
Median anxiety score (IQR)	0.30 (0.005-0.805)	0.80 (0.405-1.95)	<0.001
Median depression score (IQR)	0.62 (0.24-1.31)	1.005 (0.62-2.04)	<0.001
AUTONOMIC SYMPTOMS – COMPASS QUESTIONNAIRE			
Urinary (IQR)	0 (0-20)	30 (10-45)	<0.001
Orthostatic intolerance (IQR)	25 (0-43.75)	68.75 (56.25-81.25)	<0.001
Reflex Syncope (IQR)	0 (0-0)	0 (0-0)	0.19
Vasomotor (IQR)	0 (0-0)	56.7 (37.8-63)	<0.001
SOMATIC SYMPTOMS – PHQ15 without GI questions			
Median PHQ15adj score	6 (3-9)	13.5 (10.5-16)	<0.001
FIBROMYALGIA			
% with Fibromyalgia (CI)	4.6 (2.7-7.2)	56.8 (41.0-71.7)	<0.001
Median tender points (IQR)	0 (0-2)	8.5 (2-13)	<0.001
% CWP (CI)	10.5 (7.6-14.1)	59.1 (43.2-73.7)	<0.001
% with Insomnia (CI)	28.5 22.9-34.8)	66.7 (43.0-85.4)	<0.001
% with Memory problems (CI)	14.7 (10.5-19.9)	50.0 (27.2-72.8)	<0.001

Table 2.5: Medication use in JHS and Non-JHS patients.

Values given represent the percentage of patients who were on each class of medication. Confidence intervals are shown in brackets. JHS patients were more likely to be on opiates, NSAIDs, antidepressants and neuromodulators. PPI: Proton Pump inhibitors

Class of medication	NON-JHS (n=372)	JHS (n=44)	p
Opiates	8.6	29.6	<0.001
(CI)	(5.6-11.9)	(16.8-45.2)	
Antidepressants	7.0	25.0	<0.001
(CI)	(4.6-10.1)	(13.2-40.0)	
NSAIDS	5.6	20.4	<0.001
(CI)	(2.5-7.5)	(9.8-5.3)	
Anxiolytics	1.1	2.3	0.84
(CI)	(0.3-2.7)	(0-12.0)	
Neuromodulators	1.6	6.8	0.02
(CI)	(0.6-3.5)	(1.4-18.6)	
Antispasmodics	5.6	4.6	0.76
(CI)	(3.5-8.5)	(0.6-15.5)	
Prokinetics	7.5	6.8	0.87
(CI)	(5.1-10.7)	(1.4-18.7)	
PPI	26.3	22.7	0.60
(CI)	(5.1-10.7)	(11.5-37.8)	
Steroids	2.3	2.4	0.95
(CI)	(0-12.0)	(0.2-2.8)	
Bisphosphonates	0	1.1	0.49
(CI)	(0-8.0)	(0-1.7)	

Medication use - Table 2.5

JHS patients were significantly more likely to be on analgesics including opiates (30% vs 9%, p<0.001) and NSAIDS (20% vs 5%, p<0.001), and were significantly more likely to be on antidepressants (25% vs 7%, p<0.001). A higher proportion of JHS patients were on neuromodulators such as pregabalin (7% vs 2%, p=0.02), but this was not significant by the statistical parameters set a priori for this study. There was no difference in the use of PPI's, prokinetics (e.g. domperidone), anxiolytics (e.g. diazepam), antisapasmodics (e.g. mebeverine), steroids or bisphosphonates - Table 2.5.

2.5.6 Factors mediating association between JHS and GI symptoms

Based on univariate analyses, several factors were significantly associated with JHS and were thus potential confounders. These included orthostatic, urinary and vasomotor autonomic factors, fibromyalgia, anxiety, depression, somatosensory factors (PHQ15adj), analgesic and antidepressant use. These factors were evaluated using multiple logistic regression analyses in a stepwise fashion by adding them to a model containing JHS phenotype, age and gender as fixed variables, and GI symptoms associated with JHS (from Table 2.2 and Table 2.3) as dependent variables.

Anxiety, depression and antidepressant use did not have a significant effect on the odds ratios and were therefore not confounders. Fibromyalgia, opiate and NSAID use, somatic symptom scores and autonomic scores had an effect on the odds ratios for at least some of the symptoms, and were therefore either partly or wholly mediating the association between JHS and the GI symptoms – Table 2.6.

Table 2.6: Influence of medication, fibromyalgia, somatic symptoms, and autonomic symptoms on the association between JHS and GI symptoms. Values given are odds ratios adjusted for various factors. Confidence intervals are shown in brackets. Asterisks mark GI symptoms where the association between JHS and the symptom remains significant even after the addition of the above factors. A:Age, G:Gender, M:Opiate and NSAID Medication, FM: Fibromylagia, Aut: Autonomics, PHQ: Adjusted PHQ15 score (PHQ15adj). All: Fibromyalgia, autonomics, PHQ15adj

Symptom	ORadj (A,G)	ORadj (A,G,Med)	ORadj (A,G,FM)	ORadj (A,G,Aut)	ORadj (A,G,PHQ)	ORadj (All)
Alternating bowel habit *	4.3 (2.1-8.9)	3.6 (1.7-7.6)	5.9 (2.4-14.7)	2.69 (1.2-6.2)	3.6 (1.7-7.6)	3.9 (1.5-10.2)
Abdominal pain > 5 yrs *	4.7 (2.3-9.6)	4.8 (2.25-10.2)	4.2 (1.9-9.4)	3.7 (1.6-8.6)	4.7 (2.2-10.2)	4.3 (1.7-10.4)
Globus	3.6 (1.8-7.2)	2.3 (1.1-5.0)	2.9 (1.3-6.5)	1.5 (0.7-3.6)	1.8 (0.8-3.9)	1.4 (0.6-3.6)
Dysphagia	3.8 (1.7-8.4)	2.2 (0.9-5.3)	2.3 (0.9-5.9)	1.3 (0.5-3.5)	1.6 (0.7-3.8)	1.2 (0.4-3.2)
Regurgitation	3.0 (1.4-6.6)	2.4 (1.0-5.7)	2.4 (0.9-6.1)	1.3 (0.5-3.5)	1.6 (0.7-3.9)	1.1 (0.4-3.2)
Early satiety	4.1 (1.8-9.0)	3.8 (1.7-8.7)	2.7 (1.1-6.4)	2.1 (0.8-5.2)	2.3 (1.0-5.2)	1.6 (0.6-4.2)
Postprandial fullness	3.1 (1.5-6.1)	2.3 (1.1-4.8)	1.8 (0.8-4.1)	1.3 (0.6-3.1)	1.4 (0.6-3.0)	1.0 (0.4-2.5)
Bloating *	6.0 (2.3-16.0)	5.3 (2.0-14.4)	5.1 (1.8-14.6)	3.2 (1.1-9.5)	4.4 (1.6-12.1)	3.2 (1.1-10.0)

Opiate and NSAID use had no significant effect on the multivariate model, and only weakened the association between JHS and GI symptoms but did not abolish it. In contrast, autonomic and somatic symptom scores had a dramatic effect on the association between JHS and GI symptoms, reducing the odds ratios considerably, and resulting in a loss of significance of association between JHS and most symptoms except for alternating bowel habit, abdominal pain and bloating - Table 2.6. The presence of fibromyalgia did not have as marked an effect as did autonomic and somatic factors - its largest effect was on symptoms of postprandial fullness, regurgitation and dysphagia, and for these symptoms it reduced the odds ratios considerably.

Thus there was a differential effect of the extra-intestinal factors on different groups of symptoms. The association between JHS and alternating bowel habit, bloating and abdominal pain was independent of all the above factors. In contrast, the association between JHS and gastro-oesophageal symptoms seemed to be dependent on the various extra-intestinal factors, particularly the autonomic and somatosensory amplification factors.

Out of all the autonomic domains, only the orthostatic and urinary domains were significantly associated with symptoms. Orthostatic scores were independently associated with globus, dysphagia, early satiety, postprandial fullness and bloating. For each of these symptoms, the odds of having the symptom increased by 1.01 for each 1-point increase in orthostatic score (OR: 1.01, CI: 1.001-1.02). Urinary scores were independently associated with regurgitation, dysphagia and globus, with a 0.02 increase in the odds of the symptom per 1-point increase in urinary score (OR: 1.02, CI: 1.01-1.03). The syncope and

vasomotor domains were not independently associated with any of the GI symptoms.

2.5.7 Quality of Life

Quality of life scores in JHS were very low, particularly for all the physical domains (all with median scores less than 25), social functioning (score: 25) and pain (score: 23). These were significantly lower than in the non-JHS patients (all $p<0.001$). There was no difference in HRQOL scores for the emotional domains - Table 2.7.

Table 2.7: Quality of life scores in JHS and Non-JHS patients.

Values given are the median quality of life scores, and corresponding interquartile ranges, for each of the 8 domains of the SF36. JHS patients had significantly worse quality of life on all but the emotional domains.

QUALITY OF LIFE SF36	NON-JHS (n=372)	JHS (n=44)	p
General health (IQR)	50 (30-65)	22.5 (15-40)	<0.001
Pain (IQR)	57 (32-80)	22 (0-32)	<0.001
Energy/fatigue (IQR)	50 (30-65)	25 (10-45)	<0.001
Physical functioning (IQR)	85 (55-100)	22.5 (10-50)	<0.001
Role-limiting physical (IQR)	75 (0-100)	0 (0-0)	<0.001
Social functioning (IQR)	62 (37-100)	25 (0-43.5)	<0.001
Emotional wellbeing (IQR)	72 (52-84)	64 (44-80)	0.13
Role-limiting emotional (IQR)	100 (33-100)	83 (33-100)	0.55

2.6 Discussion

2.6.1.1 Summary of findings

This is the first comparative study of GI symptoms in patients with and without JHS in a gastroenterology setting. The main findings are: (1) JHS is significantly associated with abdominal pain, alternating bowel habit, globus, dysphagia, regurgitation, postprandial symptoms, and bloating even when correcting for differences in age and gender; (2) JHS patients have a significantly higher prevalence of FGID compared to patients without JHS; (3) JHS is significantly associated with autonomic symptoms, measures of somatic pain, psychopathology and increased analgesic and antidepressant use; (4) the association of JHS with upper GI symptoms is accounted for by autonomic symptoms and measures of somatic sensitivity (PHQ15adj and fibromyalgia); however alternating bowel habit, abdominal pain and bloating are not significantly influenced by any of the extra-intestinal factors; (5) quality of life in all but the emotional domains is markedly reduced in JHS patients.

2.6.1.2 Comparison with previous studies

The hypermobility features in our JHS group (

Table 2.1) are very similar to those reported previously (Celletti, Castori et al. 2011), suggesting that the JHS patients in our study are typical of those seen in specialist centres, thus enabling comparisons with other studies. The observation of high levels of abdominal pain, alternating bowel habit, bloating and dysphagia is consistent with previous studies of similar patients in non-GI settings (Hakim and Grahame 2004; Castori, Camerota et al. 2010; Rombaut, Malfait et al. 2011). However, with the presence of a GI control group in our study, it can be further concluded that not only are these symptoms common in

the JHS group, but they are more frequently reported than in other GI patients. High levels of nausea in JHS were previously reported in comparison with healthy controls (Hakim and Grahame 2004), but this was not replicated here. This may be due to the fact that nausea is a common symptom in a GI clinic, and therefore differences would not necessarily be found in comparison with a GI control group. The association demonstrated with globus is, to our knowledge, a newly reported one. In the absence of comprehensive GI questionnaires, this is not a symptom that would necessarily be elicited by non-GI specialists, which may explain this seemingly new finding. However these observations are not unfounded - laryngo-pharyngeal problems have been documented previously (Rombaut, Malfait et al. 2011), and features of 'globus' may have been observed in these patients. Lastly, the findings in this study add specificity to those suggesting a high prevalence of gastro-oesophageal reflux and dyspepsia in JHS (Castori, Camerota et al. 2010). Gastro-oesophageal reflux symptoms include heartburn, waterbrash and regurgitation and the results in this chapter demonstrate that it is only regurgitation that is significantly increased. Likewise, the term 'dyspepsia' describes both epigastric pain and postprandial distress type symptoms (early satiety and postprandial fullness), but it is only the latter which was observed to be overrepresented in this study.

Interestingly an association between JHS and FGID was present, and 91% of the JHS patients were eventually given a functional, as opposed to organic, GI diagnosis. The presence of FGID in JHS has only previously been documented as an observation in JHS patients attending urology, neurogastroenterology and genetics clinics, but has never been compared to a suitable control group

(Manning, Korda et al. 2003; Zarate, Farmer et al. 2009; Castori, Camerota et al. 2010). Therefore the association documented here is a new finding.

The presence of associated extra-intestinal factors cannot be ignored, as they are implicated in the development of gastrointestinal symptoms, particularly in the case of FGID. In accord with previous studies there was a significant association between JHS and autonomic symptoms (Gazit, Nahir et al. 2003; Rombaut, Malfait et al. 2011), fibromyalgia (Ofluoglu, Gunduz et al. 2006), somatosensory amplification, anxiety and depression (Baeza-Velasco, Gely-Nargeot et al. 2011; Baeza-Velasco, Gely-Nargeot et al. 2011) and with opiate and antidepressant use (Rombaut, Malfait et al. 2011). Orthostatic symptom scores were particularly high in JHS and this may be due to underlying PoTS in these patients (Mathias, Low et al. 2011).

In order to determine the effects of these extra-intestinal factors on the association between JHS and GI symptoms, they were added stepwise to a logistic regression model. Interestingly, the presence of psychopathology and medication use did not significantly confound the association between JHS and symptoms, suggesting that GI symptoms in JHS are not secondary to those factors. In contrast, autonomic scores and somatic hypersensitivity (fibromylagia presence and increasing PHQ15adj scores) were important confounders, particularly for the postprandial and oesophageal symptoms, as their inclusion into the regression model completely abolished the independent association originally observed between GI symptoms and JHS. This would suggest that presence of upper GI symptoms in JHS are dependent on the presence of autonomic and somatic symptoms.

Out of all the factors, the addition of the autonomic scores caused the greatest reduction in the strength of the association between JHS and all the GI symptoms, suggesting that this factor was the most important confounder - Table 2.6. Of all the autonomic domains, the orthostatic domain appeared to be most important not only because scores were higher than in any other domain but also because orthostatic factors mediated the association with wide-ranging upper GI symptoms (globus, dysphagia, early satiety, postprandial fullness and bloating).

Although is difficult at present to propose a mechanistic explanation for the association between orthostatic autonomic symptoms and gastro-oesophageal symptoms, this finding is supported by several observations in the literature. Firstly, it has been observed that patients with PoTS, regardless of the presence of JHS, frequently have GI symptoms including nausea, reflux, alternating bowel habit and bloating (Mathias, Low et al. 2011). Secondly, in a study using electrogastrograms in PoTS patients compared to healthy controls, PoTS patients had increased variability of the gastric pacemaker rhythm pre and postprandially, and in those with known GI symptoms, the postprandial changes were more marked (Seligman, Low et al. 2012). Hence there is evidence that orthostatic intolerance, as seen in PoTS, is associated with postprandial and other GI symptoms.

It is interesting that the association between JHS and abdominal pain, alternating bowel habit and bloating remained significant even after the addition of all the extra-intestinal factors to the regression model. This suggests that the mechanism for these symptoms involves factors other than just autonomic

dysfunction and hypersensitivity. Possibilities include altered compliance of the viscera, which is known to be associated with functional dyspepsia, a functional GI disorder associated with symptoms of abdominal pain and bloating (Oustamanolakis and Tack 2012). Another possibility is intestinal dysbiosis. The latter is particularly plausible as small bowel bacterial overgrowth is known to be associated with symptoms of abdominal pain, altered bowel habit and bloating in GI patients (Simren, Barbara et al. 2013) but has not yet been investigated in JHS.

Putting all this together it would appear that the upper and lower GI symptoms arise by different mechanisms in JHS patients, and that autonomic factors are involved in the association of JHS with all the observed GI symptoms. For the gastro-oesophageal symptoms, autonomic factors interact with somatic factors to mediate the symptom association seen in JHS. This concept is not novel – several published studies have demonstrated that the somatic hypersensitivity seen in fibromyalgia, IBS and other functional somatic syndromes is associated with abnormal autonomic function (Scully, McKernan et al. 2010; da Cunha Ribeiro, Roschel et al. 2011; White 2012).

Finally, quality of life in JHS was significantly worse in the physical, social, but not the emotional, domains. This is expected as the JHS patients had significantly more musculoskeletal symptoms than did the non-JHS patients (Table 2.1). However, what is interesting is that the QOL scores in this JHS group presenting to GI clinics, were worse than that reported in a previous study of JHS patients with predominantly musculoskeletal complaints (Rombaut, Malfait et al. 2010). This suggests that the presence of GI and other

associated symptoms in JHS causes further deterioration in quality of life and further impairs physical and social functioning.

2.6.1.3 Limitations

The current study was not without its limitations. Firstly, it is not unforeseeable that selection bias may have occurred and that JHS patients with more severe GI symptoms would have been more likely to take part, thus exaggerating the observed differences seen. However, our interest lay more in the pattern of symptoms and in the influence of various factors, which would have been less affected by selection bias. Secondly, as it was a questionnaire study it was prone to recall bias, and so patients with multiple symptoms may have been more enthusiastic in responding positively to the questions. However, if this were truly the case, we would have observed an increase in all reported GI symptoms and not only a particular selection, which turned out to be compatible with several previous findings.

The main limitation however, was that the JHS patients included in this study were an extremely selected group of patients. Not only had they presented to tertiary rheumatology clinics, but they were further referred for GI assessment. According to a previous study, 37% of JHS patients attending rheumatology clinics have significant GI symptoms (Hakim and Grahame 2004). Hence the JHS patients in our study represent a small subset of the patients who present to hypermobility clinics, which are not necessarily representative of the majority of JHS individuals anyway as most JHS individuals remain undiagnosed and do not even see a rheumatologist (Grahame 2008).This is evident from Figure 2.6 which demonstrates that 180 other patients in that cohort satisfied the

diagnostic criteria for JHS but had not seen a rheumatologist nor had they been previously diagnosed with JHS.

Although it would appear that we selected a very biased group of JHS patients for this study, these were exactly the type of patients we were interested in investigating for a number of reasons. Firstly, these were the type of patients who were the subject of previous studies, and we were interested to find out how valid previous findings were and how they compared to a GI population without JHS. Secondly, these patients represent those at the more severe end of the scale with greatest comorbidity and lowest quality of life (Rombaut, Malfait et al. 2010; Voermans and Knoop 2010; Rombaut, Malfait et al. 2012) and so they are clinically the most important. Lastly, these are the patients who will ultimately be referred to gastroenterology services and present in clinics and so from a gastroenterology point of view they are an important group to study.

With all these points in mind however, it should be remembered that because the JHS patients were highly selected, these results are only applicable to a small subset of JHS patients and it is impossible draw any firm conclusions from them. To determine if the concept of an association between JHS and GI symptoms and functional GI disorders is true and not just a by-product of severe selection and response bias we would need to demonstrate that it is present in other groups of JHS individuals, ideally in unselected individuals who are unaware of their JHS status. Firstly, to prove that GI symptoms are truly associated with JHS we would need to demonstrate the same GI symptom association in healthy subjects with JHS. This is the subject of chapter 3. Secondly, we would need to demonstrate that in an unselected group of GI

patients who are unaware of their JHS status, there exists an association between JHS and FGID – this is the subject of chapter 4. Finally, in order to confirm the importance of autonomic and somatic factors in the GI association of JHS, we would need to demonstrate that these factors are common in previously undiagnosed JHS patients, and that they are involved in the GI association observed in JHS - this is also the subject of chapter 4.

2.6.1.4 Clinical implications

With increasing knowledge and recognition of JHS, more of these patients will be referred to gastroenterology clinics. These will be the patients with widespread GI and extra-intestinal symptoms, including chronic pain and functional somatic syndromes, and those in whom quality of life is dismal despite their young age and seeming normality. It is important to elicit these extra-intestinal symptoms as they have an important impact on GI symptoms and may influence efficacy of treatments. In the absence of evidence on the best treatment approach for these patients, a holistic approach involving pain specialists, rheumatologists, autonomic neurologists, and the prescription of neruomodulators, does not seem unreasonable.

Chapter 3

Association of Gastrointestinal Symptoms with the Joint Hypermobility Syndrome in Healthy Subjects

3.1 Introduction

GI symptoms are present in 37-86% of JHS patients attending rheumatology and genetics clinics (Hakim and Grahame 2004; Castori, Camerota et al. 2010; Rombaut, Malfait et al. 2011), and are increased compared to healthy controls (Hakim and Grahame 2004). This association has been refined further in Chapter 2 where GI symptoms were characterised in patients with JHS and it was demonstrated that symptoms of alternating bowel habit, abdominal pain, bloating, postprandial discomfort, globus, dysphagia and regurgitation were over-represented in JHS patients, and were increased compared to non-hypermobile GI controls. Furthermore the combination of GI symptoms and JHS was associated with a worse quality of life compared to patients with GI symptoms but without JHS.

In addition, it was demonstrated that autonomic factors, anxiety, depression , somatosensory amplification, chronic pain, fibromyalgia and opiate use were overrepresented in the JHS patients studied, as reported in other studies of JHS patients (Gazit, Nahir et al. 2003; Ofluoglu, Gunduz et al. 2006; Baeza-Velasco, Gely-Nargeot et al. 2011; Castori, Celletti et al. 2011; Rombaut, Malfait et al. 2011; Castori, Morlino et al. 2012). Both autonomic and somatic factors, but not psychopathology or opiate use, mediated the association between JHS and the upper GI symptoms, supporting current opinion that autonomic and

somatic factors are involved in the generation of extra-articular symptoms in JHS patients (Gazit, Nahir et al. 2003; Hakim and Grahame 2004; Castori, Celletti et al. 2011).

The observations relating to JHS in Chapter 2 and in previously published studies were all based on highly selected and highly symptomatic subjects, attending tertiary or specialist clinics, and probably represented a very extreme end of the JHS spectrum. This limits the ability to generalise these findings to the JHS population as a whole and therefore restricts the conclusions that can be drawn from them. A population based study of non-patients would address all these issues.

Population based studies are free from biases present in patients studies, as they involve relatively healthy people who are not seeking medical attention. Thus conclusions drawn are more representative of the general population, and allow an estimation of the population prevalence of various factors. Such population studies of GI symptoms in JHS are lacking.

3.2 Aims

The aim of this study was to reproduce the patient study described in Chapter 2, but this time in a population of healthy individuals, to determine how generalisable our earlier findings were. Specifically, (1) to determine and compare the prevalence of individual GI symptoms and other associated factors in a population of healthy subjects with and without JHS; (2) to determine what factors were predictive of GI symptom presence in JHS in this population (3) to determine the influence of possible confounders on the association between

JHS and GI symptoms; and (4) to examine the effect of JHS on quality of life in non-patients.

3.3 Hypothesis

We hypothesised that GI and other extra-articular symptoms would be present in JHS non-patients, albeit at a lower prevalence than that quoted in previous studies of JHS patients. Furthermore, we expected upper GI symptoms to be associated with autonomic and hypersensitivity factors (as shown in the patient study in Chapter 2). We also hypothesised that subjects with JHS would have a worse quality of life than those without JHS.

3.4 Materials and methods

3.4.1 Study design

A cross sectional study in Queen Mary University Students was performed. The first part of the study involved the completion of the validated hypermobility screening questionnaire online (Hakim and Grahame 2003). Those who screened positive (score ≥ 2 out of 5) and negative (score 0 out of 5) were further invited to the second part of the study where they were assessed for JHS and fibromyalgia and then completed a set of validated questionnaires as described below. Comparisons were made between students with and without confirmed JHS.

3.4.2 Subjects

All 12,000 students at QMUL were invited to participate in the first part of the study via a university-wide email that contained a link to an online hypermobility

questionnaire and an attachment containing the information sheet for the study. Those that screened positive and negative and who had supplied their contact details were further invited to the second part of the study if they were between the ages of 16 and 35, and had a sufficient understanding of written English to be able to answer the questionnaires. Written consent was taken from all the subjects. The study was approved by Queen Mary Research Ethics Committee, Ref: QMREC2011/42**.**

3.4.3 Questionnaires

Hypermobility Screening Questionnaire

For the first part of the study, subjects completed the validated hypermobility questionnaire online . Answering in the affirmative to at least 2 of the 5 questions was considered a positive screen, as recommended for that questionnaire (Hakim and Grahame 2003). For the purposes of the study, a score of 0 was considered a negative screen.

For the second part of the study, subjects completed validated questionnaires to systematically assess for GI symptoms, psychopathology, autonomic symptoms, somatic symptoms and quality of life. Demographic information and medication histories were also collected via standardized forms. Subjects were asked to provide details of past medical history – specifically they were asked whether they had ever consulted their GP or attended a hospital for GI problems, and whether they had been given a diagnosis of IBS.

GI symptom assessment:

The Bowel Disease Questionnaire (BDQ) (Talley, Phillips et al. 1990) was used to obtain a detailed assessment of GI symptoms experienced over the past 6 months, as described in Chapter 2. For this study, GI symptoms were considered to be present if they were experienced at least a few times per month.

Autonomic symptom assessment:

The validated Composite Autonomic Symptom Scale (COMPASS questionnaire), as described in Chapter 2, was used to obtain a detailed assessment of autonomic symptoms (Suarez, Opfer-Gehrking et al. 1999). Scores are provided for various autonomic domains including constipation, gastrointestinal, diarrhoea, urinary, vasomotor, syncope, pupillary, secretomotor, sleep, psychosomatic and erectile dysfunction. A composite score for all autonomic symptoms can also be calculated. For this study, the composite score and the score for all the individual domains except for erectile dysfunction were used.

Psychological assessment:

The Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith 1983) is used to determine the levels of anxiety or depression a person is experiencing. It consists of 14 items – 7 relating to anxiety and 7 to depression. Each question can be scored from 0-3, thus scores for each of anxiety or depression can range from 0-21, with higher scores indicating a higher severity of symptoms. Scores of 11 or more out of 21 are considered indicative of the presence of anxiety or depression.

Somatic symptoms:

The validated Patient Health Questionnaire 15 (PHQ 15), which was described in detail in Chapter 2, was used to assess for somatosensory amplification (Kroenke, Spitzer et al. 2002). All 15 items were used, giving a total score between 0 and 30, with higher scores indicating a higher number of somatic symptoms.

Quality of life assessment:

Health-related QOL was evaluated using the SF-36, as described in Chapter 2 (McHorney, Ware et al. 1993).

3.4.4 Examination and structured interview

This was performed after written consent was taken and before questionnaires were completed so that the assessment of JHS and fibromyalgia was performed blinded to the subjects' symptoms.

Assessment of JHS

Diagnosis of JHS was made using the Brighton criteria (Grahame, Bird et al. 2000), as described in Chapter 2.

Skin stretch test

Skin was examined for texture, striae, scarring and for the degree of stretchiness of the skin, as described in Chapter 2.

Assessment for fibromyalgia

This was performed as described in Chapter 2. Subjects were considered to have fibromyalgia if they satisfied the 1990 or 2010 ACR criteria (Wolfe, Smythe et al. 1990; Wolfe 2010).

3.4.5 Blinding

To ensure blinding of the students to their JHS status, they were not informed of their hypermobility status until after they had completed the questionnaires. They were also blinded to the exact aim of the study and told that the study was being performed to determine if there was a link between skin and joint characteristics and the presence of GI and other symptoms – they were not informed what those skin and joint characteristics were. This reduced the likelihood of response bias in answering the questionnaires. To ensure blinding of the researcher to the presence of GI symptoms in the students, the assessment for JHS and fibromyalgia was performed before students completed the questionnaires. Once completed, questionnaires were placed in a sealed envelope and then handed to a research assistant for transcription onto an electronic database. A unique ID code was used to match examination findings with questionnaire responses on the database and prevented recognition of individual students therefore reducing bias when analysing the results.

3.4.6 Data analysis and Statistics

Univariate analysis

Data were described in terms of means and confidence intervals (normal ordinal data), medians and IQR (non-normal ordinal data) and proportions and

confidence intervals (categorical data). Comparisons of GI and associated factors in students with and without JHS were performed using the t-test (normal ordinal data), Mann Whitney U-test (non-normal ordinal data), chi squared test (categorical data) or Fisher's exact test (categorical data if proportions were less than 5%).

Identification of factors independently associated with GI symptoms

To determine which factors (independent of JHS) predicted GI symptoms, a multivariate stepwise logistic regression analyses was performed with the GI symptom of interest as the dependent variable, and JHS status and all other measured factors as the independent variables. This produced a regression model of best fit, which included all those factors that were independently associated with the GI symptom of interest , at a significance level of <0.05.

Effect of possible confounding factors on the regression model of best fit

Possible confounders were identified as those factors that were associated with both JHS and GI symptoms, in this study, or in Chapter 2. To determine the effect of these factors on the association between JHS and individual GI symptoms, a stepwise logistic regression analysis was performed. The initial regression model contained JHS, age and gender as fixed variables, as well as any other factors which were present in the regression model of best fit and therefore independently associated with the GI symptom of interest. Factors identified as potential confounders were added individually to the initial model and the effect on the odds ratio between JHS and GI symptoms was observed. Factors which decreased the odds ratio considerably, were considered to confound or mediate the association between JHS and GI symptoms.

3.5 Results

3.5.1 Subjects

All 12,000 students at Queen Mary University London were invited, via email, to complete the online hypermobility screening questionnaire (Figure 3.1). 1998 students completed the questionnaire but only 1576 supplied their contact details. Of the 1576, 497 had negative screens (score=0/5), 575 had positive screens (score ≥ 2/5), and 504 scored 1/5. Of the 575 positive screens, 125 consented to attend the second part of the study; on assessment only 74 of these had JHS (screen positive and JHS positive). Of the 497 negative screens, 98 consented to attend the second part of the study; on assessment 88 were confirmed not to have JHS (screen negative, JHS negative) (Figure 3.1). Thus 73 JHS students and 89 non-JHS students were finally included in the study.

3.5.2 Demographics and hypermobility features

There were no significant gender differences in the 2 groups - Table 3.1. JHS students were significantly younger (21.6 vs 22.8, p=0.048) and had a lower BMI (22.0 vs 23.4, p=0.05). The JHS students were also more likely to be White (69% vs 52%, p=0.02), and more likely to drink alcohol (86% vs 72%, p=0.02) – Table 3.1. Students with JHS had a higher median Beighton score (5 vs 1, p<0.001) - Figure 3.2. They also had a significantly higher incidence of other hypermobility features including polyarthralgia, scoliosis, dislocations, soft tissue injuries, Marfanoid habitus, skin signs, and affected first degree relative (all p<0.005) - Table 3.2. JHS students also had higher skin extensibility scores (Median CSES: 15 vs 11, p<0.001) - Figure 3.3.

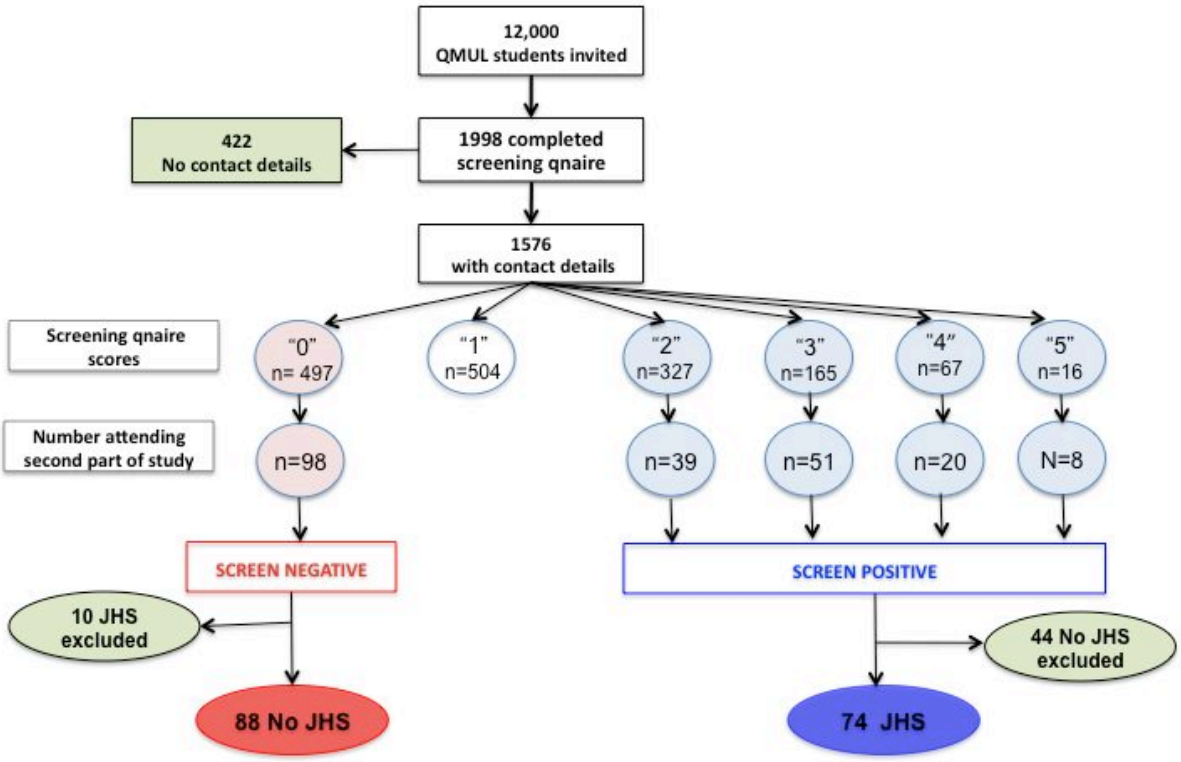


Figure 3.1: Flowchart of subject selection for Chapter 3.

Of the 1576 students who completed the screening questionnaire and supplied their contact details, 497 had negative screens and 575 had positive screens. 98/497 negative screens and 118/575 positive screens attended the second part of the study. After examination, 88 students without JHS and 74 students with JHS were included.

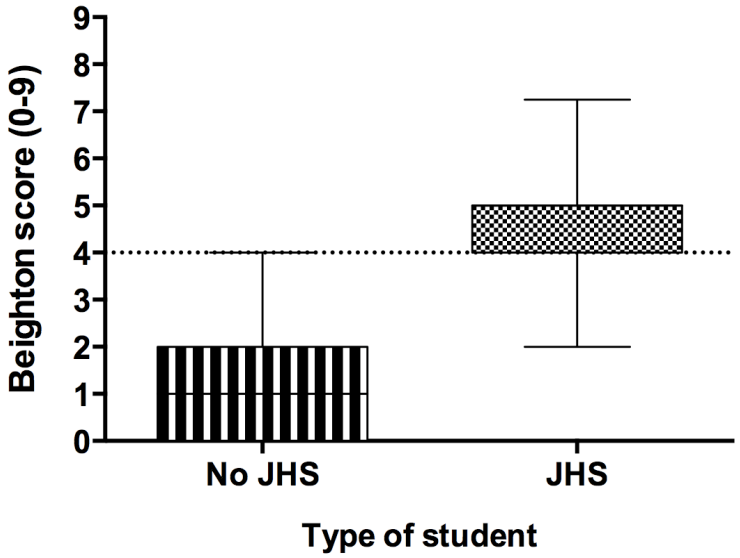


Figure 3.2: Beighton scores in students with and without JHS.
The dotted line represents a score of 4 out of 9 which is the cut-off for GJH.

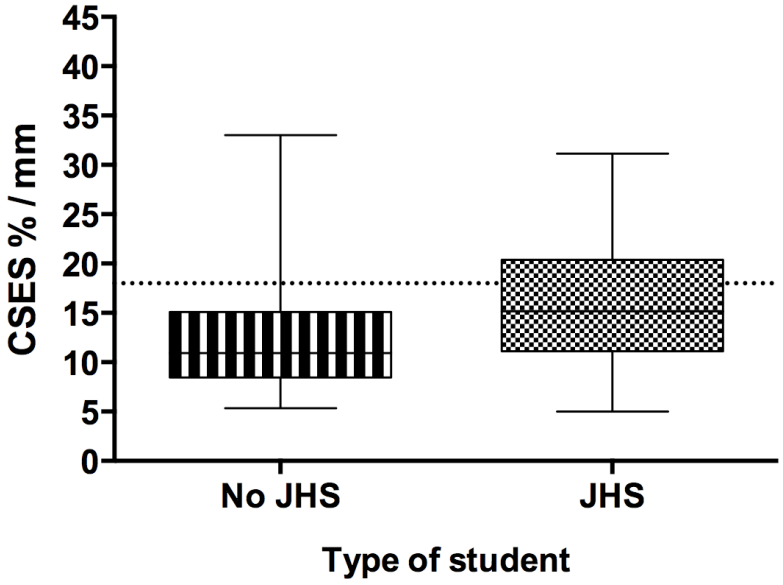


Figure 3.3: Skin extensibility (CSES) in students with and without JHS. The dotted line represents a CSES of 18 which has the highest sensitivity and specificity for discriminating between those with GJH

Table 3.1 Comparison of demographic features in students with and without JHS.

Values given are percentages of students and the 95% confidence intervals for each group. BMI: Body Mass Index

	No JHS (n=88)	JHS (n=74)	p
Female (%) (CI)	53.4 (42.8-62.0)	64.9 (53.7-76.0)	0.14
Mean age (CI)	22.8 (22.0-23.7)	21.6 (20.7-22.5)	0.05
BMI (CI)	23.4 (22.3-24.5)	22.04 (21.3-22.8)	0.05
Ethnicity			
Asian (%) (CI)	28.4 (18.8-38.0)	16.4 (7.7-25.1)	0.07
Black (%) (CI)	3.4 (0.5-7.3)	1.4 (0-4.1)	0.4
White (%) (CI)	52.3 (41.6-62.9)	68.9 (59.1-80.6)	0.02
Chinese (%) (CI)	6.8 (1.4-12.2)	2.7 (1.1-6.6)	0.24
Mixed (%) (CI)	4.6 (0.1-9.0)	8.1 (1.8-14.7)	0.34
Other (%) (CI)	4.5 (0.1-9.0)	1.4 (0-4.1)	0.25
Social History			
Smoker (%) (CI)	13.6 (6.3-20.9)	13.5 (5.5-21.5)	0.98
Alcohol use (%) (CI)	71.6 (62.0-81.2)	86.5 (78.5-94.4)	0.02

Table 3.2: Comparison of features of Brighton classification in students with and without JHS.

Values given are the percentages of students who had each feature.

	No JHS (n=88)	**JHS (n=74)**	**p**
Median Beighton score (IQR)	1 (0-2)	5 (4-5)	<0.001
JHM (Beighton ≥ 4) (CI)	7.9 (2.2-13.7)	82.4 (73.6-91.3)	<0.001
Arthralgia ≥ 4 joints (CI)	2.3 (0-5.4)	18.9 (9.8-28.0)	<0.001
Arhralgia 1-3 joints (CI)	13.6 (6.3-20.9)	29.7 (19.1-40.4)	0.012
Back pain (CI)	7.9 (2.2-13.7)	18.9 (10.9-29.6)	0.004
Spondylosis, scoliosis (CI)	4.6 (0.1-9.0)	18.9 (9.8-28.0)	0.004
Dislocation,subluxation (CI)	7.9 (2.2-13.7)	52.7 (41.1-64.3)	<0.001
Soft tissue problems (CI)	4.6 (0.1-9.0)	33.8 (22.8-44.8)	<0.001
Marfanoid habitus (CI)	11.4 (4.6-18.1)	29.7 (19.1-40.4)	0.003
Skin changes (CI)	36.4 (26.1-46.6)	64.9 (53.7-76.0)	<0.001
Eye signs (CI)	29.6 (19.8-39.3)	37.8 (26.5-49.2)	0.3
Varicose veins (CI)	1.1 (0-3.4)	4.1 (0-8.6)	0.33
Hernia (CI)	4.6 (0.1-9.0)	4.1 (0.5-8.6)	1.0
Organ prolapse (CI)	0 (0-0)	0 (0-0)	-
Affected first degree relative (CI)	1.1 (1.1-3.4)	25.7 (15.5-38.9)	<0.001

3.5.3 GI symptoms in students with and without JHS

52.7% of the JHS students experienced at least 3 GI symptoms more than once a month, and this was significantly increased compared to the non-JHS students (29.5%, p=0.003). To determine which symptoms were particularly different in the groups, the prevalence of individual lower and upper GI symptoms which were experienced more than once per month were compared - Table 3.3 and Table 3.4. There was no significant difference in the prevalence of any of the lower GI symptoms, however the prevalence of proctalgia was twice as high in the JHS group (14% vs 7%, p=0.19) - Table 3.3. There was no significant difference in bowel habit, though constipation was over twice as common in the JHS group (8% vs 3%, p=0.2) - Table 3.3. The most prevalent upper GI symptoms in JHS were abdominal pain (43%), postprandial fullness (34%), early satiety (32%) and bloating (26%). However, only postprandial fullness and early satiety showed a significant increase when compared with non-JHS students (postprandial fullness: 16%, p=0.01.; early satiety: 17%, p=0.03) - Table 3.4.

There was no difference in the proportion of JHS and non-JHS students who had seen their GP for GI problems (25.6% vs 26.4%, p=0.9), been to hospital for GI problems (9.5% vs 4.5%, p=0.2), or been diagnosed with IBS (5.4% vs 10.3%, p=0.3).

Table 3.3: Comparison of lower GI symptoms in students with and without JHS.

Values given are percentages of students in each group who experience the symptom at least 'often'.

	No JHS (n=88)	JHS (n=74)	p
Constipation (CI)	3.4 (0-7.3)	8.1 (1.7-14.4)	0.30
Diarrhoea (CI)	1.1 (0-3.4)	1.4 (1.3-4.0)	1.0
Alternating bowel habit (CI)	11.5 (4.6-18.3)	12.2 (4.5-19.8)	0.90
Lumpy stool (CI)	19.8 (11.1-28.3)	21.6 (12.0-31.2)	0.77
Watery stool (CI)	2.3 (0.9-5.5)	6.8 (0.9-12.6)	0.25
Straining (CI)	17.2 (9.1-21.3)	14.8 (6.6-23.2)	0.68
Incomplete evacuation (CI)	23.0 (14.0-32.0)	24.3 (14.3-24.3)	0.84
Blocked sensation in rectum (CI)	9.2 (3.0-15.4)	8.1 (1.7-14.4)	0.81
Poor relaxation of sphincter (CI)	3.5 (0.5-7.4)	8.2 (1.8-14.7)	0.85
Manual manoeuvres for rectal evacuation (CI)	2.3 (0.9-5.5)	0 (0-0)	0.50
Faecal incontinence (CI)	3.5 (0.5-17.4)	2.7 (1.1-6.4)	1.0
Faecal urgency (CI)	10.3 (3.8-16.9)	6.8 (0.9-12.6)	0.58
Anal pain (proctalgia) (CI)	6.9 (1.5-12.3)	13.7 (5.6-21.8)	0.19

Table 3.4 : **Comparison of upper GI symptoms (from BDQ) in students with and without JHS.**

Values given are percentages of students in each group who experience the symptom at least '2-3 times per month'.

	No JHS (n=88)	**JHS (n=74)**	**p**
Abdominal pain (CI)	34.1 (23.8-44.4)	42.6 (30.6-54.7)	0.28
Globus (CI)	6.8 (1.4-12.2)	6.8 (0.9-12.8)	1.0
Retrosternal chest pain (CI)	16.1 (8.2-24.0)	12.3 (4.6-20.0)	0.50
Heartburn (CI)	11.4 (4.6-18.1)	13.5 (5.5-21.5)	0.68
Waterbrash (CI)	10.3 (3.8-16.9)	13.5 (5.5-21.5)	0.54
Dysphagia (CI)	3.5 (0-7.5)	2.7 (1.1-6.6)	1.0
Epigastric discomfort (CI)	5.7 (0.8-10.7)	12.2 (4.5-19.8)	0.17
Postprandial fullness (CI)	15.9 (8.1-23.7)	34.4 (21.6-43.3)	0.01
Early satiety (CI)	17.0 (9.0-25.0)	31.5 (20.6-42.4)	0.03
Nausea (CI)	11.4 (4.6-18.1)	16.2 (7.6-24.8)	0.37
Vomiting (CI)	1.1 (1.1-3.4)	2.7 (1.1-6.6)	0.59
Regurgitation (CI)	2.3 (0-5.4)	5.5 (0.1-10.8)	0.41
Belching (CI)	11.4 (4.6-18.1)	16.4 (7.7-25.1)	0.35
Bloating (CI)	22.7 (13.8-31.7)	26.4 (16.0-36.8)	0.59

3.5.4 Comparison of extra-intestinal features: psychopathology, somatic symptoms and fibromyalgia

JHS students did not have increased anxiety or depression - Table 3.5. They did however, have increased somatic sensitivity as manifest by increased scores on the PHQ15 (7 vs 4, p=0.03).

The number of positive tender points in both groups ranged from 0-11 out of a maximum 20, and had a very skewed distribution towards the lower scores with a median score of 1 in students with JHS (IQR: 0-4), and 0 in students without JHS (IQR: 0-1). This was significant using the Mann-Whitney U test (p=0.004), however analysing the number of tender points as a continuous variable did not give a very good idea of the real spread of positive tender points in the 2 groups. To enable this, the number of tender points was converted into a categorical variable and the number of students with 0 tender points, 1-4 positive tender points, 5-8 positive tender points and 9-11 tender points was compared in each group. JHS students were significantly more likely to have positive tender points (54.1 vs 31.8, p=0.004) - Figure 3.4.

There was no difference in the prevalence of chronic widespread pain, insomnia, memory problems, all of which were features of the revised classification for fibromyalgia - Table 3.5. Only 1 student (JHS) was diagnosed with fibromyalgia but this was not significant.

Table 3.5: **Comparison of psychopathology, fibromyalgia and somatosensory amplification in students with and without JHS.**
For categorical variables, values given are proportions for that group

	No JHS (n=88)	JHS (n=74)	p
PSYCHOPATHOLOGY (HADS)			
Anxiety score (CI)	6.49 (0.43)	6.50 (0.44)	0.98
Depression score (CI)	2.42 (0.27)	2.51 (0.28)	0.69
FIBROMYALGIA			
Chronic widespread pain (CI)	2.3 (0-5.4)	1.4 (1.3-4.0)	1.0
Insomnia (CI)	14.8 (7.2-22.3)	24.3 (14.3-34.3)	0.12
Memory problems (CI)	8.0 (2.2-13.7)	4.0 (0.5-8.6)	0.35
Positive tender points (CI)	31.8 (22.3-42.6)	54.1 (42.1-65.7)	0.004
% with fibromyalgia (1990/2010) (CI)	0 (0-0)	1.3 (1.3-4.0)	0.46
SOMATIC SYMPTOMS (PHQ15)			
PHQ15 (IQR)	4 (3-8.5)	7 (4-9)	0.04

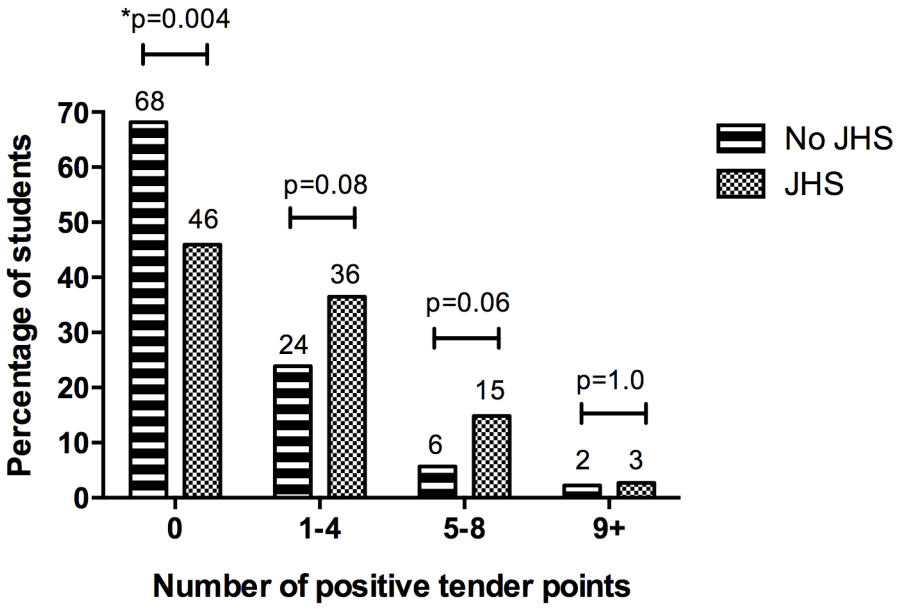


Figure 3.4: **Number of positive tender points in students with and without JHS.**

Students with JHS were significantly less likely to have no positive tender points

3.5.5 Comparison of extra-intestinal features: autonomic symptoms

Overall autonomic scores were higher in the JHS students (14.4 ± 1.0 vs 9.7 ± 0.8, $p<0.001$). When the scores were broken up into the individual domains, differences were only seen in the orthostatic domain (31.3 ± 2.5 vs 21.3 ± 2.0, $p=0.002$) and diarrhoea domain (15.9 ± 2.5 vs 7.5 ± 1.5, $p=0.003$) - Figure 3.5. There was no difference in vasomotor scores (10.3 ± 2.5 vs 5.8 ± 1.8, $p=0.1$), secretomotor scores (13.5 ± 1.4 vs 12.1 ± 1.4, $p=0.5$), gastrointestinal scores (7.4 ± 1.6 vs 4.0 ± 1.0, $p=0.06$), constipation scores (9.3 ± 1.6 vs 8.1 ± 1.6, $p=0.6$), urinary scores (6.5 ± 1.5 vs 4.0 ± 1.0, $p=0.2$), pupillary scores (13.9 ± 2.1 vs 10.3 ± 1.9, $p=0.2$), sleep scores (7.0 ± 1.0 vs 4.9 ± 1.0, $p=0.1$) or syncope scores (1.9 ± 0.7 vs 1.1 ± 0.5, $p=0.4$). Psychosomatic scores were

not increased in the JHS students compared to the non-JHS students (0.12 ± 0.12 vs 0.93 ± 0.93, p=0.43).

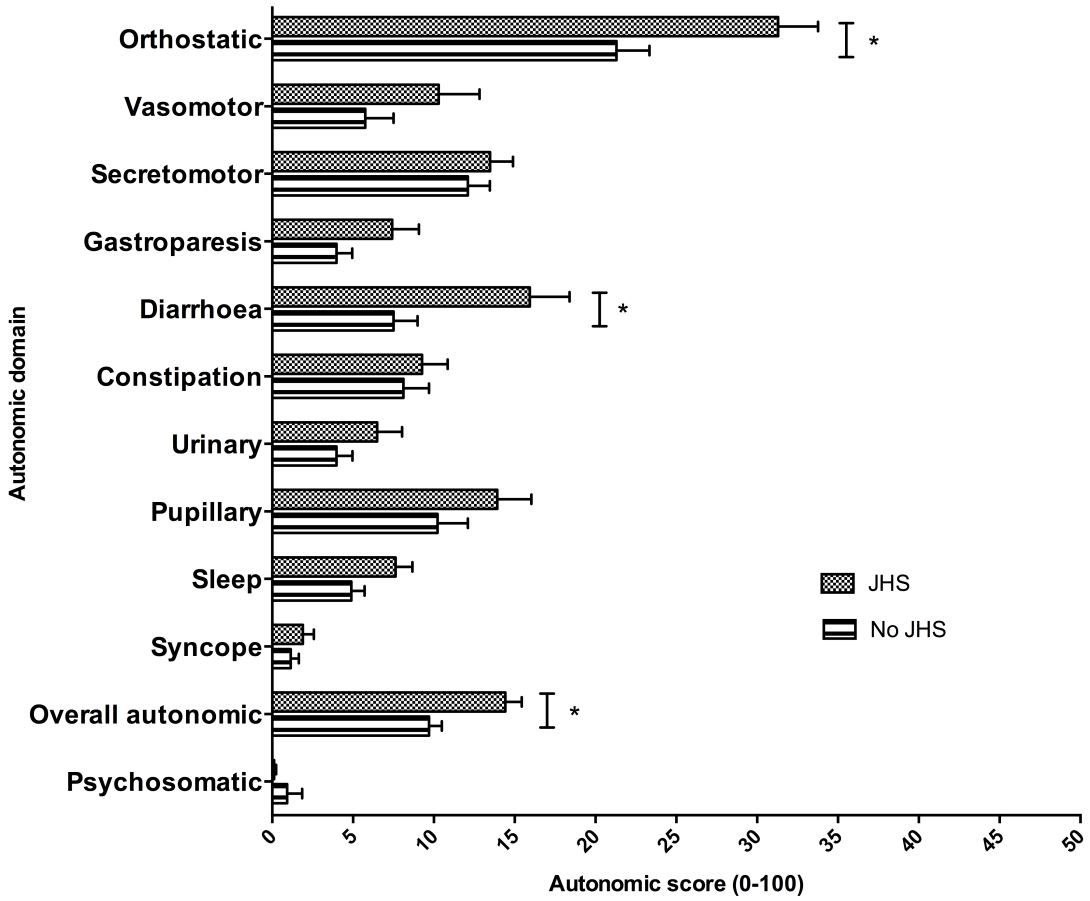


Figure 3.5: Comparison of autonomic scores (from COMPASS) in students with and without JHS.
Asterisks represent significant comparisons (p<0.05).

3.5.6 Medication use and past medical history

Past medical histories included asthma, migraines, eczema, irritable bowel syndrome, hay fever, diabetes, dental problems, polycystic ovary syndrome, renal problems, orthopaedic problems, and musculoskeletal problems e.g. muscle sprains. Apart from musculoskeletal problems, which were significantly increased in JHS (13.7% vs 4.5%, p=0.02), there were no significant differences in the prevalence of medical problems in the 2 groups.

Nor were there any differences in medication use in the 2 groups. Medications included antidepressants, simple analgesics, bronchodilators, antibiotics, antispasmodics, antihistamines, the oral contraceptive pill and proton pump inhibitors. No students were taking opiates.

3.5.7 Factors predicting GI symptoms

To determine whether JHS was independently associated with GI symptoms, a multivariate logistic regression analysis was performed with the symptom of interest as the dependent variable, JHS, age and gender as fixed independent variables and all other measured factors (autonomic scores, number of tender points, PHQ15 scores, anxiety and depression levels) as covariates.

The logistic regression analysis was first run for GI symptom presence (at least 3 GI symptoms over the past 3 months) as the dependent variable. In this model, the presence of JHS was independently associated with GI symptom presence (OR: 2.71, CI: 1.11-6.58, $p=0.03$) even after adjusting for all the other variables. In addition, anxiety levels ($p<0.001$), autonomic scores ($p=0.004$) and number of tender points ($p=0.05$) were independently associated with GI symptom presence. Hence JHS, as well as autonomic and anxiety scores and number of tender points, were all independent predictors of GI symptoms.

To look specifically at postprandial fullness and early satiety, which were earlier shown to be significantly associated with JHS, a similar logistic regression analysis was run with either postprandial fullness or early satiety as the dependent variable. This time, only JHS and anxiety scores were significantly associated with both symptoms. Hence JHS is an independent predictor of both

postprandial fullness (p=0.04) and early satiety (p=0.046), even after adjusting for all other factors.

3.5.8 Effect of autonomic and somatic factors on the association between JHS and postprandial symptoms.

Autonomic symptoms and somatic hypersensitivity (PHQ15 scores and fibromyalgia) have previously been shown to confound the association between JHS and postprandial symptoms in patients (Chapter 2). To determine whether this was also the case in non-patients, a logistic regression analysis was performed as described in the methods section. This was run twice – once for early satiety and once for postprandial fullness. The regression model contained as independent variables those factors that were independently associated with postprandial symptoms (i.e. JHS and anxiety) as well as age and gender; and as dependent variables, either postprandial fullness or early satiety. Autonomic scores, tender points (as a surrogate for fibromyalgia) and PHQ15 scores were added stepwise to this model, and the effect on the association between JHS and postprandial symptoms (adjusted odds ratio) was observed (Table 3.6)

None of the factors had a substantial effect on the association between JHS and postprandial symptoms, as manifest by an adjusted odds ratio which did not change significantly from that of the initial model. PHQ15 scores had practically no effect on the JHS-postprandial symptom association. The number of positive tender points, reduced the strength of the association between JHS and early satiety only, but this effect was small - Table 3.6.

Table 3.6: Effect of orthostatic symptoms, number of tender points, PHQ15 scores on the association between JHS and GI symptoms.
Results of the multivariate logistic regression analysis: Values given are odds ratios for the association between JHS and symptoms, adjusted for various factors. Confidence intervals are given in brackets. Anx: anxiety scores, ortho: orthostatic autonomic scores. Tenderpt: number of positive tender points.

	Postprandial fullness	**Early satiety**
ORadj (age, gender, anx)	2.79 (1.19-6.54)	2.21 (1.00-4.86)
ORadj (age, gender, anx, autonomic)	2.55 (1.05-6.18)	2.42 (1.06-5.53)
ORadj (age, gender, anx, ortho)	2.49 (1.04-5.96)	2.48 (1.09-5.63)
ORadj (age, gender,anx, PHQ15)	2.83 (1.20-6.69)	2.26 (1.02-5.01)
ORadj (age, gender, anx, tenderpt)	2.74 (1.16-6.47)	2.10 (0.95-4.70)

3.5.9 Quality of life in JHS and non JHS

All 74 JHS students were initially compared to all 88 Non-JHS students. Those with JHS had lower QOL scores on the pain component of the SF36 (80 vs 90, p=0.03). There were no other differences in the scores on any of the physical, emotional or social domains.

When comparisons were made between students who had more than 3 GI symptoms, Non-JHS students had significantly worse scores for energy and fatigue (45 vs 55, p=0.005) and for general health (40 vs 70, p=0.004) - Table 3.7 .

Table 3.7: **Median SF36 scores in JHS and non-JHS students who had GI symptoms**

SF36 domain	No JHS (n=26)	JHS (n=39)	p
General health (IQR)	40 (35-65)	70 (45-85)	0.004
Physical function (IQR)	95 (85-100)	100 (95-100)	0.06
Role limiting physical (IQR)	100 (75-100)	100 (50-100)	0.88
Emotional well-being (IQR)	60 (48-72)	68 (52-76)	0.35
Role limiting emotional (IQR)	66 (0-100)	100 (0-100)	0.24
Energy and fatigue (IQR)	45 (30-60)	55 (45-70)	0.005
Pain (IQR)	73.5 (67-90)	77 (57-90)	0.99
Social function (IQR)	75 (62-100)	75 (62-100)	0.42

3.6 Discussion

3.6.1 Summary of results

We have demonstrated that 53% of young JHS non-patients experience 3 or more GI symptoms more than once a month, and that abdominal pain, bloating, postprandial fullness and early satiety are the most commonly experienced symptoms. When compared to students without JHS, those with JHS had significantly more GI symptoms, and more extra-intestinal features, as manifest by higher autonomic scores, somatic symptom scores and greater number of positive tender points. There was a significant and independent association between JHS and dyspeptic symptoms (early satiety and postprandial fullness), which was not related to autonomic, somatic or psychological factors. Quality of life scores in JHS non-patients were generally high, and moreover, JHS students with GI symptoms had higher quality of life scores than did their non-JHS counterparts.

3.6.2 Comparison with previous studies

The prevalence of GI symptoms in the non-JHS students was comparable to previous population studies (Stanghellini 1999; Bytzer, Talley et al. 2001) suggesting that our students were typical non-patients. The prevalence of GI symptoms in our JHS group was twice as high, and was within the range quoted in JHS patient studies (37-86%) (Hakim and Grahame 2004; Castori, Camerota et al. 2010; Rombaut, Malfait et al. 2011). This large range quoted previously is most likely due to the fact that each of the studies used different methods to obtain GI symptom information. Some used information obtained on medical interview (Rombaut, Malfait et al. 2011), some used non-validated questionnaires (Hakim and Grahame 2004), and others used non-GI specific

validated questionnaires (Castori, Camerota et al. 2010). The frequency with which GI symptoms were experienced, and the time frame within which they were experienced, were not clearly specified in the above studies, and this is likely to account for the variability in quoted prevalence. For example, the prevalence of GI symptoms would clearly be much higher if 'symptom presence' referred to the presence of at least one GI symptom experienced at least once a month, than if it referred to the presence of at least 4 symptoms experienced daily. In our study, the BDQ was used which allows the subject to specify the frequency with which the symptoms occurred over the past 3 months. In view of the fact that our subjects were young and non-patients, GI symptom presence was defined as the presence of at least 3 symptoms experienced more than once a month. Despite this conservative definition, we observed a significantly increased prevalence of GI symptoms in JHS compared to non-JHS, echoing the results found in rheumatology patients (Hakim and Grahame 2004), and in our study in GI patients (Chapter 2), suggesting that the presence of JHS is associated with increased GI symptoms, in any setting.

To further characterise this association, the prevalence of individual symptoms was compared in the 2 groups. Only postprandial fullness and early satiety, which are considered dyspeptic symptoms, were significantly increased in the JHS students, and were twice as high as the quoted population prevalence (12-16%) of these symptoms (Tougas, Chen et al. 1999; Sobieraj, Coleman et al. 2011). This association of JHS with postprandial (dyspeptic) symptoms was previously described in JHS patients attending genetics clinics (Castori, Camerota et al. 2010), as well as JHS patients referred from rheumatology to GI

clinics (Chapter 2). Thus with respect to postprandial symptoms, findings in non-patients mimic those in patients.

For non-dyspeptic symptoms, our findings differed to those in patient studies. Constipation and proctalgia were twice as high in JHS compared to non-JHS students, but the comparisons were not significant. Other symptoms which have previously been shown to be associated with JHS in patient studies e.g. alternating bowel habit, bloating, abdominal pain, reflux and dysphagia, (Hakim and Grahame 2004; Castori, Camerota et al. 2010) and in Chapter 2 of this thesis did not show a similar association in our non-patients. There are two possible explanations for this. Firstly, subjects in this study were much younger than those in patient studies and it is believed that GI and non-GI symptoms increase with age (Castori, Sperduti et al. 2012). In the absence of a longitudinal study, it is impossible to determine whether JHS students who are asymptomatic, will go on to develop GI symptoms, nor indeed whether those with postprandial symptoms, will further develop the other symptoms seen commonly in JHS patients. Secondly, patient studies are biased, as they include patients who present to specialty clinics and who thus have a more pronounced hypermobility presentation, as well as associated comorbidity, both of which might contribute to the increased range of GI symptoms in patients with JHS. In this way, patient studies may represent findings at the more severe end of the JHS spectrum, whereas non-patient studies provide evidence for the milder end. Thus it would appear that postprandial symptoms, but not other symptoms, are significantly increased in mild asymptomatic JHS individuals who have no knowledge of their hypermobility status, and that other symptoms

become more important as JHS progresses and the individual turns into a patient with other associated comorbidities.

With regards to extra-intestinal features, there was an increased incidence of autonomic symptoms in the JHS group, and this was mainly due to increased orthostatic symptoms, consistent with previous JHS patient studies (Gazit, Nahir et al. 2003; Mathias, Low et al. 2011). This supports the growing literature in patients on the association between JHS, orthostatic symptoms and PoTS (Gazit, Nahir et al. 2003; Kanjwal, Saeed et al. 2010; Mathias, Low et al. 2011), but to our knowledge, this is the first description of such an association in non-patients. The presence of increased autonomic symptoms in young JHS individuals who are attending university, and who are healthy and highly functioning, would suggest that the autonomic features are not secondary to deconditioning (De Wandele, Rombaut et al. 2013). Instead, it suggests that orthostatic symptoms may inherently be associated with JHS from an early age, slowly increasing over time, until they cause decompensation and the eventual syndrome of POTS.

In addition to autonomic symptoms, JHS students had a greater number of somatic symptoms. PHQ15 scores, which are thought to represent somatosensory amplification, were higher in the JHS students, and this supports a previous study in French undergraduate students (Baeza-Velasco, Gely-Nargeot et al. 2011). These findings are also in line with the observation that JHS patients have an increased incidence of functional somatic syndromes (Castori, Celletti et al. 2011; Castori 2012) including fibromyalgia. Although only one JHS student fulfilled the criteria for fibromyalgia, there was a higher

proportion of students with positive tender points in the JHS group, which provides objective evidence of somatic hypersensitivity in this group.

Interestingly, anxiety and depression scores were not increased in JHS students. This is in contrast to longitudinal studies which showed that JHS is a predictor of future anxiety (Bulbena, Gago et al. 2011) and that there is an association between JHS and anxiety even in non-patients (Baeza-Velasco, Gely-Nargeot et al. 2011). Once again, this can be explained by age differences in the 2 studies. In the longitudinal study, the association was only manifest in the follow-up period, when the JHS individuals were in their mid-thirties. The students in our study were substantially younger, with a mean age of 22, and anxiety may not have yet developed.

The increased number of somatic symptoms and tender points in JHS students in spite of the absence of anxiety and depression, would suggest that somatosensory amplification is not a consequence of psychopathology and somatisation (Rief and Isaac 2007). Instead, it might be secondary to altered sensory or pain processing in JHS, which leads to the development of several functional somatic syndromes e.g. chronic fatigue syndrome, fibromyalgia, pelvic pain, irritable bowel syndrome (Castori, Celletti et al. 2011). Furthermore, the increase in tender points in the absence of all the other features of fibromyalgia would suggest that as was postulated for the other symptoms, these somatic features may increase over time and ultimately lead to overt syndromes such as fibromyalgia, which have been associated with JHS in a relatively older cohort.

Previous studies performed in JHS patients have demonstrated that the presence of GI symptoms is associated with multiple somatic and autonomic symptoms (Castori, Celletti et al. 2011) and it has been hypothesised that an underlying dysautonomia leads to visceral and somatic hypersensitivity which then results in GI and unexplained somatic symptoms (Castori, Celletti et al. 2011). Other hypotheses, based on patient studies, have suggested that the GI symptoms are either due to deconditioning (due to physical inactivity), opiate use, or genetic factors (De Wandele, Rombaut et al. 2013). We were able to address some of these hypotheses with our non-patient study. As none of the students were on opiates, and all were healthy and active with no evidence or cause for deconditioning, we could rule out those 2 factors as an explanation for the observed increase in JHS symptoms.

The autonomic/hypersensitivity theory was not as clear-cut. Students with JHS had increased autonomic and somatic symptoms as well as GI symptoms so it was more difficult to tease these factors apart. Our study in GI patients (chapter 2) demonstrated that postprandial symptoms, were mediated by a combination of autonomic and somatic factors, and that those factors accounted for most of the association between JHS and symptoms. This was not the case in this student study. Interestingly, JHS was independently associated with postprandial symptoms, and was not substantially affected by autonomic or somatic symptoms (PHQ15), nor by the number of positive tender points. Thus in young JHS students, as compared to older JHS patients, the presence of JHS is independently associated with postprandial symptoms, and autonomic and somatic factors have no effect on this.

Lastly, the effects of these increased symptoms on quality of life were examined. Interestingly, JHS students had very good quality of life scores, which were much higher than scores published for patients (Castori, Camerota et al. 2010; Rombaut, Malfait et al. 2010), and which did not differ to scores in non-JHS students except for the 'pain' component. The latter is to be expected, as JHS students had more arthralgia (Table 3.2). To examine the effect of GI symptoms on quality of life, quality of life scores were compared in JHS and non-JHS students who had GI symptoms. Surprisingly, JHS students had better quality of life scores for general health and energy and fatigue, and were comparable to the non-JHS students for all other quality of life measures. This is in complete contrast to findings in JHS patients in Chapter 2 and in the literature whereby the combination of JHS and multiple extra-articular symptoms is associated with severe impairments in quality of life, (Castori, Camerota et al. 2010; Rombaut, Malfait et al. 2010) and would suggest that at an early stage, the increase in all symptoms does not affect quality of life, and that JHS patients cope relatively well. However, over time, the increased burden of multiple symptoms, possibly leads to increased pain, reducing physical and social functioning and resulting in impaired general health.

Putting this all together it would seem that in younger healthy JHS individuals who are non-patients, JHS is independently associated with dyspepsia, autonomic and somatic symptoms, but none of these are pathological, nor do they affect general health, social or physical functioning. With time, the number of autonomic and somatic symptoms increase (Castori, Sperduti et al. 2012), and the combination of these factors may lead to an increased range and prevalence of GI symptoms, as seen in Chapter 2. The presence of all these

comorbid symptoms significantly affects quality of life and affects physical and social functioning, motivating them to seek specialist help, by which time they have multiple associated symptoms, widespread organ involvement and very poor health.

3.6.3 Limitations

The study was not without limitations. Firstly, the required sample size was not achieved, due to a lower than expected response rate, and so the study was underpowered. Despite this, several significant differences in the groups were observed, which were supportive of previous studies. However it is possible that several of the symptoms which showed a non-significant trend e.g. constipation and proctalgia, would in fact show a significant difference, had the required sample size been recruited.

Secondly, multiple comparisons were performed in our study, which increases the chances that significant results were obtained by chance. However in view of the fact that the significant findings in our study supported previous studies, this explanation for our significant results is less likely.

Thirdly, the study was questionnaire-based and so it was subject to recall bias. However, most questions related to symptoms which were being experienced in the previous few months, making this less likely. An additional problem faced with questionnaires, is that symptoms picked up are not always equivalent to measureable pathology. As an example, autonomic symptoms are relatively non-specific, and so a high autonomic score is not equivalent to autonomic

dysfunction. To reduce the chances of this we used questionnaires which had previously been validated.

Fourthly, the possibility of response bias cannot be ignored. The information sheet sent out to the students during the first part of the study, explained that the aim was to investigate GI symptoms in certain populations of students. It is therefore likely that students with GI symptoms were more likely to take part in the study. However, if this were the case, it would have applied to both the JHS and non-JHS group and would not have accounted for the differences seen between them.

Lastly, our study was cross-sectional and was performed in young students, and therefore not necessarily representative of the entire population. Hence the extrapolation of our findings to different groups of healthy JHS individuals must be done with caution.

3.6.4 Implications for future research

Symptoms of postprandial fullness and early satiety are typical of functional dyspepsia and are thought to be secondary to abnormal sensation, motility or accommodation of the stomach, which can arise for a variety of reasons including autonomic dysfunction, hypersensitivity, somatisation, medication use, or gastric compliance (Oustamanolakis and Tack 2012). Our findings would suggest that in JHS non-patients these symptoms are not due to abnormal autonomic function, medication or somatisation, which leaves the possibility of altered biomechanics and/or motility. All these factors need to be investigated with physiological testing in the future.

Furthermore, the understanding of how symptoms progress over time, what other factors precipitate the worsening of symptoms and which factors predict the development of GI disorders (as opposed to symptoms) in these young individuals require longitudinal studies. This has yet to be done.

3.6.5 Clinical implications

This study demonstrates that despite the increased prevalence of autonomic, somatic and GI symptoms in young JHS individuals, their quality of life is preserved. This is clearly not the case when they eventually present to doctors as patients, by which point they have widespread organ involvement, multiple complications and poor quality of life. Hence earlier identification and management of JHS may retard the progression of GI and associated symptoms, and improve quality of life. As these individuals will initially present to primary care it is important for GP's to consider the diagnosis of JHS in young patients with postprandial symptoms, widespread musculoskeletal problems and hypermobile joints.

3.7 Conclusion

Over 50% of students with JHS experience GI symptoms regularly and there exists an association between JHS and GI symptoms in this young and healthy JHS population. This association is independent of autonomic and somatic factors which confound the association in patient studies suggesting that other factors present in JHS are involved. Although these JHS individuals have increased GI, autonomic and somatic symptoms, quality of life remains good at this early stage.

Chapter 4

Investigating the Association between the Joint Hypermobility Syndrome and Gastrointestinal Disorders

4.1 Introduction

The JHS literature provides consistent evidence that JHS patients attending specialist clinics have a high prevalence of GI symptoms (Hakim and Grahame 2004; Castori, Camerota et al. 2010; Rombaut, Malfait et al. 2011) which are predominantly 'functional' in nature e.g. globus, bloating, postprandial fullness and early satiety, and the studies described in Chapters 2 and 3 support this link. I have confirmed not only that GI symptoms occur in JHS patients presenting to rheumatology clinics, (Chapter 2), but that they also occur in healthy students with JHS who are non-patients (Chapter 3). Moreover, in the student study, the presence of JHS was an independent predictor for postprandial symptoms, suggesting that the JHS phenotype is a risk factor for these functional symptoms.

However, no large epidemiology studies have been performed to determine whether JHS is associated with GI disorders, as opposed to only GI symptoms, and specifically to determine whether there exists an association between JHS and FGID. The available evidence is mixed. Evidence from case series, and small observational studies demonstrate that hypermobility in the form of either JHS or generalised joint hypermobility (GJH), is associated with wide-ranging GI disorders, with very little consistency between the studies.

In case series a high prevalence of IBS, gastritis, gastro-oesophageal reflux disease (GORD), diverticular disease and celiac disease have been reported in patients with JHS (Castori, Camerota et al. 2010; Danese, Castori et al. 2011; Castori, Sperduti et al. 2012). In case control studies of patients with lower urinary tract symptoms, those with JHS were more likely to report a previous diagnosis of IBS (Manning, Korda et al. 2003). In an observational study of patients attending a neurogastroenterology clinic, those with JHS had a high incidence of GI dysmotility (Zarate, Farmer et al. 2009).

Other studies have used the presence of GJH as a surrogate for JHS. Case control studies that used the Beighton score to define GJH found an association with slow transit constipation (Reilly, Chase et al. 2008), and Crohn's Disease, but not Ulcerative Colitis (Vounotrypidis, Efremidou et al. 2009). Case control studies that used the screening questionnaire to define GJH demonstrated an association with unexplained GI disorders (Zarate, Farmer et al. 2009) and with rectal evacuatory dysfunction (Mohammed, Lunniss et al. 2010).

Hence it is clear that the available literature does not provide consistent evidence for an association between JHS and any type or group of GI disorders. Furthermore, the above studies all have several important limitations and should be interpreted with caution. These limitations include selection bias (Manning, Korda et al. 2003; Zarate, Farmer et al. 2009; Castori, Camerota et al. 2010), small size (Castori, Camerota et al. 2010), unblinded studies (Vounotrypidis, Efremidou et al. 2009), lack of control groups for comparison (Castori, Camerota et al. 2010), differing definitions of hypermobility with lack of distinction between JHS and GJH (Vounotrypidis, Efremidou et al. 2009; Zarate,

Farmer et al. 2009; Mohammed, Lunniss et al. 2010) and finally, differing methods of assessing for hypermobility, including the use of a screening questionnaire (Zarate, Farmer et al. 2009; Mohammed, Lunniss et al. 2010), measurement of the Beighton score, (Vounotrypidis, Efremidou et al. 2009) , or the Brighton criteria and/or the Villefranche criteria (Castori, Camerota et al. 2010).

In our study of GI symptoms in JHS (Chapter 2) we provided preliminary evidence for an association between JHS and FGID, and demonstrated that 91% of JHS patients referred from hypermobility clinics to GI clinics had FGID. We also demonstrated that autonomic and somatic factors were involved in the association of JHS with GI symptoms. However, even this study was biased, as JHS patients were highly selected from rheumatology clinics and both patients and physicians were aware of JHS status, potentially influencing the diagnostic label they were eventually given. Hence there was a need to perform a large unbiased study to determine if there was a true association between JHS and FGID.

4.2 Aims

The aim of the study was to determine if there was an association between JHS and GI disorders in a secondary care setting. The primary aims were 1) to determine if there is an increased prevalence of JHS in patients with FGID, compared to both patients with organic GI disorders (positive controls) and to patients without GI disorders (negative controls); 2) to determine if there is an increased prevalence of JHS in any organic GI disorders; (3) to determine if there is an association between JHS and particular ROME III categories of

FGID. The secondary aims were (1) to determine whether autonomic and somatic hypersensitivity factors are involved in the association between JHS and GI disorders, just as they are with GI symptoms in patients with established JHS; (2) to determine whether the presence of JHS in FGID was associated with increased comorbidity, and decreased quality of life and was therefore clinically relevant.

4.3 Hypothesis

We anticipated an increased prevalence of JHS in patients with FGID compared to patients with organic GI disorders, and to patients without GI disorders. In view of the specific GI symptoms found to be associated with JHS in Chapter 2, we hypothesized that the association with FGID would specifically be with functional dyspepsia and IBS-M. We expected patients with FGID and JHS to have more autonomic and somatic symptoms, more psychopathology and opiate use compared to FGID patients without JHS, and therefore expected them to have increased comorbidity and worse quality of life. In line with previous patient studies (Chapter 2) demonstrating that autonomic and somatic hypersensitivity factors were involved in the association between JHS and GI symptoms, we also expected those factors to be involved in the association of JHS with FGID.

4.4 Materials and Methods

4.4.1 Study design

A nested case control study in secondary care gastroenterology clinics at Barts and the London NHS Trust and Mile End Hospital was undertaken. Consecutive

'new' patients attending general gastroenterology clinics for their first visit between April 2010 and April 2012 completed a set of validated questionnaires, and were assessed for JHS and fibromyalgia (see below) before their initial clinical consult with the attending gastroenterologist who was blinded to their hypermobility status. Throughout their gastroenterology consultations, patients underwent routine investigations as deemed appropriate by their gastroenterologist and were eventually given a diagnosis, which was either functional or organic. A negative control group consisting of patients who were referred by their GP's to secondary care for non-gastroenterology problems underwent the same protocol, except that they were not seen by a gastroenterologist. The prevalence of JHS and other associated factors was compared in patients with functional GI disorders, organic GI disorders and in non-GI controls.

4.4.2 Subjects

4.4.2.1 Recruitment

GI patients

New referrals to the GI clinic were identified by searching the hospital computerized booking system. These were all sent a study pack consisting of an invitation letter, an information sheet, a consent form and a questionnaire booklet. A few days prior to their appointment, they were contacted by the research team to ensure that they had received the invite, to clarify what the study would involve, and to answer any questions they may have had. Those that were interested in taking part were asked to attend their clinic appointment with sufficient time to be assessed by the research team prior to their clinical

consult, and they were asked to complete the questionnaires prior to their hospital visit.

Non-GI patients

Non-GI controls were recruited from 3 GP practices within the catchment area of Barts and the London and Mile End Hospital. Controls were identified by using the eligibility criteria to run a search on the EMIS-based GP practice registries. Suitable patients were sent an information sheet and an invitation letter. Contact details of the research tem were provided. Upon contact, eligibility criteria were assessed again to ensure that they were suitable for the study and a meeting was arranged.

4.4.2.2 Eligibility criteria

GI group

Patients aged 18-70, who had GI symptoms and were newly referred to secondary care gastroenterology clinics at Barts and the London NHS Trust and Mile End Hospital were eligible to take part. Patients who were illiterate or who could not speak English were excluded as the study relied heavily on questionnaires. Patients who were pregnant, or attending for bowel cancer screening or hepatology problems or those with a known diagnosis of JHS were also excluded.

Non-GI control group

Patients aged between 18-70 who had been referred by their GP to secondary care in the past 5 years for non-GI related problems were eligible to take part. Patients with known GI diagnoses or ongoing GI symptoms, diabetes, inflammatory arthritides (e.g. rheumatoid arthritis, psoriatic arthritis), a

generalized neuropathy or myopathy, severe psychiatric disorders requiring treatment and those who were pregnant were excluded, as those factors are known to be associated with GI symptoms and pathology. Patients who were illiterate or who did not have a sufficient understanding of written English were also excluded.

All subjects were recruited after informed written consent. The study was approved by the East London and City Research Ethics Committee: REC Ref: 09/H0704/72.

4.4.3 Questionnaires

Subjects completed validated questionnaires to systematically assess GI symptoms, somatic symptoms, psychopathology, autonomic symptoms, personality and quality of life. Demographic information and medication histories were also collected via standardized case report forms.

GI symptom assessment:

The Bowel Disease Questionnaire (BDQ) (Talley, Phillips et al. 1990) was used to elicit GI symptoms as described in Chapter 2. It consists of the questions used for the ROME III classification of FGID and therefore additionally enables the categorisation of FGID patients into a particular ROME III category.

Autonomic symptom assessment:

The COMPASS questionnaire was used to determine the presence and type of autonomic symptoms, as described in Chapter 2 (Suarez, Opfer-Gehrking et al. 1999). Scores are provided for various autonomic domains; for this study, scores relating to constipation, gastrointestinal, diarrhoea, urinary, vasomotor

and syncope domains were used. Scores range from 0 to 100, with higher scores representing more severe symptoms.

Psychological assessment:

Raw scores for anxiety and depression were obtained using the validated SCL-90 questionnaire as described in Chapter 2 (Derogatis, Rickels et al. 1976).

Somatic symptoms:

The validated PHQ15 assesses for the range of somatic symptoms and the severity of somatosensory amplification and was used as described in Chapter 2 (Kroenke, Spitzer et al. 2002). In addition to the total PHQ15 score (0-30), and adjusted score which was calculated without the GI symptom scores (PHQ15 adj, range: 0-24) was used.

Quality of life assessment:

Health-related QOL was evaluated using the SF-36, as described in Chapter 2 (McHorney, Ware et al. 1993).

4.4.4 Examination and structured interview

Structured interviews and examinations were performed by myself. All assessments were conducted blind to the results of questionnaires. Examination was used to assess for JHS and fibromyalgia as described in Chapter 2. Fibromyalgia was considered to be present if the 1990 or 2010 American College of Rheumatology diagnostic criteria for fibromyalgia were satisfied (Wolfe, Smythe et al. 1990; Wolfe 2010).

4.4.5 GI diagnosis

As part of their routine gastroenterology workup, GI patients were assessed by a gastroenterologist who was not part of the study. After clinical assessment and relevant investigations, organised by the attending gastroenterologist, they were eventually given a diagnosis for their GI symptoms. This was obtained from the patients' notes after recruitment of all patients was complete. In certain instances, no diagnosis was specified, but organic conditions had been excluded and the patient was discharged back to the general practitioner. In such cases, the diagnosis was considered to be functional. Gastro-oesophageal reflux in the absence of any other diagnosis was considered a separate category and not included as either organic or functional. Further categorisation of FGID was possible using the ROME III classification and the questions from the BDQ.

4.4.6 Blinding

Patients were not informed of their hypermobility status until after the questionnaires had been collected, thus ensuring that they were blinded to their JHS status when they were completing the questionnaires. Questionnaires were collected and placed in a sealed envelope to ensure blinding of the researchers to questionnaire responses when the assessment of JHS and FM was being performed. Physicians consulting the patients were not involved in the study and would not have been aware of the patients' hypermobility status, so the GI diagnosis reached would have been independent of the presence or absence of JHS.

4.4.7 Sample size and statistical calculations:

The study was powered to detect a 10% difference in the prevalence of JHS between the groups. According to our hypothesis, JHS is associated with FGID and not organic GI disease. Hence the prevalence of JHS in the organic GI disease group should be the same as that in the general population - 15% (Garcia Campayo, Asso et al. 2010). Assuming a difference in prevalence of 10% (i.e. 25% JHS in patients with FGID), one would need a sample size of 270 to achieve a power of 80% at a significance level of 0.05. In general, 40% of patients attending a general gastroenterology end up with a functional GI diagnosis, therefore we would need to assess 675 new patients to ensure that 270 patients end up in the FGID group. 270 non-GI controls would also be needed - Figure 4.1.

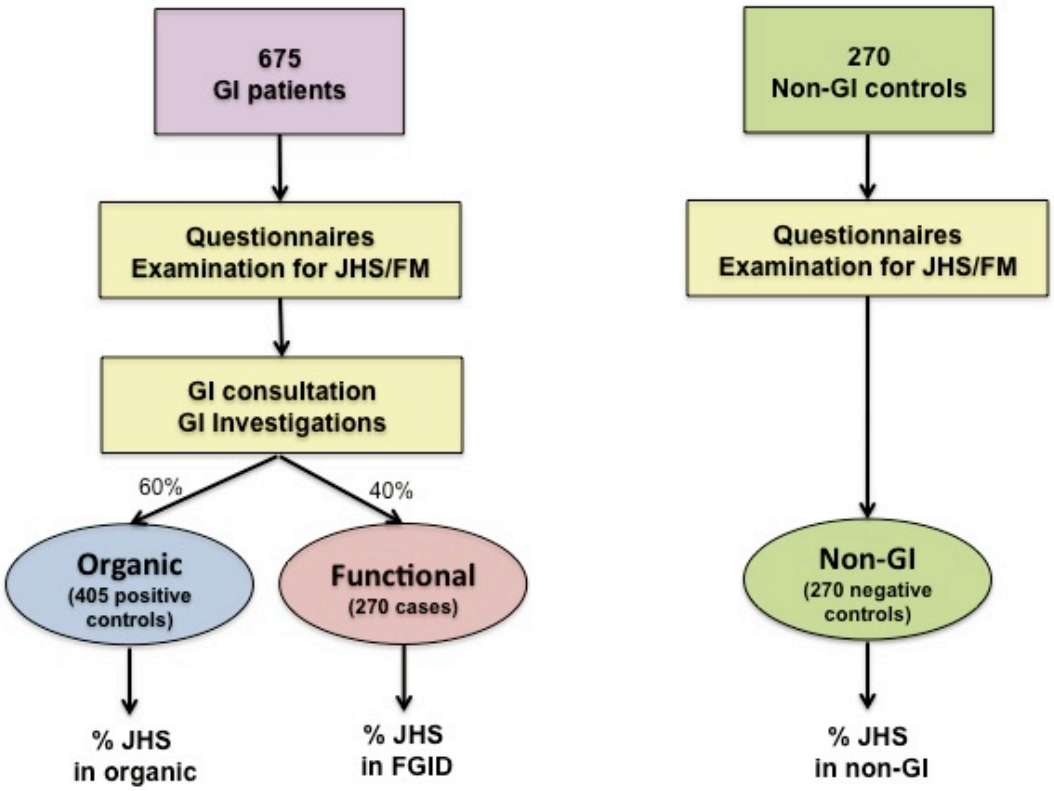


Figure 4.1: Flowchart of study design in Chapter 4

4.4.8 Data analysis and Statistics

Data were described in terms of means and standard errors (normal ordinal data), medians and IQR (non-normal ordinal data) and proportions and confidence intervals (categorical data).

Prevalence of JHS in GI disorders

The GI and Non-GI groups were first compared in terms of age (t-test), gender (chi-squared) and ethnicity (chi-squared) to ensure they were comparable. The prevalence of JHS was measured in patients with functional disorders, other GI disorders and in non-GI controls. Comparisons of the prevalence of JHS were made with the non-GI group (negative controls), and with the organic group (positive control), and were adjusted for age and gender. In line with external statistical advice this was performed as a two-stage analysis to resemble derivation and validation cohorts, with the first cohort analysed after half the patients had been recruited. As the data were similar in the two cohorts a pooled analysis is presented in this thesis to increase the statistical power and significance of the association.

To determine the prevalence of JHS across the range of primary diagnoses the patients were given, the prevalence of JHS was measured in the individual organic disorders, reflux disorders and in FGID and were compared to the prevalence of JHS in the non-GI control group, using Pearson's chi-squared test.

Prevalence of JHS in ROME III classes and subcategories

Patients with FGID and who had a complete set of questionnaires could be further subdivided into a ROME III class (e.g. functional oesophageal disorders) and subcategory (e.g. functional dysphagia). The prevalence of JHS was first measured in each ROME III class. Due to the fact that patients could fulfill criteria for more than one class, a stepwise logistic regression analysis was performed, which assessed for an association between JHS and each of the classes, independent of all the other classes.

The classes were then further subdivided into subcategories, to enable a comparison of the prevalence of JHS within individual ROME III categories. In many cases, this did result in small numbers of patients within the groups, and so this comparison was largely observational. However, in addition, a stepwise logistic regression analysis was performed as with the ROME III classes, to explore whether any subcategories did show a significant independent association with JHS.

Influence of extra-intestinal factors on the association between JHS and GI disorders

The next part of the analysis aimed to determine the effect of potential confounders on the association between JHS and GI disorders. We were particularly interested to find out if autonomic, somatosensory and fibromyalgia factors, which were involved in the association between JHS and GI symptoms in Chapter 2, were also involved in the association between JHS and GI disorders. The first stage involved the comparison of all these factors between the JHS and non-JHS patients to determine which factors were associated with

this group of JHS patients. Those factors that were associated with JHS and known to be associated with GI disorders were considered possible confounding factors. They were added to a multivariate logistic regression model which contained the GI diagnosis as the dependent variable, JHS as the independent variable and the other confounding factors, including age and gender, as the covariates. This produced an adjusted odds ratio which was a measure of the strength of the association between JHS and each GI diagnosis, after adjusting for all the confounding factors. A significant adjusted ratio ($p<0.05$) suggested that the association between JHS and the relevant GI diagnosis was independent of all the confounding factors. A non-significant adjusted odds ratio ($p>0.05$) suggested that the association between JHS and the GI disorder was dependent on one or more of the covariates. To determine which of the covariates (confounding factors) was important, each factor was added individually to the multiple logistic regression model, and the effect of the addition on the adjusted odds ratio for the GI-JHS association was observed. Factors which reduced the odds ratios considerably were interpreted as being involved in the association between JHS and the GI disorder.

Comorbidity and quality of life in FGID patients with and without JHS

The final analysis involved the comparison of FGID patients with and without JHS, with respect to GI symptoms, non-GI symptoms and quality of life, to determine if the presence of JHS was clinically relevant. Comparisons were performed using the t-test (normal ordinal data), Mann Whitney U-test (non-normal ordinal data), Pearson's chi squared test (categorical data), or Fisher's exact test (categorical data, and small proportions (<5%)). For all comparisons, a p value of less than 0.05 was considered significant.

4.5 Results

4.5.1 Subjects

GI patients - Figure 4.2

As described in Chapter 2, 2445 new patients scheduled to attend GI clinics were invited to take part in the study and 778 of these consented. Of these, 15 were excluded because they were hepatology patients or were undergoing bowel screening and 21 did not undergo a complete physical examination. 54 had an established diagnosis of JHS (JHS-Rh) and were included in the study in Chapter 2, but excluded from this study analysis. This left 688 patients who were finally included in the study. Of these, 341 (49.6%) had a functional diagnosis, 254 (36.9%) had an organic diagnosis and 53 (7.7%) had a reflux diagnosis. As the reflux group was large, and did not clearly belong to either the organic or functional group, this remained as a separate category. The remaining 40 patients (5.8%) were not assigned a diagnosis, either because they did not attend for investigations or for follow-up. These patients were excluded from the analysis, leaving 648 patients in the final analysis.

Non-GI controls - Figure 4.2

The computer search identified 3160 patients who met the inclusion criteria for the study and these were all invited to take part. 107 (3%) of these made contact with the research team and eligibility was re-assessed. A total of 92 were eligible and they were included in the study.

Hence a total of 740 patients in 4 groups were included in the analysis: 341 patients with FGID, 254 patients with organic GI disorders, 53 patients with reflux disease and 92 non-GI controls. Out of the 740 patients, only 604 had

complete questionnaires, and so comparisons which required the use of questionnaire data (in the final stages of analysis) were only performed in this subgroup.

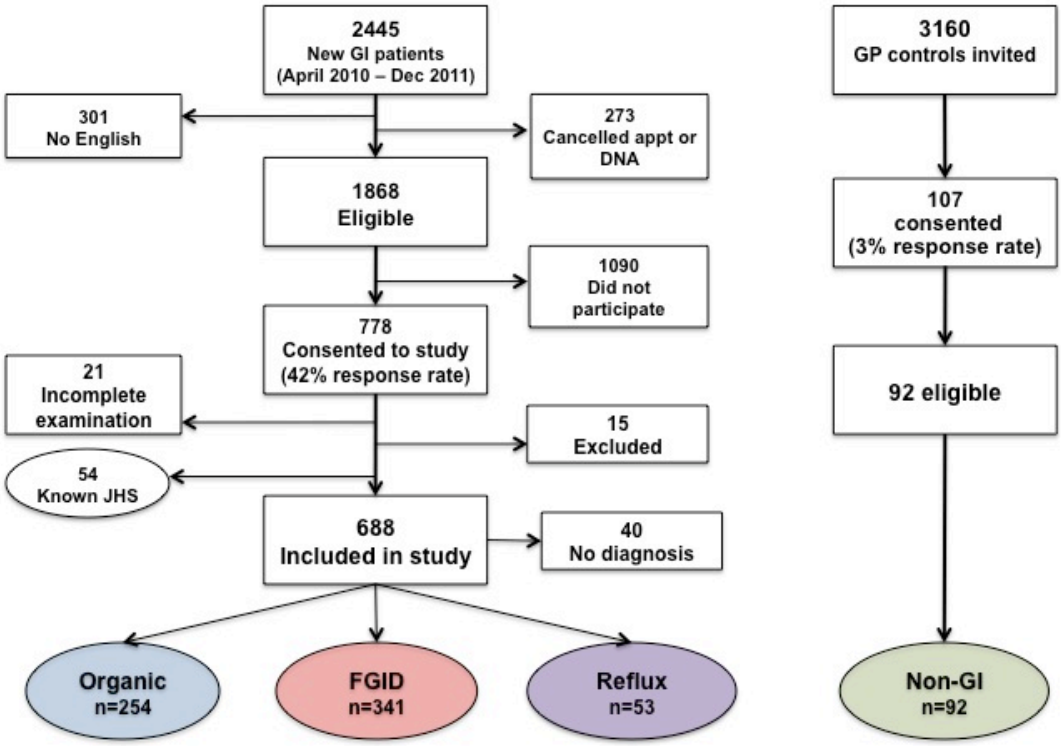


Figure 4.2: Flowchart of subjects included in the study in Chapter 4

4.5.2 Demographics

Gender distribution

There were 65.1% females in the FGID group, 54.7% in the organic group, 39.6% in the reflux group and 67.4% in the non-GI group. There was a significant difference in the proportion of females across the groups, ($p<0.001$). The proportion of females in the reflux group was significantly lower than in the FGID group ($p<0.001$), organic group ($p=0.04$), and in the non-GI group ($p=0.001$) (Fig 4.2).

Age distribution

The mean age of the patients was highest in the reflux group (46.3 ± 1.9), followed by the organic group (43.5 ± 0.93), non-GI group (42.9 ± 1.51) and FGID group (40.1 ± 0.71). There was a significant difference in the mean ages across the groups (p=0.003). The reflux patients were significantly older than both the FGID patients (p=0.002) and the organic patients (p=0.04) - Figure 4.3.

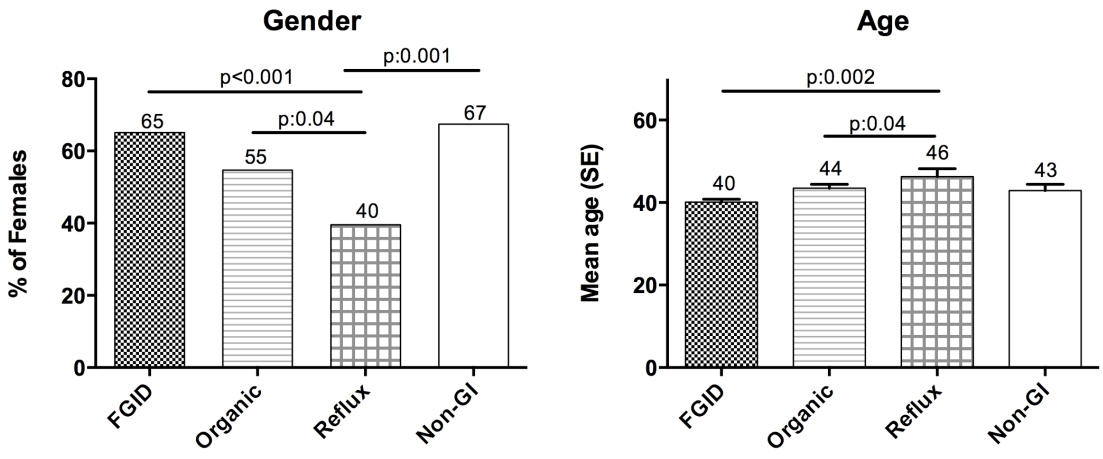


Figure 4.3: Gender and age distribution in each of the 4 groups.
Patients were older and less likely to be female in the reflux group compared to the other GI and non-GI groups.

Ethnicity - Figure 4.4

The ethnic distribution of the patients in each of the 4 groups was comparable: most patients were White, followed by Asians and Afro-Caribbeans (Figure 4.4). There were no patients of Chinese or Mixed ethnicity in the Reflux group. There was no difference in the proportion of White patients in each group (p=0.7).

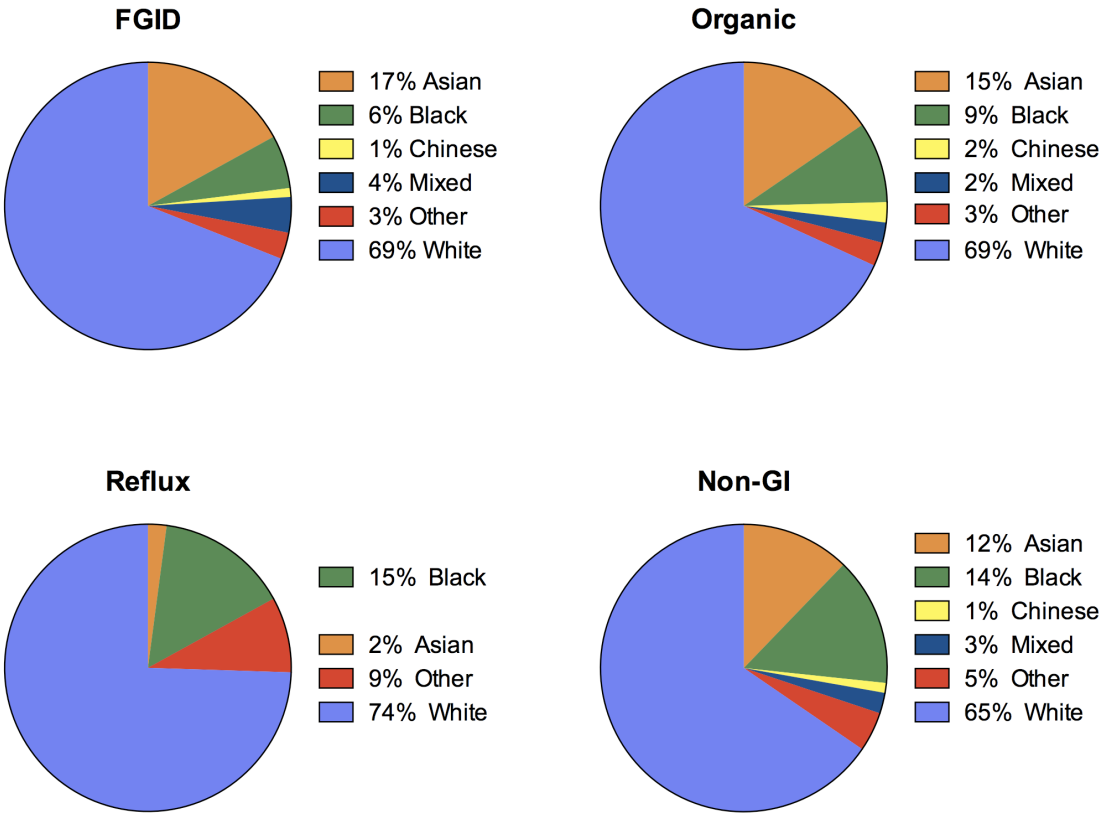


Figure 4.4: Ethnic distribution of patients in the 4 groups.

4.5.3 Prevalence of JHS in GI and Non-GI groups

JHS was present in 33.5% of GI patients: 38.4% in FGID, 25.6% in organic GI disorders and 39.6% in reflux. The prevalence of JHS in non-GI patients was 26.1% - Figure 4.5.

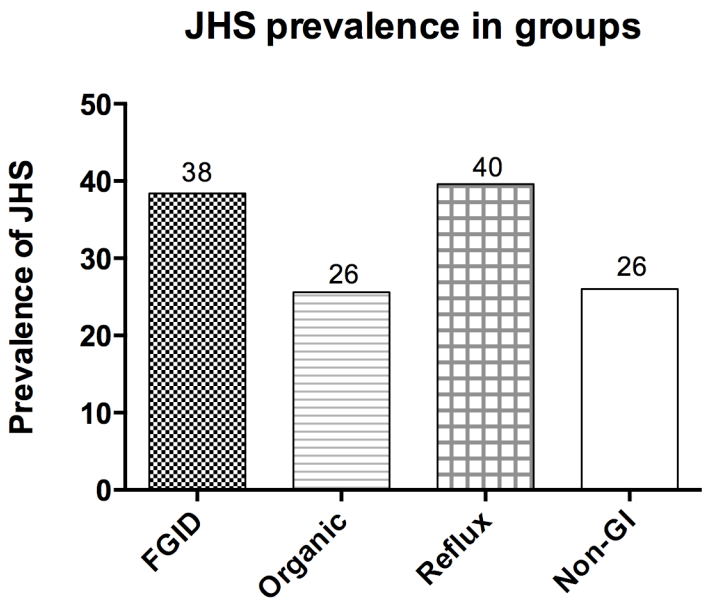


Figure 4.5: Prevalence of JHS in FGID, organic disorders, reflux disorders and non-GI patients.

The prevalence of JHS was highest in reflux and FGID. The prevalence of JHS in organic GI disorders was the same as the prevalence in the non-GI patients.

Comparisons between the groups were adjusted for age and gender using logistic regression analysis. When compared to non-GI patients, there was a significant association of JHS with both FGID (ORadj: 1.71, CI: 1.02-2.88, p=0.04), and with reflux (ORadj: 2.24, CI: 1.07-4.68, p=0.03), but not between JHS and organic GI disorders (ORadj: 1.03, CI: 0.59-1.79, p=0.92). The FGID and reflux groups were then compared to the organic group, to determine if there were significant differences within the GI groups. Compared to the organic group, there was a significantly higher prevalence of JHS in FGID (ORadj: 1.67, CI: 1.16-2.39, p=0.006) and in reflux disorders (ORadj: 2.18, CI: 1.16-4.08, p=0.015).

4.5.4 Prevalence of JHS by primary diagnoses

The primary GI diagnoses were grouped into various categories as shown in Figure 4.6. 'Other colitis' included microscopic, ischaemic and infectious colitis. 'Dysmotility' included achalasia and other oesophageal dysmotilities, gastroparesis and small bowel dysmotility. 'Panc-bil' diagnoses included bile salt malabsorption, gallstones and cholecystitis and pancreatitis. 'Perianal problems' included haemorrhoids, abscesses, non-IBD fistulae and anal fissures.

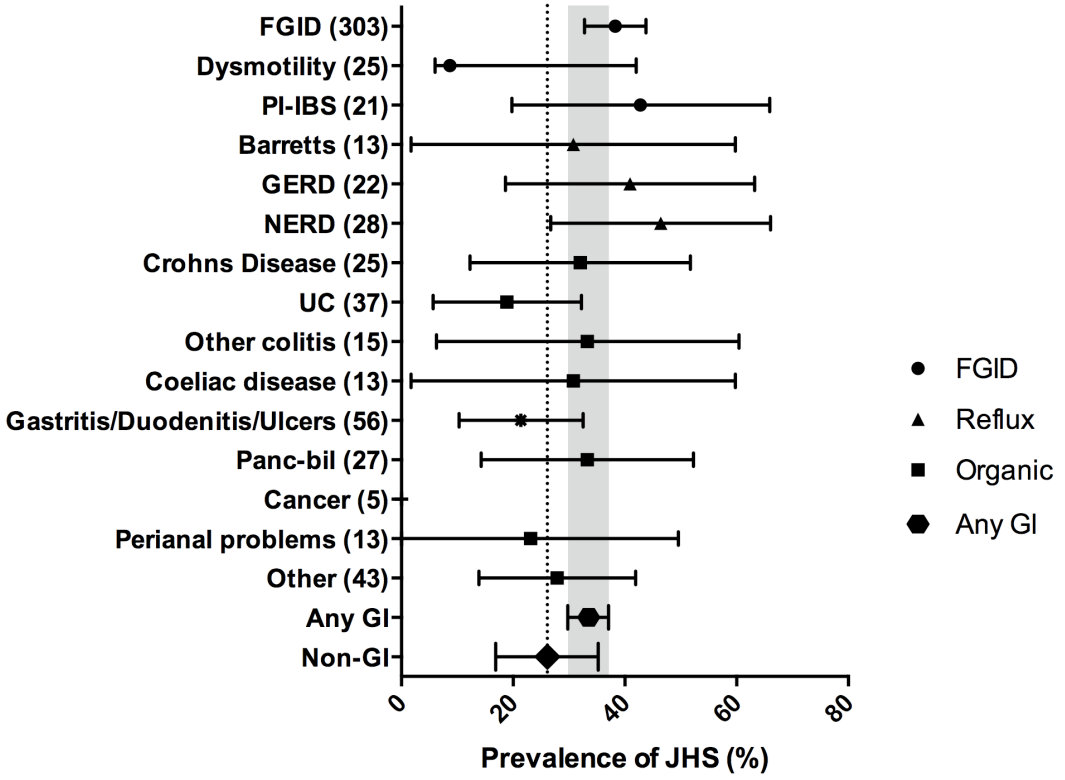


Figure 4.6: Prevalence of JHS by primary diagnosis.
Numbers in brackets represent the number of patients in that group. The dotted line represents the prevalence in non-GI controls. The shaded grey column represents the mean prevalence in GI patients. PI-IBS: Post infectious IBS, GERD: Erosive reflux disease, NERD: non-erosive reflux disease, UC: ulcerative colitis

The prevalence of JHS was highest in NERD (46%), post-infectious IBS (43%), erosive reflux disease (GERD) (41%) and FGID (38%) and lowest in dysmotility (8.7%), ulcerative colitis (18.9%), patients with gastritis, duodenitits or peptic ulcer disease (21.4%) and patients with perianal problems (23.1%) - Figure 4.6. Within the organic group, the prevalence of JHS in disorders such as Crohn's disease (32%), Coeliac disease (30%) and pancreatico-biliary problems (33%) was higher than that in other organic conditions such as ulcerative colitis (19%) organic gastroduodenal problems e.g. gastritis and peptic ulcers (21%), and higher than in non-GI controls (26%) but these comparisons were not significant. Compared to non-GI patients the only disorders where the prevalence of JHS was significantly increased was in patients with FGID (p=0.03), and in patients with NERD (p=0.04).

4.5.5 Prevalence of JHS in ROME III classes of FGID

The FGID group in Figure 4.6 was very large, and consisted of a variety of functional disorders. Although the categorisation of FGID was not consistently performed by the physician, it was possible, using the BDQ, to do this for the patients with completed questionnaires. This enabled the comparison of JHS prevalence in the different ROME III classes and subcategories.

Out of the 258 FGID patients with fully completed questionnaires, 47 (18%) had a functional oesophageal disorder, 113 (44%) had a functional gastro-duodenal disorder, 198 (77%) had a functional bowel disorder, 3 (1%) had functional abdominal pain syndrome, 18 (7%) had a functional gallbladder or sphincter of oddi disorder, and 57 (22%) had a functional anorectal disorder. 34% of

patients fulfilled criteria for more than ROME III category, with functional gastro-duodenal and functional bowel disorders frequently overlapping.

The prevalence of JHS in the different ROME III classes is shown in Figure 4.7. Functional abdominal pain was not included as there were only 3 patients in that group. The prevalence of JHS was highest in functional gallbladder and SOD disorders (44%) followed by functional gastroduodenal disorders (43%) and functional anorectal disorders (42%).

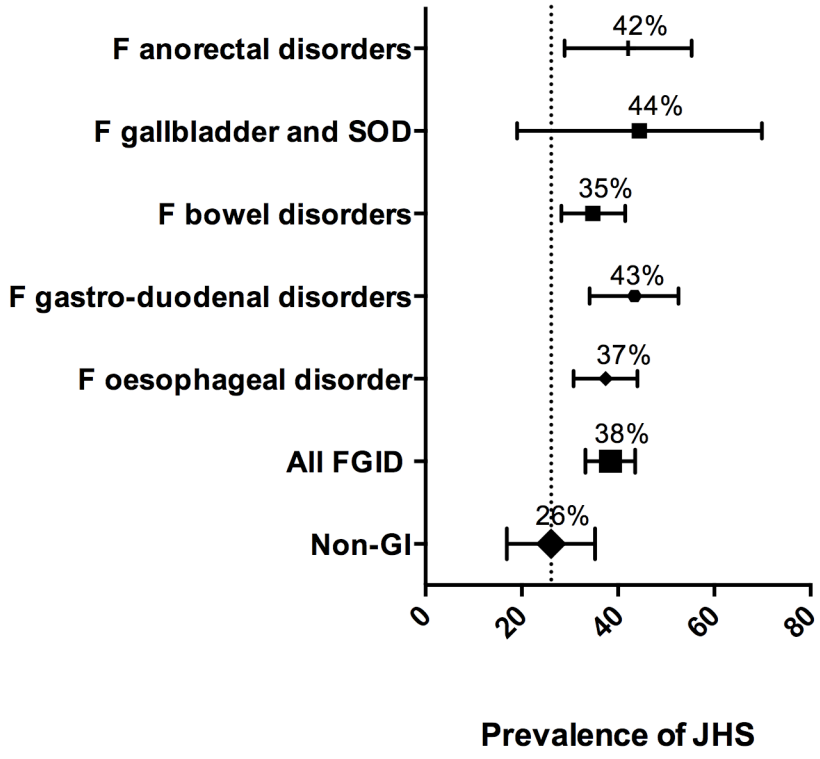


Figure 4.7: Prevalence of JHS in ROME III functional GI categories. Proportions and 95% confidence intervals of JHS in each category are displayed. The dotted line represents the prevalence of JHS in non-GI controls.

In view of the overlap between the different classes, a step-wise logistic regression was performed to determine if any of the ROME III classes were independently associated with JHS. Only functional gastroduodenal disorders were independently associated with JHS (OR: 1.83, CI: 1.15-2.91, p=0.01).

4.5.6 Prevalence of JHS in ROME III subcategories

The prevalence of JHS was further compared in the individual ROME III subcategories - Figure 4.8. Categories that included 5 patients or fewer – functional defecation disorder (4), aerophagia (5), functional heartburn (2), unspecified excessive belching (3), cyclical vomiting (0), rumination (0), functional bloating (0) and functional abdominal pain (3) - were not included as there were too few patients to make meaningful comparisons.

The prevalence of JHS in chronic proctalgia (50%), PI-IBS (50%), functional vomiting (46.2%), idiopathic nausea (50%), postprandial distress (51%) and functional chest pain (47.1%) was higher than the mean prevalence of JHS in FGID but this was not significant. Using stepwise logistic regression analyses only postprandial distress showed a significant and independent association with JHS (OR: 2.24, CI: 1.18-2.24, p=0.01).

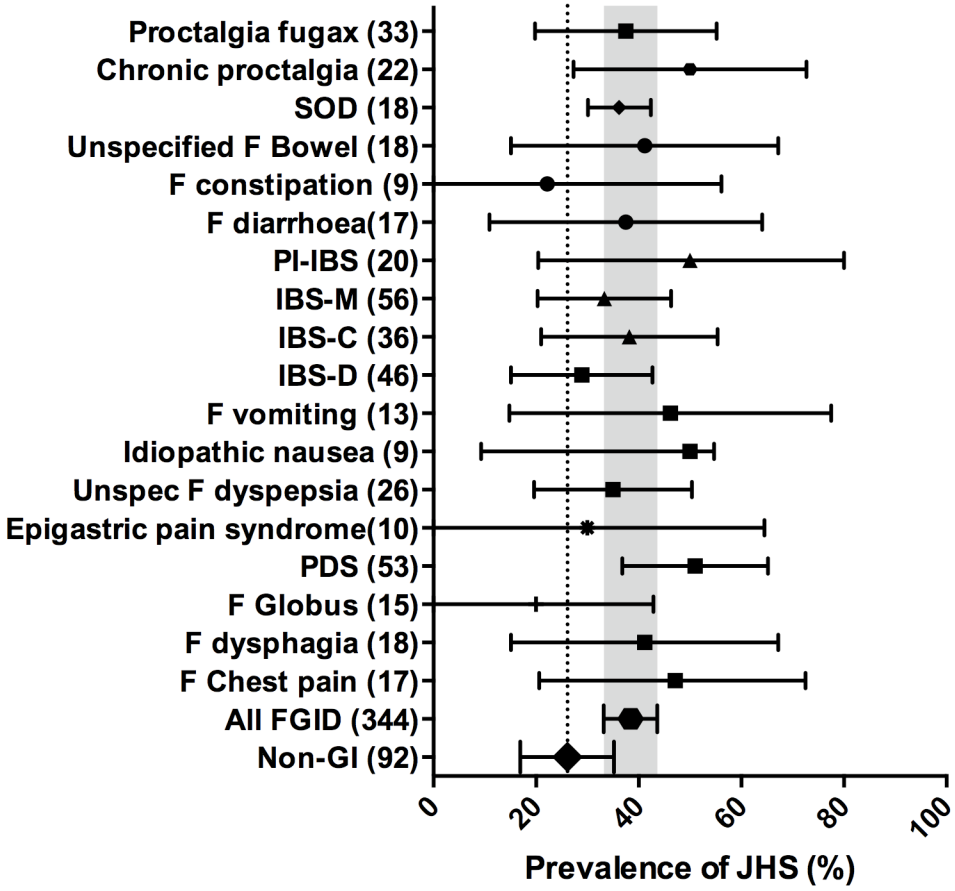


Figure 4.8:Prevalence of JHS in ROME III subcategories.
Numbers in brackets represent the number of patients in each of the subcategories. The dotted line represents the prevalence of JHS in Non-GI controls. The shaded grey column represents the 95% confidence intervals for prevalence of JHS in FGID. SOD: Sphincter of Oddi. F: Functional.

4.5.7 Identification of factors involved in the association between JHS and GI disorders

We demonstrated earlier that there exists an association between JHS and FGID, and between JHS and reflux disorders, when compared to both non-GI patients and to patients with organic disorders. To explore what factors may have been contributing to this association, and to determine specifically if

autonomic and somatic factors were involved, a multiple logistic regression analysis was carried out.

4.5.7.1 Identification of factors associated with JHS (i.e. potential confounding factors) – Table 4.1 and Table 4.2

JHS patients were more likely to be female (66% vs 57%, p=0.02) and they were significantly younger (39.3 ± 0.88 vs 43.4 ± 0.63, p<0.001). JHS patients had more chronic widespread pain, insomnia, memory problems, and positive tender points, compared to patients without JHS. In line with this, JHS patients were more likely to have fibromyalgia (p=0.001) - Table 4.1. There was no difference in the use of opiates (6.2 vs 6.6, p=0.8), antispasmodics (6.5 vs 6.1, p=0.5), PPIs (21.9 vs 27.7, p=0.09) or prokinetics (8.8 vs 7.8, p=0.4) in subjects with and without JHS.

Autonomic scores were very skewed towards 0 on all domains which made statistical comparisons difficult using the Mann-Whitney U test. In order to enable more meaningful comparisons the autonomic scores were converted into categories using a cut-off score of 25. The proportion of patients with a score > 25 was then compared for each domain using the Pearson's Chi squared test. JHS patients were more likely to have significantly higher autonomic symptom scores for the urinary and gastrointestinal domain (p=0.03, p=0.02 respectively). They were also more likely to have higher orthostatic symptom scores but this was not significant (51% vs 41%, p=0.06) - Table 4.2.

Total PHQ15 scores were significantly higher in JHS both with and without the inclusion of the GI questions ($p<0.001$). Patients with JHS also had higher anxiety ($p<0.001$) and depression ($p=0.03$) scores.

Table 4.1: Comparison of fibromyalgia and chronic pain features in subjects with and without JHS

	No JHS (n=499)	**JHS (n=241)**	**p**
Chronic widespread pain (CI)	9.6 (7.2-12.6)	21.2 (16.2-26.9)	<0.001
Positive tender points (CI)	35.6 (31.5-40.0)	56.0 (49.5-62.4)	<0.001
Memory problems (CI)	8.0 (5.8-10.8)	15.3 (11.0-20.5)	0.009
Insomnia (CI)	15.4 (12.4-18.9)	24.5 (19.2-30.4)	0.01
Fibromyalgia (CI)	4.4 (2.8-6.6)	11.6 (7.9-16.4)	<0.001
Opiate use (CI)	6.6 (4.6-9.2)	6.2 (3.5-10.1)	0.8

Table 4.2: Comparison of autonomic scores, somatic sensitivity scores and psychopathology in subjects with and without JHS

Questionnaire data	No JHS (n=411)	JHS (n=193)	
SOMATIC SENSITIVITY SCORES			
Median PHQ15 (IQR)	8 (4-13)	10 (6-15)	<0.001
Median PHQ15 adj (IQR)	5 (3-8)	6 (4-9)	<0.001
PSYCHOPATHOLOGY			
Anxiety score	0.305 (0.005-0.705)	0.405 (0.105-1.06)	<0.001
Depression score	0.58 (0.24-1.2)	0.76 (0.31-1.5)	0.03
AUTONOMICS: proportion with scores>25			
Urinary	16.6 (13.1-20.5)	23.8 (18.0-30.5)	0.03
Orthostatic	43.1 (38.2-48.0)	51.3 (44.0-58.5)	0.06
Syncope	1.5 (0.5-3.2)	1.6 (0.3-4.4)	0.93
Vasomotor	17.5 (14.0-21.5)	22.8 (17.1-29.4)	0.12
Diarrhoea	37.2 (32.5-42.1)	42.5 (35.4-49.8)	0.22
Constipation	31.6 (27.2-36.3)	35.2 (28.6-42.4)	0.38
Gastrointestinal	30.7 (26.2-35.4)	39.9 (32.9-47.2)	0.02

4.5.8 Influence of extra-intestinal factors on the association between JHS and GI disorders

Fibromyalgia features, anxiety, depression, autonomic symptoms, somatic sensitivity, younger age and female gender are all factors known to be associated with FGID and they were also associated with the JHS patients in this study (Table 4.1 and Table 4.2). Hence these were all considered as potential confounders. There was no association between medication use and JHS (Table 4.1), and thus it was not considered a confounding factor.

To determine if the high prevalence of JHS in FGID and in reflux, but not in organic disease, was due to the co-existence of these extra-intestinal factors, all these possible confounding factors were entered into a logistic regression model. This was done for both FGID and for reflux, and compared to patients with organic GI disease. For FGID, the association with JHS lost its significance after adjusting for all those factors, (ORadj: 1.43, CI: 0.94-2.17) suggesting that some or all of those factors were responsible for the association seen between FGID and JHS. For reflux, the association remained significant even with the addition of all the other factors, (ORadj: 2.58, CI: 1.27-5.24), suggesting that psychopathology, fibromyalgia, somatic and autonomic symptoms were not confounders in the case of reflux.

4.5.9 Influence of autonomic, psychological, fibromyalgia and somatosensory factors on the association between JHS and FGID

The individual effect of psychological, fibromyalgia, autonomic and somatosensory factors on the association between JHS and FGID was determined using a multiple logistic regression model as described in the methods section. A similar analysis was also performed to determine the effect of those factors on the specific association between JHS and postprandial distress syndrome. The effect of the addition of each of those factors on the strength of the association (adjusted odds ratio) between JHS and either FGID or postprandial distress syndrome is shown in Table 4.3.

In the case of FGID, none of the factors had a very large effect on the adjusted odds ratio. The addition of autonomic symptoms seemed to have the largest effect on reducing the adjusted odds ratio.

The effect of the individual factors was seen more clearly in the case of PDS. Apart from somatosensory scores, the addition of each of the other factors, particularly the autonomic symptoms, reduced the odds ratio between JHS and PDS. Of all the extra-intestinal factors, only orthostatic symptom scores were independently associated with PDS - the odds of having PDS increased by 1.03 (CI: 1.01-1.04) for every 1-point increase in orthostatic scores.

Table 4.3 : Effect of psychopathology, fibromyalgia, somatic sensitivity, autonomic factors and the combination of all 4 on the association between JHS and FGID and between JHS and PDS

	FGID	PDS
ORadj (age, gender)	1.48 (0.99-2.22)	2.31 (1.27-4.22)
ORadj (age, gender, FM)	1.45 (0.96-2.18)	2.13 (1.15-3.93)
ORadj (age, gender, auton)	1.40 (0.92-2.11)	1.88 (0.97-3.65)
ORadj (age, gender, PHQ15adj)	1.51 (1.0-2.27)	2.39 (1.30-4.38)
ORadj (age, gender, psych)	1.44 (0.96-2.19)	2.06 (1.10-3.83)
ORadj (all)	1.43 (0.94-2.17)	1.90 (0.98-3.74)

4.5.10 Comparison of intestinal and extra-intestinal factors in FGID patients with and without JHS

To find out if the presence of JHS in patients with FGID was clinically relevant, comorbidity and quality of life was compared in the JHS and non-JHS patients who were diagnosed with FGID and shown in Table 4.4.

There were no differences in age or gender in the 2 groups. Patients with JHS were more likely to have chronic widespread pain (23.2% vs 11.7%, p=0.01), positive tender points (60% vs 41.1%, p=0.003) and more likely to fulfil criteria for fibromyalgia (12.6% vs 4.9%, p=0.02). They were also more likely to have a higher number of somatic symptoms as measured by the PHQ15 (13 vs 10,p=0.001), but not if the GI questions were excluded i.e. PHQ15adj scores (6 vs 6, p=0.6). Anxiety scores were higher in JHS (0.5 vs 0.36, p=0.02), but depression scores did not differ. JHS patients were more likely to have high urinary autonomic scores (30.5% vs 19.6%, p=0.047). There was no difference in the proportion of patients with high scores on any of the other autonomic domains.

Compared to FGID patients without JHS, those with JHS had worse quality of life scores for the SF36 pain domain (45 vs 63.5, p=0.007), and role-limiting emotional domain (66 vs 100, p=0.01) - Table 4.5. No differences were observed in any of the other domains.

Table 4.4: Comparison of extra-intestinal features in FGID patients with and without JHS

	NO JHS (n=163)	JHS (n=95)	p
DEMOGRAPHICS			
% Female (CI)	62.6	73.7	0.07
Mean age (SE)	42.0 (1.02)	39.3 (1.4)	0.11
CHRONIC PAIN AND FIBROMYALGIA			
Fibromyalgia (CI)	4.9 (1.6-8.2)	12.6 (5.8-19.4)	0.02
Chronic widespread pain (CI)	11.7 (6.7-16.6)	23.2 (14.5-31.8)	0.01
% positive tender points (CI)	41.1 (33.5-48.7)	60.0 (50.0-70.0)	0.003
SOMATIC SENSITIVITY			
PHQ15 (IQR)	10 (6-14)	13 (9-17)	0.001
PHQ15 – no GI (IQR)	6 (3-9)	6 (3-10)	0.67
PSYCHOPATHOLOGY			
Anxiety (IQR)	0.36 (0.005-0.80)	0.5 (0.205-1.1)	0.02
Depression (IQR)	0.62 (0.24-1.4)	0.85 (0.31-1.5)	0.1
AUTONOMICS: % with score>25			
Urinary (CI)	19.6 (13.5-25.8)	30.5 (21.1-39.9)	0.047
Orthostatic (CI)	48.5 (40.7-56.2)	57.9 (47.8-68.0)	0.14
Syncope (CI)	2.5 (0.0-4.8)	1.1 (0.0-3.1)	0.3
Vasomotor (CI)	20.2 (14.0-26.5)	21.1 (12.7-29.4)	0.9

Table 4.5: **Comparison of quality of life in FGID patients with and without JHS**

SF36 domain	NO JHS (n=163)	JHS (n=95)	p
Physical function (IQR)	85 (50-95)	82.5 (47.5-95)	0.5
Role limiting physical (IQR)	75 (0-100)	50 (0-100)	0.1
Emotional well being (IQR)	68 (52-80)	68 (52-80)	0.9
Role limiting emotional (IQR)	100 (33-100)	66 (0-100)	0.01
Energy fatigue (IQR)	45 (30-60)	45 (27.5-60)	0.6
Pain (IQR)	63.5 (32-80)	45 (22-67)	0.007
Social function (IQR)	62 (37-87)	62 (25-87)	0.4
General health (IQR)	50 (30-65)	45 (25-60)	0.4

4.6 Discussion

4.6.1 Summary of results

In this nested case-control study we aimed to determine if there was an association between JHS and GI disorders i.e. if there existed a high prevalence of JHS in general GI clinics and if there was an association between JHS and particular GI disorders. We demonstrated that 33% of patients attending a general gastroenterology clinic in secondary care fulfil criteria for JHS, and this was especially high in patients with FGID (38%) and patients with reflux (39%).

FGID was significantly associated with JHS, compared to patients with no GI disease, and to patients with organic GI disease. The association between JHS and FGID appeared to be dependent on autonomic factors, and appeared to mostly relate to postprandial distress syndrome, although the prevalence of JHS in PI-IBS and chronic proctalgia were also high. Within the FGID group, patients with and without JHS differed with respect to extra-intestinal symptoms. Those with JHS had more chronic pain, fibromyalgia, positive tender points, somatic symptoms, anxiety and urinary autonomic symptoms.

Unexpectedly, reflux was also significantly associated with JHS compared to non-GI controls and to patients with organic GI disorders. Interestingly, the association between JHS and reflux was independent of all measured factors, and appeared to mostly relate to NERD.

There was no significant association between JHS and organic GI disorders, but there was variability in the prevalence of JHS in different organic disorders.

The prevalence of JHS was high in Crohn's disease, Coeliac disease and pancreatico-biliary disorders, and low in ulcerative colitis and organic gastroduodenal disorders.

Hence JHS appears to be associated with FGID and reflux, but not with organic GI disorders.

4.6.2 Comparison with previous studies

This is the first epidemiology study of JHS in a secondary care gastroenterology setting, and it was surprising to find that a third of all-comers to general gastroenterology clinics had previously undiagnosed JHS. The prevalence of JHS in the non-GI controls (26%) may also appear high but it is in fact comparable to previous studies in a healthy population (Baeza-Velasco, Gely-Nargeot et al. ; Bulbena, Gago et al. 2011). The lack of previous diagnosis of JHS in both GI and non-GI patients is compatible with previous studies which suggest that JHS is a grossly undiagnosed condition (Adib, Davies et al. 2005).

4.6.3 Association between JHS and FGID

38% of patients with FGID attending non-specialist GI clinics satisfied the Brighton criteria for JHS. This is the first time that the prevalence of JHS has been measured in such a GI setting, and so a comparison with other studies is not possible. The only other GI study which measured the prevalence of hypermobility, did so in a specialist neurogastroenterology setting and did not have a control group for comparison (Zarate, Farmer et al. 2009). In that study, GJH (not JHS) was assessed using the 5-point hypermobility questionnaire and it was found that 49% of patients with FGID attending these specialist clinics

had GJH. However, due to the different setting and different methods of assessment, these studies are not directly comparable.

Although previous studies suggest an association between JHS and FGID, (Ross and Grahame; Castori 2012), this is the only study which conclusively demonstrates this on a large scale. Although reports of an association between JHS and IBS have been published, our study did not find such an association. Instead the association was with postprandial distress syndrome (PDS), a subtype of functional dyspepsia. To our knowledge, this has never been previously reported, although one study of JHS patients attending a genetics clinic did report a high prevalence of 'gastritis' in their patients (Castori, Camerota et al. 2010). It is unknown whether those patients actually had endoscopic evidence of gastritis, which is an organic cause of dyspepsia, or whether they had a normal endoscopy and dyspeptic symptoms, in which case they would have fulfilled criteria for functional dyspepsia.

The association between JHS and PDS is not surprising in view of the association between JHS and postprandial symptoms in the literature (Castori, Camerota et al. 2010) and in this thesis (Chapter 2 and 3). The association between JHS and symptoms of postprandial fullness and early satiety were present in both patients with established JHS (Chapter 2), and in healthy students with JHS (Chapter 3). Furthermore, published studies in JHS patients document a high prevalence of nausea, vomiting, dyspepsia and bloating,(Hakim and Grahame 2004; Rombaut, Malfait et al. 2011) all of which are features of functional dyspepsia, and more compatible with the PDS subtype than the epigastric pain syndrome subtype.

Within the FGID group, although it was only PDS which showed a significant association with JHS, it deserves mention that the highest prevalence of JHS was seen in both PI-IBS and chronic proctalgia, each of which will be discussed in turn.

The lack of an independent association between IBS and JHS is surprising, not only because of the presence of small series in the literature which document such an association, but also because published literature and data from our study in JHS patients (Chapter 2) both demonstrate an association between JHS and symptoms of abdominal pain, alternating bowel habit and bloating, all of which are core features of IBS. There are three possible explanations for this. The first is that IBS-C, IBS-D and IBS-M are differentially associated with JHS, and therefore by combining them, any association that would have been seen with the subtypes would be obliterated. This notion is supported by the fact that when the IBS subtypes were separated, the highest prevalence was seen in IBS-C, lowest in IBS-D, and intermediate in IBS-M. However despite the separation of the subtypes, the prevalence of JHS in IBS-C was still not significant. This may be because of the resultant small number of patients in each group and therefore a lack of power to detect a difference, especially as the study was only powered to detect a difference in the large diagnostic groups but not the small subcategories. Thus lack of power is the second possible explanation for why the prevalence of JHS was not significantly increased in IBS. The third explanation is that IBS and functional dyspepsia frequently overlap in up to two thirds of patients (Cremonini and Talley 2004; Ford, Marwaha et al. 2010). Using step-wise logistic regression, we demonstrated that IBS was not independently associated with JHS i.e. there was no

association between JHS and IBS in the absence of PDS. However this does not exclude the fact that patients with JHS and PDS may have coexistent IBS and this is what is reported in the literature. In fact, in this study, 58% of the patients with JHS and PDS also had IBS, and the majority of this was IBS-M.

Interestingly the prevalence of JHS was very high in PI-IBS. This suggests that JHS individuals are more predisposed to developing IBS following an infection compared to individuals without JHS. In the Walkerton study, it was found that the susceptibility to PI-IBS following an outbreak of gastroenteritis is associated with the presence of genes that encode proteins involved in epithelial cell barrier function and the innate immune response to enteric bacteria (Villani, Lemire et al. 2010). However before embarking on speculation that individuals with JHS have abnormal intestinal permeability or host immunity, it should be noted that the association between JHS and PI-IBS in our study was not significant but simply showed a trend in a small number of patients, and would need to be replicated in a larger study before any conclusions can be drawn. Furthermore, meta-analyses and systematic reviews demonstrate that younger age, female gender and associated anxiety and depression are risk factors for development of PI-IBS (Thabane, Kottachchi et al. 2007), and in fact these are all factors which are present in the JHS group. Therefore an alternative explanation for this seeming association between JHS and PI-IBS is simply due to the fact that the JHS individuals had the relevant demographic and psychological risk factors, and that it is not related to intrinsic differences in JHS per se.

In our study, 1 in 2 patients who satisfied the ROME III criteria for chronic proctalgia had JHS; this was not the case for proctalgia fugax where only a third of patients had JHS. This is a novel observation not previously described in the literature. In our study of university students (Chapter 3) twice as many students with JHS complained of proctalgia compared to students without JHS (14% vs 7%), suggesting that there is a basis for the observation in this study. In a recent study to investigate possible mechanisms for chronic proctalgia, it was found that 59% of patients with chronic proctalgia had a high grade internal rectal prolapse and this was associated with obstructive defecation, suggesting that rectal prolapse underlies chronic proctalgia (Hompes, Jones et al. 2011), particularly in patients with obstructed defecation. In our study we had only 3 patients with functional defecation disorders, and so it was impossible to draw any conclusions relating to this. However, rectal prolapse is associated with JHS and in fact, forms part of the diagnostic Brighton criteria (Table 1.5). Furthermore JHS has been shown to be associated with obstructive defecation, particularly in patients with lower urinary tract symptoms (Manning, Korda et al. 2003). Hence JHS patients are more likely to have obstructive defecation and rectal prolapses, both of which are associated with chronic proctalgia, and may therefore explain the high prevalence of JHS in chronic proctalgia. Future studies in a lower GI physiology setting may help shine more light on the matter.

4.6.4 Association between JHS and reflux disorders

39% of patients in general GI clinics with a reflux diagnosis (either Barretts, GERD or NERD, but not functional heartburn) satisfied the Brighton criteria for JHS, and this association was independent of anxiety, chronic pain, somatic

and autonomic factors. Furthermore, of the different reflux disorders, it was NERD which was most strongly associated. Although this was contrary to our expectations, it should not have come as a complete surprise. Firstly, other studies based on small numbers of JHS patients attending genetics clinics have documented a high prevalence of gastro-oesophageal reflux in JHS (Castori, Camerota et al. 2010). Secondly, our study of GI symptoms in JHS (Chapter 2) showed a significantly increased prevalence of regurgitation compared to GI patients without JHS. Thirdly, there exists literature to suggest that there is an overlap between reflux disease, IBS and functional dyspepsia, and furthermore, that IBS and functional dyspepsia symptoms are most common in NERD, compared to GERD and Barretts (Stanghellini, Tosetti et al. 1999; Neumann, Monkemuller et al. 2008). In our analysis using logistic regression we found the association between JHS and reflux to be independent of FGID, and therefore the explanation could not lie in the fact that patients with NERD were the patients with functional dyspepsia. Another explanation is that the same underlying pathophysiological mechanism is responsible for both NERD and functional dyspepsia (Talley 2006) and that this is present in JHS. One possibility is anxiety – this is known to be associated with JHS and is an independent predictor for overlap between NERD and functional dyspepsia in population studies (Lee, Lee et al. 2009). However, in our study, anxiety was not significantly involved in the association between JHS and FGID or reflux. Another common aetiological possibility is altered sensorimotor function which can lead to visceral hypersensitivity, dysmotility, and altered compliance, all of which have been implicated in both NERD (Thoua, Khoo et al. 2008; Kwiatek, Pandolfino et al. 2010; Porter, Kumar et al. 2012) and functional dyspepsia (Oustamanolakis and Tack 2012). This notion is supported by a study which

confirmed that gastroparesis was present in patients with reflux disease and with functional dyspepsia, and in patients with an overlap of both disorders (Gonlachanvit, Maurer et al. 2006). Furthermore, reflux disease was associated with more proximal gastric retention, and this pattern of gastroparesis was associated with symptoms of early satiety, regurgitation, bloating, and nausea, all symptoms that were confirmed to be increased in JHS (Chapter 2). A systematic study of proximal and distal gastroparesis in JHS patients with GI symptoms has never been performed, and will need to be addressed in the future.

4.6.5 Association between JHS and organic GI disorders

In our study 26% of patients with organic GI disorders satisfied the Brighton criteria for JHS and this was no different to non-GI controls, thus excluding an association between JHS and organic disorders in general. However, in view of the literature proposing an association between JHS and gastritis (Castori, Camerota et al. 2010), Coeliac disease (Danese, Castori et al. 2011) and between hypermobility and Crohn's disease (Vounotrypidis, Efremidou et al. 2009), we were keen to explore this further, and so divided the organic group into individual diagnoses. The prevalence of JHS in gastritis and duodenitis in our study was low (19%), which is in contrast to the proposition by Castori (Castori, Camerota et al. 2010; Castori, Sperduti et al. 2012) that JHS patients have a high prevalence of gastritis. As described earlier, it is unclear what 'gastritis' referred to in the Castori study – it may have referred to dyspeptic symptoms in the absence of endoscopic evidence of gastritis, in which case it might really have referred to functional dyspepsia, which would be consistent with our findings in PDS. Furthermore, Castori's study was very small with only

21 selected patients in genetics clinics, thus introducing a lot of selection bias. Hence it is more likely that our larger study of unselected patients is more representative of JHS patients in general.

Although we did not demonstrate a significant association between JHS and either Coeliac disease or Crohn's disease, the prevalence of JHS in these disorders (32% and 30% respectively) was much higher than the prevalence in other organic GI disorders suggesting that a trend did exist. Both Coeliac disease and Crohn's Disease (CD) have features which overlap with FGID, particularly IBS, and this may explain this relatively high prevalence. IBS symptoms are significantly higher in Crohn's disease than in non-IBD controls and in patients with UC (Halpin and Ford 2012). Furthermore, Crohn's disease and IBS have many other features in common including decreased variability of gut microbiota, increased gut permeability, altered immune activation particularly in response to stress, and upregulation of Toll-like receptors (especially TLR-4) (Spiller and Lam 2011). Moreover, all these observations are supported by the fact that both Crohn's disease and IBS share common susceptibility genes (Zucchelli, Camilleri et al. 2011), particularly relating to neural, mast cell or barrier function, and these are also associated with slow transit (Camilleri, Carlson et al. 2011) suggesting that the overlap is between CD and IBS-C. Interestingly, out of all the IBS subtypes, it was IBS-C which was most strongly associated with JHS.

In the case of coeliac disease, published studies have suggested an association with IBS (Sanders, Carter et al. 2001). Furthermore, patients with IBS can develop non-coeliac gluten sensitivity (Pietzak 2012; Sanders and Aziz

2012) suggesting again that IBS and coeliac disease share features in common.

All this suggests that similar mechanisms may underlie symptoms in Crohn's disease and IBS, and in Coeliac disease and IBS and some of these mechanisms may exist in JHS thus explaining the trends with both organic disorders. However, in view of the small numbers of patients in each organic group, no meaningful or significant conclusions could be drawn. To further address this, much larger studies will be required, and inferences should be postponed until robust associations are established in much larger samples.

4.6.6 Influence of autonomic and somatic factors on the association between JHS and FGID

Anxiety, depression, fibromyalgia, somatic sensitivity (PHQ15) autonomic symptoms, younger age and female gender are all factors known to be associated with FGID, and these were all increased in patients with JHS, suggesting they were possible confounders. From chapter 2 it was evident that fibromyalgia, somatic sensitivity and autonomic symptoms were important in mediating the association between JHS and gastro-oesophageal symptoms, and so we performed a multiple logistic regression analysis to determine if they were also involved in the association with FGID.

None of the extra-intestinal factors had a large effect on the observed association between JHS and FGID, which was contrary to our expectations. This may have been because the FGID group was large and heterogeneous,

and included several different functional GI diagnoses, many of which were not associated with JHS - Figure 4.8. Thus any individual differences between the groups ROME III subcategories would not be observed. To overcome this problem, the effect of the extra-intestinal factors was further explored in patients with PDS, a diagnosis we had shown to be independently associated with JHS. In the case of PDS, the presence of fibromyalgia, anxiety and depression reduced the strength of the association between JHS and PDS, but did not abolish it, suggesting that these factors were partly, but not substantially, involved in the association. Autonomic factors were the strongest confounders, and the addition of the autonomic symptom scores to the regression model, completely abolished the association between JHS and PDS, suggesting that the association of JHS and PDS was only present in those patients with high autonomic symptom scores. Furthermore, of all the autonomic domains it was the orthostatic domain that was responsible for this confounding effect and in fact it was independently associated with PDS. This supports our results in Chapter 2, where it was found that orthostatic symptoms are particularly important in mediating the postprandial symptoms. It also suggests that PDS occurs in patients with orthostatic dysfunction, or POTS. Preliminary support for this concept comes from the fact that POTS patients have postprandial symptoms (Mathias, Low et al. 2011) and this is associated with increased variability of the gastric pacemaker postprandially (Seligman, Low et al. 2012). These are early observations and will require further study in larger groups of patients.

Interestingly, somatic sensitivity (PHQ15adj scores) did not confound the association between JHS and either FGID or PDS. This is compatible with our

study in university students, where somatisation did not influence the association between JHS and GI symptoms. However it contrasts with the study of JHS patients in Chapter 2 where somatic factors were very important in mediating the association between JHS and GI symptoms. One possible explanation is that somatic symptoms are not that important in determining GI symptoms early on, but become more important later in the progression of disease, when musculoskeletal and chronic pain symptoms become prominent, possibly as a result of peripheral and central sensitisation. This is supported by the fact that patients without musculoskeletal symptoms do not have many other symptoms (De Wandele, Rombaut et al. 2013), and that published studies demonstrating an association between JHS and functional somatic syndromes have all been performed in patients with musculoskeletal symptoms and an established diagnosis of JHS (Hakim and Grahame 2004; Castori, Celletti et al. 2011).

4.6.7 Influence of autonomic and somatic factors on the association between JHS and reflux disorders

Although we did not initially aim to perform a detailed investigation of reflux disorders, the association of JHS with reflux was interesting and unexpected. To preliminarily explore whether this association was due to autonomic, psychological, pain and somatic factors, the multiple logistic regression analysis was also performed to investigate the effect of these extra-intestinal factors in patients with reflux. Interestingly, the association between JHS and reflux appeared to be independent of all these factors, suggesting that some other factor intrinsic to JHS is responsible for the development of reflux disorders. This requires further study and replication in a larger number of reflux patients.

4.6.8 Differential presentations of JHS and non-JHS patients with FGID

It was interesting that JHS patients and non-JHS patients with the same type of GI disorder (FGID) differed with respect to several extra-intestinal factors and the JHS patients had more chronic pain, fibromyalgia, positive tender points, somatic symptoms, anxiety and urinary autonomic symptoms. Furthermore, their quality of life scores were worse for pain. This is all consistent with the data on JHS, as presented in the introduction. What is surprising is that in contrast to other studies which have compared JHS patients to healthy controls, our study compared JHS patients who were previously undiagnosed, to patients without JHS who had exactly the same kind of GI disorder. This makes it very unlikely that the differences seen are due to recall bias, and more likely that the association with these extra-intestinal symptoms is due to a true association with JHS. It also highlights the importance of identifying JHS in patients with a combination of FGID and associated fibromyalgia, autonomic symptoms and widespread somatic symptoms. These are the classical 'heart-sink' patients who have multiple unexplained symptoms and respond poorly to conventional treatment. Identifying JHS may enable other therapeutic options to be explored, including cognitive behavioural therapy, which appears to be most effective for JHS patients with multiple symptoms (Daniel 2010).

4.6.9 Future research implications

The over-representation of JHS in PDS and NERD suggests that some underlying aetiology, which is present in JHS, predisposes these patients to these subtypes of GI disorders, as well as to FM, and chronic pain. Possibilities include autonomic dysfunction, somatic and visceral hypersensitivity, and abnormal biomechanical properties of the stomach and gastro-oesophageal

junction, all of which will need to be assessed in JHS to further our understanding of why these patients are prone to GI dysfunction. Understanding the mechanism of development of GI symptoms may also help explain why these patients are predisposed to developing other functional somatic syndromes.

In addition, the high prevalence of JHS in NERD and PDS provides an opportunity to categorise these conditions by JHS phenotype. This may be more meaningful than an arbitrary symptom-based classification and may enable more meaningful genetic, physiological or molecular conclusions to be drawn.

4.6.10 Limitations

In this large blinded nested case-control study in GI clinics, where we compared patients with no prior knowledge of their JHS status, to a non-GI control group, we managed to overcome several of the limitations of previous studies. However, we were left with a few new limitations. Firstly, our study was powered to detect a 10% difference in the prevalence of JHS in FGID vs organic patients, and was not designed to detect differences in the individual diagnostic subcategories. Thus any association, or lack of, with the smaller groups of patients should be interpreted with caution. This also applies to the reflux group which is much smaller than the FGID and organic GI group. However, our significant findings in the smaller groups are consistent with previous literature and so are unlikely to be simply due to chance. Secondly, our GP control group (92 patients) was much smaller than we had planned for (270 patients). This was due to an extremely poor response rate despite the

involvement of multiple large GP practices. The consequence of this small control group is that the variability in this group was high, making it less generaliseable to the population. Thirdly, in line with this, our control group consisted of patients who had been referred to secondary care, rather than healthy controls, as we had wanted them to be as comparable to the GI patients as possible. Thus, our findings should be interpreted as being relative to a non-GI *patient* group, rather than to a healthy population. Lastly, in the absence of a biomarker for the diagnosis of JHS, assessment was purely clinical and relied on the fulfilment on several major and minor criteria. Although some of these were objective (e.g. scoliosis, Marfanoid habitus, papyraceous scarring, Beighton score) others were fairly subjective and could have easily been affected by recall and response bias on the part of the patient. For example, particularly enthusiastic and hypervigilant patients with pain and anxiety issues may answer 'yes' to the 'presence of arthralgia in more than 4 joints','back pain' and 'multiple soft tissue injuries'. Thus there was a bias towards a positive diagnosis in patients with anxiety and chronic pain. However, this bias would have been expected to occur in all the different groups, thus although it might account for the very high absolute prevalence of JHS seen, it cannot explain the differential prevalence in the different GI categories.

Conclusions

JHS is present in a third of patients attending GI clinics. It is a risk factor for FGID and reflux disorders, specifically NERD and PDS, but not organic GI disorders. Autonomic and pain factors, but not somatic factors seem to be important in the association with FGID, but not with reflux.

Chapter 5

Observations of Gastro-oesophageal Sensori-Motor Function in patients with the Joint Hypermobility Syndrome and Symptoms of Dysphagia, Reflux and Dyspepsia

5.1 Introduction

It is evident from the Chapter 2 that patients with JHS have, in addition to their musculoskeletal symptoms, an excess of upper GI symptoms particularly reflux, dysphagia and dyspepsia which adversely affects their quality of life. Effective treatment requires an understanding of the mechanisms underlying these upper GI symptoms, and this is so far lacking. Data presented in Chapter 4 of this thesis suggests that JHS is associated with FGID and gastro-oesophageal reflux disease (GORD), but not organic GI disorders (Chapter 4), so it is possible that mechanisms that are implicated in the pathophysiology of functional GI disorders and GORD may also be relevant to patients with JHS and GI symptoms.

Mechanisms underlying functional disorders include abnormalities in sensitivity (centrally and peripherally), motility and biomechanics, and this is certainly true for gastro-oesophageal symptoms. For example, visceral hypersensitivity of the oesophagus is implicated in GORD (Thoua, Khoo et al. 2008), and abnormal gastric sensitivity is associated with functional dyspepsia (Tack, Caenepeel et al. 2001; Oustamanolakis and Tack 2012). Decreased compliance of the oesophageal body is associated with dysphagia in eosinophilic oesophagitis

(Kwiatek, Pandolfino et al. 2010) and impaired gastric accommodation is associated with functional dyspepsia (Tack, Piessevaux et al. 1998; Oustamanolakis and Tack 2012). Dysmotility of the oesophagus is associated with dysphagia (Clouse 2003; Roman, Lin et al. 2011), and gastroparesis is associated with early satiety and postprandial fullness, both features of Postprandial Distress Syndrome (Sarnelli, Caenepeel et al. 2003). Hence it is clear that symptoms of GORD, dysphagia and dyspepsia can arise secondary to sensori-motor and biomechanical abnormalities.

Reflux symptoms can be due to pathological acid reflux, oesophageal hypersensitivity to physiological reflux or to functional heartburn. The latter refers to the presence of reflux symptoms in the absence of pathological or physiological reflux and it is incompletely understood compared to the other reflux subtypes. Oesophageal hypersensitivity is thought to be secondary to sensorineural processes occurring either peripherally or centrally (Sarkar, Aziz et al. 2000; Lottrup, Olesen et al. 2011). Pathological acid reflux is due to either an increase in the number of reflux episodes or an increase in the exposure of the oesophagus to acid. It is associated with anatomical changes in the gastro-oesophageal junction (e.g. hypotensive lower oeosphageal sphincter and hiatus hernias), as well as with more physiological abnormalities such as increased compliance of the gastro-oesophageal junction (Kwiatek, Pandolfino et al. 2010), and dysmotility of the stomach and oesophagus (Galindo, Vassalle et al. 2012).

A study of upper GI physiology in patients with JHS and upper GI symptoms has never been performed and so it is unknown whether there are

demonstrable physiological abnormalities that can account for GI symptoms in these patients, or whether symptoms are truly unexplained and may possibly be related to psychosomatic factors. One published case series demonstrated that upper GI dysmotility, including gastroparesis and oesophageal hypomotility, was present in some symptomatic JHS patients attending a tertiary neurogastroenterology clinic (Zarate, Farmer et al. 2009), suggesting that GI dysmotility has been documented in a small proportion of symptomatic JHS patients. However, it is difficult to draw any firm conclusions from this, as it was simply an observation in a small number of selected patients. Furthermore, it did not include a control group and so it remains unknown how upper GI physiology in symptomatic JHS patients compares to that in non-hypermobile patients with similar symptoms.

Whereas a detailed study of visceral sensori-motor function in JHS patients has not yet been undertaken, several studies of the skin and skeletal muscle of JHS patients demonstrate that biomechanical and sensori-motor abnormalities are present in musculoskeletal tissue in JHS, and these are thought to underlie several somatic symptoms. For example, patients with JHS have increased compliance of their skin (Henry, Goffin et al. 1996; Hakim and Sahota 2006; Grahame and Hakim 2008), increased somatic hypersensitivity associated with fibromyalgia (Castori 2012), and myopathic features in skeletal muscle which are associated with decreased muscle strength and tone, and with myalgia and fatigue (Voermans, van Alfen et al. 2009; Rombaut, Malfait et al. 2012; Rombaut, Malfait et al. 2012). Thus, sensori-motor and biomechanical abnormalities do underlie other symptoms in JHS, and it is not inconceivable

that they may also be present in the upper GI tract and be associated with symptoms.

5.2 Aims

The aims of this study were (1) to determine if physiological abnormalities in the stomach and oesophagus are present in JHS patients with symptoms of dysphagia, and reflux; (2) to determine how GI physiology findings compare to those observed in non-hypermobile patients with similar symptoms; and (3) to determine if compliance is increased in the GOJ in patients with JHS and reflux symptoms.

5.3 Hypothesis

We hypothesised that the connective tissue abnormality in JHS is not localised to the musculoskeletal system but also present in the GI tract where it affects the biomechanics of the gut, leading to altered physiology including dysmotility, and therefore symptoms. Hence, we expected symptoms in JHS patients to be associated with physiological and compliance abnormalities.

5.4 Materials and methods

5.4.1 Study design

A prospective characterisation of upper GI physiology findings was carried out in consecutive patients with established JHS attending the upper GI physiology unit between June 2011 and December 2012. JHS patients completed a set of validated questionnaires to assess for upper GI symptoms, and then underwent a combination of high-resolution manometry (HRM) and 24-hour combined

ambulatory pH-impedance testing (MII). The study design was 'pragmatic' and therefore other tests, including gastric emptying testing using ^{13}C Octanoic Acid breath tests, were only performed if requested by the physician. Results of physiological testing were compared to that in a group of age-matched controls without hypermobility who were attending the GI physiology department for investigation of similar symptoms.

Halfway through the study an endoflip tool, which is used for the assessment of GOJ distensibility, was acquired by the department. As part of the department policy, JHS patients who had reflux disease and who were attending the unit for investigation after this time also underwent Endoflip testing. Data from the endoflip was compared to healthy control data obtained from a previously published study.

5.4.2 Subjects

JHS patients

Adult patients (>18 years) who had a confirmed diagnosis of JHS, and who were attending the GI physiology unit for investigation of dysphagia or reflux were included.

Non-hypermobile controls

Control data was obtained from a database of all patients who had attended the GI physiology unit between Jan 2010 and December 2011 for investigation of upper GI symptoms. This database contained demographic information, symptom profiles, responses to the hypermobility screening questionnaire and the results of physiology testing. All patients who were between the ages of 18

and 65, who had fully completed and screened negatively on the hypermobility questionnaire, and who had symptoms of dysphagia and/or reflux were selected as controls. Patients with diabetes, connective tissue disorders or vasculitides were excluded, as were patients with incomplete tests and those with faulty test results secondary to technical problems.

Exclusion criteria

Both JHS patients and non-hypermobile controls were excluded if they had undergone previous surgery to the stomach or oesophagus, or therapeutic endoscopic procedures e.g. oesophageal dilation, Botox injection, or if they were on PPI or prokinetics at the time of HRM or MII testing.

5.4.3 Questionnaires

JHS patients completed a detailed set of validated questionnaires to assess for reflux and dysphagia symptoms.

Reflux disease questionnaire (RDQ)

This is a self-administered questionnaire that has been validated to identify patients with gastro-oesophageal reflux disease in primary care (Ofman, Shaw et al. 2002). It scores 12 individual items relating to the frequency and severity of reflux, using a Likert scale, where 0 represents the most positive option and 5 the most negative one. A raw score is calculated for domains of heartburn (score: 0-20) and regurgitation (score: 0-20), both of which can be combined to give a total GERD score (0-40). A cut-off of 9 for the GERD domain has 83% sensitivity and 83% specificity for identifying the presence of gastro-oesophageal reflux symptoms (Ofman, Shaw et al. 2002).

Dysphagia Odynophagia Questionnaire

This is a validated 10-item questionnaire that assesses the frequency of dysphagia, food impaction and odynophagia. Items are scored from 0-5, using a Likert scale where higher scores represent worse symptoms. A total score out of 50 is calculated - higher scores represent more severe dysphagia. A score ≥ 6 has 86% sensitivity and 97% specificity for identifying the presence of dysphagia (Escobar, Pandolfino et al. 2011).

Dyspepsia questionnaire

This consists of 9 dyspeptic symptoms and 1 heartburn symptom, each of which is scored from 0-3 to indicate the severity and relevance of the symptoms over the past 3 months. A maximum score out of 30 was obtained, with higher scores indicating greater severity of dyspepsia (Tack, Caenepeel et al. 2001).

5.4.4 Physiology assessment

All subjects were studied having been fasted for at least 6 hours, and medication that could affect oesophageal motor function or the presence of reflux (e.g. prokinetics, smooth muscle relaxants, proton pump inhibitors, antacids) were discontinued for at least 5 days prior to the study.

5.4.4.1 High Resolution Manometry (HRM)

A solid-state HRM assembly with 36 solid-state sensors spaced at 1-cm intervals was used (Sierra Scientific Instruments Inc., Los Angeles, CA). Each sensor is circumferentially sensitive, accurate to within 1 mmHg, and capable of recording transient pressure changes in excess of 6,000 mmHg/s - Figure 5.1.

The catheter was calibrated and zeroed to atmospheric pressure, prior to each study.

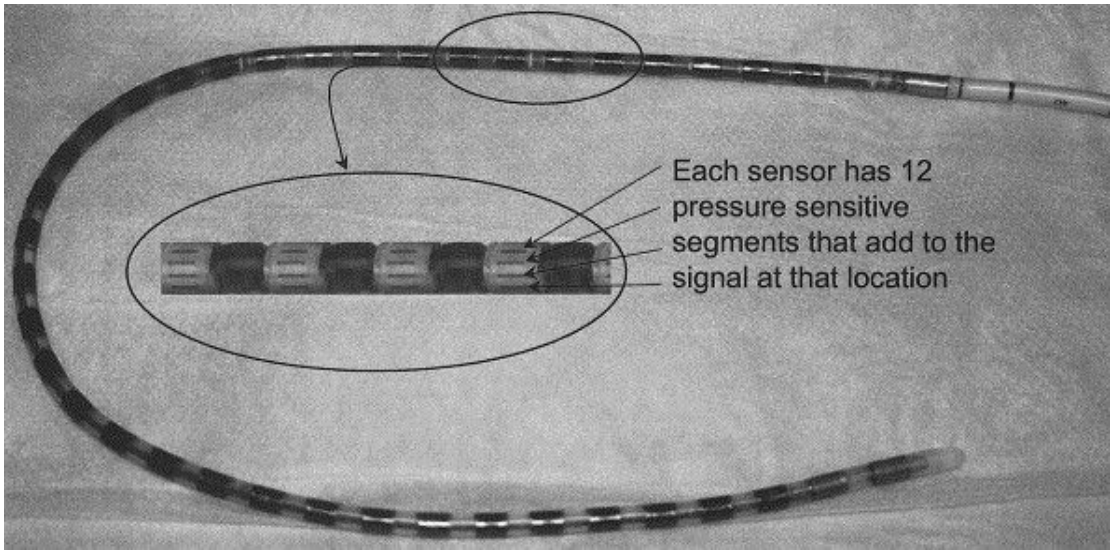


Figure 5.1: HRM catheter.
The HRM catheter consists of 36 solid-state sensors spaced 1cm apart.

Studies were performed with the patient in a semi-recumbent position. The catheter was passed transnasally and positioned until both the upper oesophageal sphincter (UOS) and lower oesophageal sphincter (LOS) could be visualized in the recording frame, with at least 3 intragastric sensors visible. The catheter was fixed in place by taping it to the side of the face. The patient was given 5 minutes to settle, before a 30 second swallow-free period (landmark frame) was recorded. This was used to assess the oesophageal landmarks - Figure 5.2 - and to obtain the resting (basal) UOS and LOS pressures. Following this, recordings of 10 water swallows (5ml of water spaced at least 30 seconds apart), and 2-3 multiple rapid swallows (MRS) (five 2 mL water swallows 2-3s apart) were obtained. The latter was used to assess the neuromuscular integrity of the oesophagus and has been found to be useful in

the assessment of patients with hypomotility (Fornari 2009 NGM). Pressure data were acquired using a computerized HRM acquisition, display and analysis system (Manoscan, Manoview; Sierra Scientific Instruments/Given Imaging).

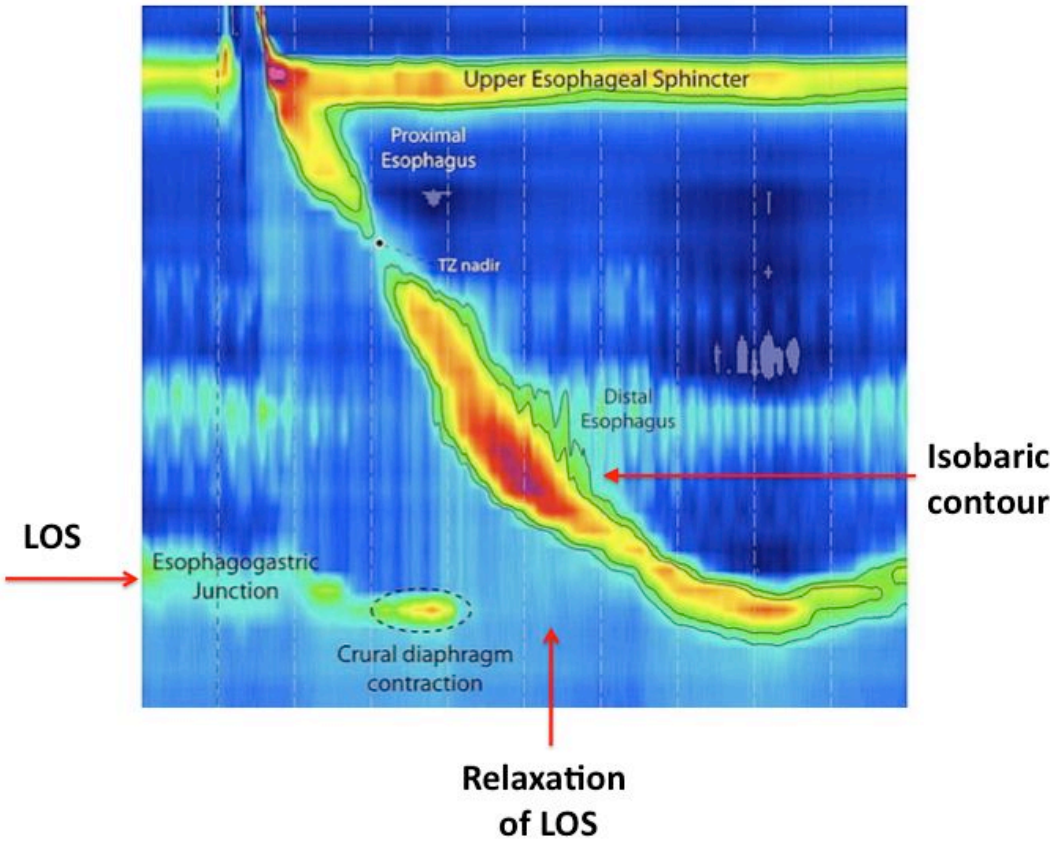


Figure 5.2: High-resolution manometry tracing of a water swallow.
A normal swallow is associated with relaxation of the upper and lower oesophageal sphincters, and peristaltic contraction of the oesophageal body. The black solid line surrounding the peristaltic contraction is the isobaric contour, which can be set at any pressure. Breaks larger than 2cm in the 20mm Hg isobaric contour are indicative of hypomotility.

Analysis of manometry studies was performed using Sierra ManoView software version 2 (Sierra Scientific Instruments). UOS basal and residual pressure, LOS basal and residual pressure, and the distal contractile integral (DCI) were calculated. The 20mm Hg isobaric contour was used to detect the presence of breaks in the peristaltic waves. In this way, the number of swallows with small

breaks (2-5cm), large breaks (>5cm) and the number of failed swallows was counted for each of the patients, and used to determine the motility pattern, as per the Chicago classification (Bredenoord, Fox et al. 2012). Furthermore, the presence of a hiatus hernia, and the response to MRS was noted.

5.4.4.2 Multichannel Intraluminal Impedance Monitoring (MII)

Combined oesophageal impedance-pH monitoring was performed using a Sleuth® Multi-channel Intraluminal Impedance ambulatory system (Sandhill Scientific, Inc.; Highland Ranch, CO). The system includes a portable data logger with impedance-pH amplifiers and a catheter containing one antimony pH electrode and eight impedance electrodes at 2, 4, 6, 8, 10, 14, 16, and 18 cm from the tip of the catheter. Each pair of adjacent electrodes represents an impedance-measuring segment, 2 cm in length, corresponding to one recording channel. The impedance amplifier delivers AC voltage in a range of 1–2 kHz with resulting current flow variations in response to intraluminal impedance changes. The six impedance and pH signals were recorded at 50 Hz on a 128 MB CompactFlash card for further analysis. The studies were performed 'off' PPIs, following the HRM protocol. Before the start of the recordings, the pH recorder was calibrated using pH 4.0 and 7.0 buffer solutions.

After LOS location by HRM, the impedance-pH catheter was passed transnasally and positioned in the esophageal body to record pH at 5 cm and impedance at 3, 5, 7, 9, 15, and 17 cm proximal to the LOS. Subjects were encouraged to maintain normal activities, sleep schedule, and eat their usual meals at their normal times. Event markers on the data-logger recorded symptoms, meal times, and posture changes.

Analysis of the MII-pH tracings was performed by computer with software from Sandhill Scientific (BioView Analysis version 5.6.0). The tracings were revised visually and manually for bolus and symptom events and for bolus–symptom correlation. The final reports included the number of acid and non-acid reflux episodes - Figure 5.3 - (both total and those with proximal extent), the total acid exposure, split into the upright and the recumbent components, the number of symptoms, and 2 measures of the reflux-symptom correlation: the symptom index (SI), and the symptom association profile (SAP).

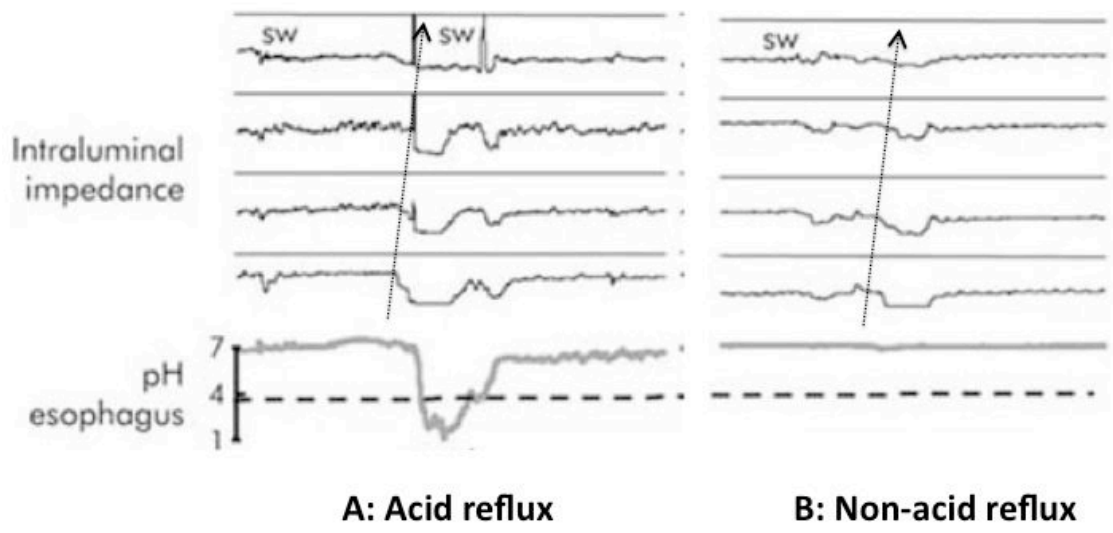


Figure 5.3: MII tracings of acid and non-acid reflux events.
In both events the drop in impedance (dashed arrow) starts distally and travels proximally, confirming reflux. In acid reflux (A) the reflux event is accompanied by a drop in pH. In non-acid reflux (B) there is no accompanying drop in pH.

5.4.4.3 Gastric emptying testing

Gastric emptying was measured using the previously validated breath test. Briefly, all studies were performed after a 6-hour fast. Baseline end alveolar breath samples were taken followed by a test meal, which was either solid or

semi-solid. The solid meal consisted of scrambled egg labeled with 100mg ^{13}C octanoic acid, and 2 slices of toast. The semi-solid meal consisted of plain oats and milk mixed and labeled with 100mg ^{13}C acetic acid. Following the meal, end-alveolar breath samples were taken every 15 minutes for 2 hours and then every 30 minutes for a further 2 hours. Gastric half emptying time ($T_{1/2}$) was calculated by measuring the presence of exhaled $^{13}CO2$ by isotope-selective nondispersive infrared spectrometry (IRIS; Wagner/Analysen Technik). Gastric emptying was considered delayed when the $T_{1/2}$ exceeded 135 minutes in solids, and 80 in semi-solids (Schadewaldt, Schommartz et al. 1997).

5.4.4.4 Endoflip assessment

Distensibility of the GOJ was determined using the commercially available EndoFLIP system (McMahon, Frokjaer et al. 2007) - Figure 5.4. In this technique, a probe is inserted into the oesophagus and placed at the level of the GOJ. The probe consists of a 240-cm catheter with a 14-cm bag attached to its distal end, which is compliant to a maximal diameter of 25 mm. Within the inflatable bag, 17 electrodes are placed at 4-mm intervals. An excitation current of 100 μA is generated between 2 adjacent electrodes at a frequency of 5 kHz. Using impedance planimetry, cross-sectional areas (CSAs) are determined for the 16 balloon cross-sections during volume-controlled distensions. Additionally, 2 pressure sensors are located on the probe to determine intrabag pressure, allowing assessment of GOJ distensibility. The distention probe and the pressure transducers were calibrated by the manufacturer.

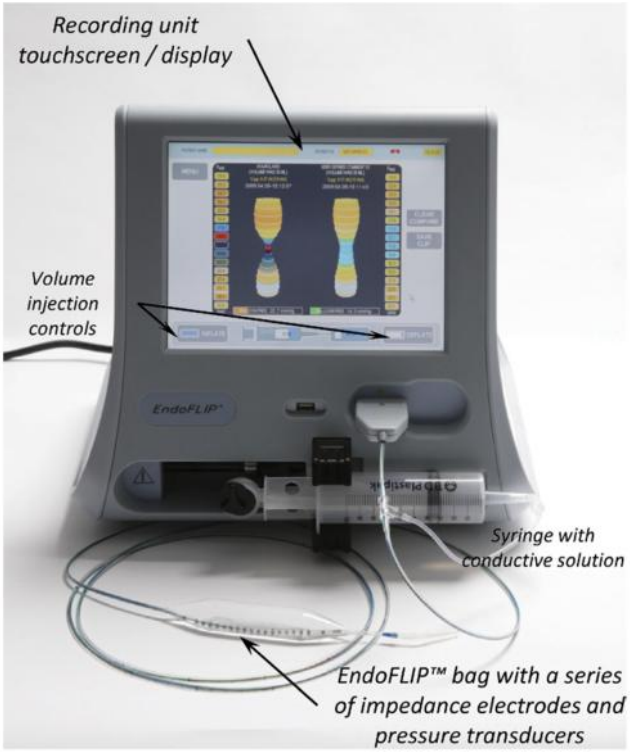


Figure 5.4: Endoflip assembly. A pre-filled syringe containing conducting solution is attached to the recording unit, and to the endoflip catheter, which has its end an inflatable balloon which contains the impedance electrodes and the pressure sensors. Inflation and deflation of the bag with the conducting solution is operated using the touchscreen display.

The pressure sensor was zeroed before insertion of the catheter, and subsequently the deflated catheter was inserted through an anesthetized nostril. HRM readings were used to position the balloon at the level of the GOJ. The catheter was manually held in place by anchoring it at the nostril, as the inflations frequently resulted in peristaltic contractions and a caudal migration of the catheter. The balloon was inflated from 10ml to a maximum of 50ml in 5 ml increments, as tolerated by the patient. Pressures and CSAs were collected at a rate of 10Hz. Median values of intrabag pressure and minimum CSA at each of the above volumes was assessed by analyzing peristalsis-free intervals. Distensibility was calculated at each of the time frames over the peristalsis-free period, by dividing the minimum CSA by the intrabag pressure. The

distensibility calculated at each of the distending volumes was the median distensibility over that time frame.

5.4.5 Terminology and parameters

The terms used in this chapter are defined in Table 5.1 and Table 5.2. The motility patterns in Table 5.1 are taken from the Chicago classification of motility disorders (Bredenoord, Fox et al. 2012). Patients were considered to have pathological acid reflux if they had an increase number of reflux events i.e. > 45 reflux events, or >35 acid reflux events (Zerbib, Roman et al. 2012); or if they had increased acid exposure i.e. >4.2% total acid exposure, >6.3% upright acid exposure or >1.2% recumbent acid exposure (Zerbib, Des Varannes et al. 2005).

Table 5.1: Terms and definitions used for the HRM studies.

Term	Definition
LOS basal pressure	Mean of the minimum pressures at the LOS during respiration. Hypotensive if less than 4.8 mmHg
Integrated relaxation pressure (IRP)	Represents LOS relaxation during a swallow. IRP>15 indicates incomplete LOS relaxation
Distal contractile integral (DCI)	Represents the force of oesophageal contraction during a swallow. DCI<450 indicates hypomotility. DCI>5000 indicates hypertensive contractions.
Weak peristalsis with small breaks	Small breaks (2-5cm) in the 20 mmHg isobaric contour in more than 3 wet swallows
Weak peristalsis with large breaks	Large breaks (>5cm) in the 20 mmHg isobaric contour in 3 or more wet swallows
Frequent failed peristalsis	Failure of oesophageal contractions in more than 3 out of 10 swallows.
Absent peristalsis	Absence of oesophageal contractions on all wet swallows in the presence of a normal IRP
Oesophageal hypomotility	Collective term to describe weak peristalsis, frequent failed peristalsis and absent peristalsis
Achalasia	Incompletely relaxing LOS (high IRP) and failure of normal peristalsis
Oesophageal spasm	Rapid oesophageal contractions
Hypertensive peristalsis	Oesophageal contractions with DCI>5000
Functional GOJ obstruction	Incompletely relaxing LOS in the presence of preserved peristaltic contractions

Table 5.2: Terms and definitions used for the reflux studies.

Terms	Definitions
Symptom Index (SI)	Measure of the association between reflux episodes and symptoms. Positive if SI>50
Symptom Association Probability (SAP)	Another measure of the association between reflux episodes and symptoms. Positive if SAP>95
Erosive reflux disease (GERD)	Presence of oesophagitis or Barrett's oesophagus on endoscopy
Non-erosive reflux disease (NERD)	Reflux in the absence of positive endoscopic findings. Includes both Non-erosive pathological GOR and Hypersensitive oesophagus
Pathological GOR – Non erosive	Increased acid exposure or increased reflux episodes on 24-hour reflux testing in the absence of a positive endoscopy
Hypersensitive oesophagus	Normal acid exposure with a positive association between reflux episodes and symptoms
Functional heartburn	Reflux symptoms in the absence of pathological acid reflux episodes or pathological acid exposure and the absence of a positive reflux-symptom correlation.
Acid reflux	Reflux episodes accompanied by a drop in pH<4.5
Non-acid reflux	Reflux episodes not accompanied by a drop in pH<4.5

5.4.6 Data analysis and statistics

Data were described in terms of means and standard errors (normal ordinal data), medians and IQR (non-normal ordinal data) and proportions and confidence intervals (categorical data). Comparisons between JHS patients and controls were performed using the t-test (normal ordinal data), Mann Whitney U-test (non-normal ordinal data), chi squared test (categorical data) or Fisher's exact test (categorical data with values of less than 5%). For all comparisons, p values <0.05 were considered statistically significant.

5.5 Results

5.5.1 Subjects

JHS patients

30 JHS patients (28 female, age range: 18-62) attended the GI physiology unit between June 2011 and December 2012. HRM and MII were performed as basic tests on all subjects. 16 of the 30 had additional gastric emptying tests, and 8 of the 30 had endoflip testing - Figure 5.5. Symptom characteristics, and results of motility, reflux and gastric emptying testing for each of the 30 patients is shown in Table 5.3, Table 5.4 and Table 5.5.

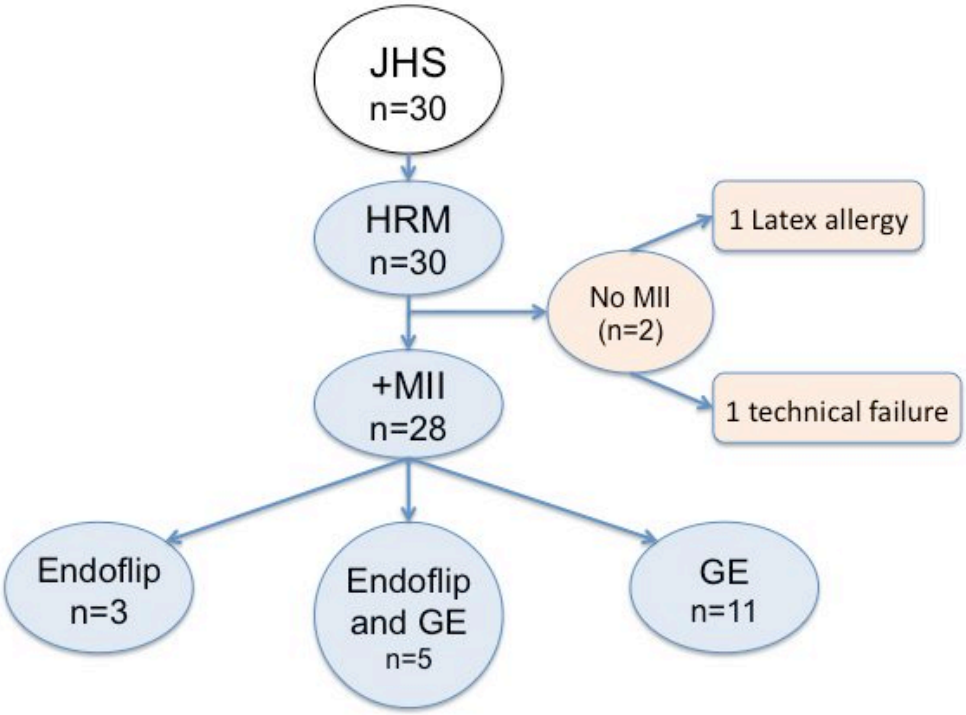


Figure 5.5: Flowchart of JHS patients undergoing GI physiology testing

Table 5.3: Characteristics of each of the 30 JHS patients

Sx: symptoms, POTS: Presence of postural orthostatic tachycardia syndrome
Dysphagia symptoms based on dysphagia score: - : 0-6; +: 6-25; ++: 26-50
Reflux symptoms based on RDQ GERD score: -: 0-9; +: 10-25; ++: 26-40
Dyspepsia, based on dyspepsia score: - : 0-10; +: 11-20; ++: 21-30
OGD findings: HH: Hiatus hernia; NA: OGD not done; N: Normal; HP: H Pylori; G: Gastritis; D: Duodenitis

Patient	Age	Sex	POTS	Dysphagia Sx	Reflux sx	Dyspepsia Sx	OGD findings
1	35	F	-	++	+	++	NA
2	25	F	+	+	+	+	NA
3	26	M	-	+	+	+	HH
4	40	F	+	++	++	++	Gastric polyps
5	27	F	+	++	+	+	N
6	31	F	-	-	-	+	N
7	20	F	-	-	++	+	N
8	30	F	+	+	++	-	N
9	24	F	+	++	++	++	NA
10	38	F	-	+	-	++	N
11	20	F	+	++	++	++	N
12	32	F	-	+	++	++	HH
13	25	F	+	+	+	+	NA
14	48	F	-	+	-	+	HP Gastritis
15	34	F	+	++	++	++	NA
16	46	F	+	+	+	+	N
17	40	F	+	+	+	+	NA
18	18	F	+	-	+	+	NA
19	45	F	-	+	+	+	HH
20	28	M	-	-	+	+	NA
21	29	F	-	-	++	+	NA
22	62	F	-	+	+	+	Gastric polyps, HH
23	30	F	+	+	+	+	NA
24	32	F	+	++	++	++	NA
25	24	F	+	+	++	++	NA
26	28	F	-	+	+	+	NA
27	23	F	+	+	-	+	NA
28	48	F	+	+	++	+	NA
29	26	F	+	+	+	+	Food residue
30	21	F	+	++	++	++	Food residue, G, D

Table 5.4: Oesophageal motility and gastric emptying in JHS patients

LOS basal pressure: L: Low, N: Normal, H:High ; LOS relaxation: Y: complete relaxation (IRP<15), N: incomplete relaxation; DCI: Distal contractile integral: L: Hypotensive (DCI<450), N: Normal (DCI: 450-5000); HH: hiatus hernia, -: No hiatus hernia; Motility pattern: N:Normal, FF: Frequent failed peristalsis, LD: Weak peristalsis with large defects, SD: Weak peristalsis with small defects; MRS pattern:N: Normal; Weak: Weak after-contraction, Inc Inh: Incomplete inhibition of contractions ; Gastric emptying: NA: Not performed, N: Normal, D: Delayed, SD: Severely delayed

Patient	LOS Basal P	LOS relaxation	DCI	HH	Motility	MRS	Gastric emptying
1	N	Y	N	-	N	N	NA
2	N	Y	N	3cm	FF	N	D
3	N	Y	N	-	LD	N	NA
4	N	Y	N	-	N	Inc Inh	NA
5	L	Y	L	1cm	LD	N	NA
6	L	Y	L	-	LD	Weak	NA
7	N	Y	N	-	N	Inc Inh	D
8	N	Y	N	-	N	N	D
9	N	Y	N	-	N	N	D
10	N	Y	N	-	LD	N	D
11	L	Y	L	-	LD	Weak	SD
12	N	Y	L	<1cm	SD	Weak	NA
13	N	Y	L	-	SD	N	D
14	H	N	N	-	N	Inc Inh	D
15	N	N	N	-	LD	Weak	NA
16	N	Y	N	<1cm	N	N	NA
17	N	Y	N	-	SD	N	D
18	L	Y	L	-	FF	N	NA
19	N	Y	N	<1cm	LD	Weak	NA
20	L	Y	N	-	N	Weak	NA
21	L	Y	N	<1cm	N	N	D
22	L	Y	N	-	N	N	NA
23	L	Y	L	-	FF	N	SD
24	N	Y	L	-	LD	Weak	D
25	N	Y	L	-	FF	N	N
26	N	Y	L	-	N	N	N
27	N	Y	N	<1cm	N	N	NA
28	N	Y	N	-	N	N	SD
29	N	Y	N	-	N	N	D
30	N	Y	L	-	FF	Weak	NA

Table 5.5: Reflux findings in JHS patients

Ep: Episodes; Exp: Exposure; Sx : Symptom; Dx: Diagnosis ; NA: Not measured; Total reflux episodes: N: Normal (<45), +: High (>45), ++: very high (>80); Acid reflux ep: N: Normal (<35), +: High (≥35); Non-acid reflux ep: N: Normal (<12), +: High (>12); Total acid exp : N: Normal (<4.2), +: High (>4.2), ++: Very high (> 10); Upright acid exp : N: Normal (<6.3), +: High (>6.3), ++: Very high (>12); Recumbent acid exp: N: Normal (<1.2), +: High (1.2-10), ++: Very high (10.1-20), +++: Extremely high (>20); Symptom correln: -: No correln H: positive correln with heartburn, R: positive correln with regurgitation; Diagnosis: AR: Pathological acid reflux, HO: hypersensitive oesophagus, F: Functional reflux symptoms

Patient	Total reflux ep	Acid reflux ep	Non-ac reflux ep	Total acid exp	Upright acid exp	Recumb acid exp	Sx correln	Dx
1	+	+	H	N	N	+	R	HO
2	N	N	N	N	N	N	-	F
3	N	N	H	N	N	N	-	F
4	+	N	H	+	++	N	H	AR
5	+	N	H	N	N	N	H,R	HO
6	N	N	N	N	N	N	-	F
7	N	N	H	N	N	N	-	F
8	+	+	H	+	+	N	H,R	AR
9	NA	NA	NA	NA	NA	N	-	NA
10	NA	NA	NA	NA	NA	N	-	NA
11	N	N	N	N	N	N	-	AR
12	N	N	H	++	N	++	R	AR
13	++	+	H	N	N	N	H,R	AR
14	N	N	N	N	N	N	-	F
15	N	N	N	N	N	N	-	F
16	N	N	N	+	++	N	R	AR
17	+	N	H	N	N	+	R	AR
18	+	+	N	++	N	+++	-	AR
19	+	N	H	N	N	+	-	AR
20	N	N	N	++	++	+++	H	AR
21	+	N	H	N	N	N	R	HO
22	+	+	H	++	N	+++	-	AR
23	+	+	H	+	N	+	H	AR
24	N	N	N	+	N	++	H	AR
25	+	N	H	N	N	N	H,R	HO
26	+	N	H	N	N	N	R	HO
27	N	N	N	N	N	N	-	F
28	N	N	N	N	N	N	R	HO
29	++	NA	NA	N	+	+	R	AR
30	N	N	H	+	+	N	R	AR

Non-hypermobile control patients

1108 patients underwent GI physiology testing between Jan 2010 and December 2011. 382 scored 0 out of 5 on the screening hypermobility questionnaire, and therefore screened negative for JHS. Of these, 311 were between the ages of 18 and 65, and 259 were eligible for inclusion into the study - Figure 5.6. 98 patients had dysphagia and complete HRM data (56 female, age range 20-65), and 108 had reflux symptoms and had complete HRM and MII testing off PPI (61 female, age range 18-65).

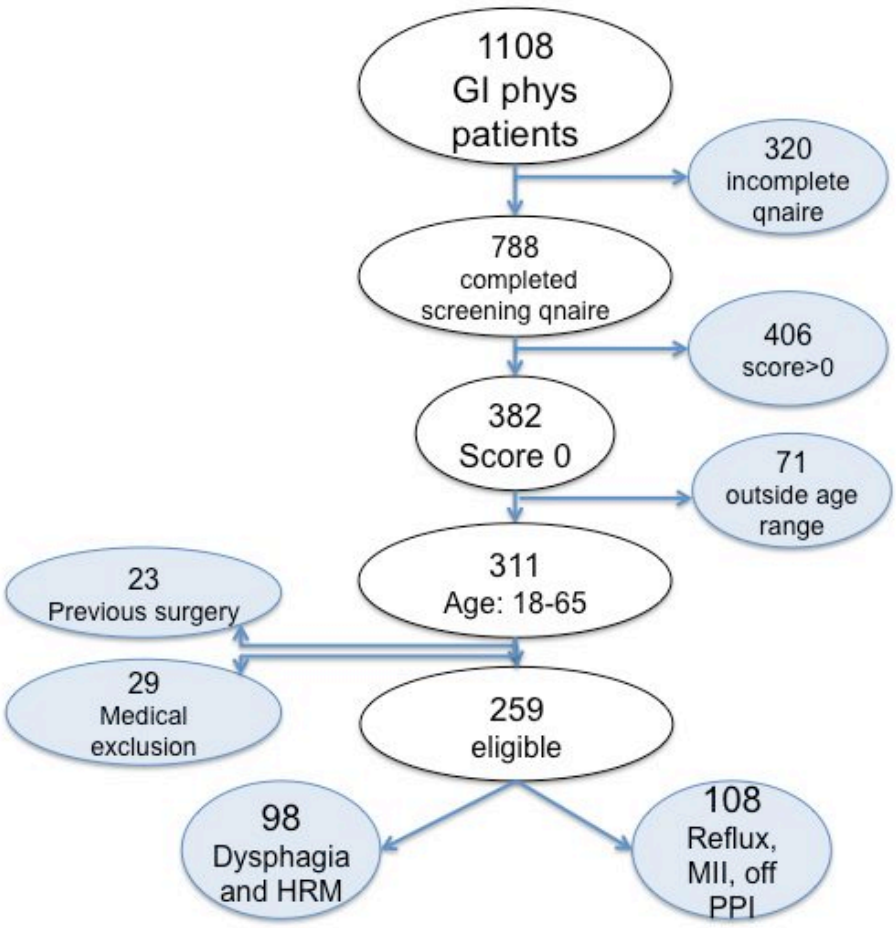


Figure 5.6: Selection of non-hypermobile controls

To understand the individual symptoms and enable appropriate comparisons with the control group, both JHS and non-hypermobile patients were divided into those with predominant symptom of dysphagia (25 JHS, 98 controls) and those with predominant symptoms of reflux (26 JHS, 108 controls) and the physiology findings were compared in patients with the same symptom. Hence the results will be split into three parts. The first part relates to dysphagia, the second part to reflux and the third part to GOJ compliance. For each part, GI physiology in JHS will be characterised and will then be compared to the control group.

5.5.2 Dysphagia in JHS

25 of the JHS patients (93% female, age range 18-62) had symptoms of dysphagia, and their dysphagia scores ranged from 6 to 45 out of 50 - Figure 5.7. None of the JHS patients had an obstructive cause for dysphagia on endoscopy or barium swallow. To investigate for other possible mechanisms for dysphagia, the characteristics of the gastro-oesophageal junction and the motility patterns were analysed on the HRM tracings.

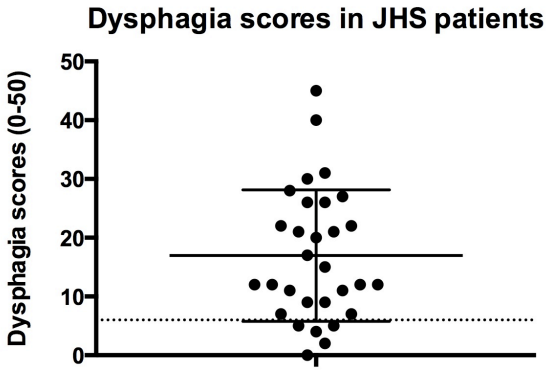


Figure 5.7: Dysphagia scores in JHS patients.
The dotted line represents the cut-off score of 6 which is used to identify the presence of dysphagia. 25 of the 30 patients had scores > 6.

5.5.2.1 HRM findings in JHS patients with dysphagia

Gastro-oesophageal junction

2 out of the 25 patients had a high IRP (incompletely relaxing LOS), and both these patients had high or borderline high basal LOS pressures - Figure 5.8. In both these patients, peristalsis was present thus excluding the diagnosis of achalasia. Subsequent barium swallows in these patients revealed clear passage of contrast into the stomach with no hold-up in the oesophagus, thereby suggesting that the high IRP was no responsible for the dysphagia.

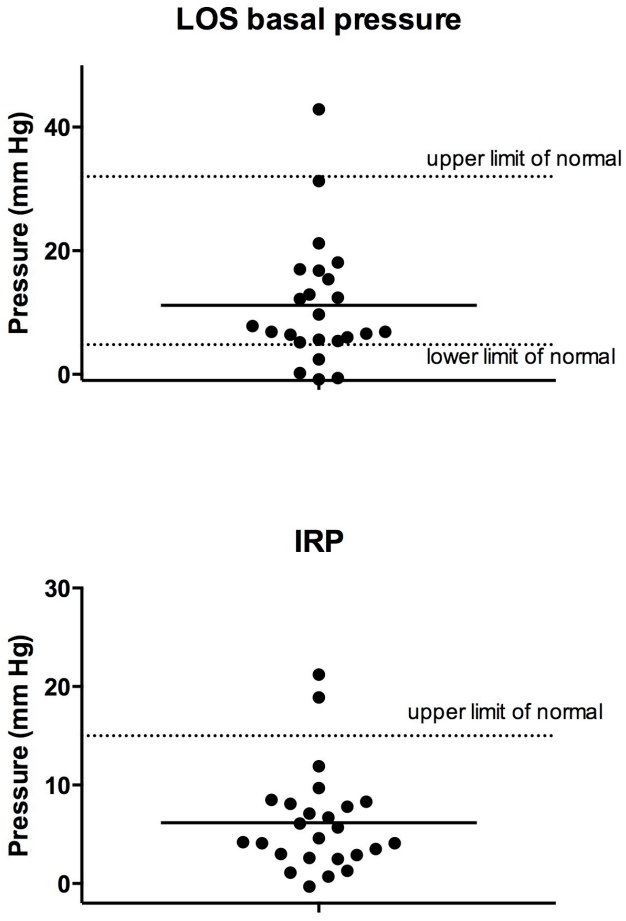


Figure 5.8: **Characteristics of GOJ in JHS patients with dysphagia.**
Most patients had normal basal LOS pressures and a completely relaxing LOS. 2 patients had a high IRP i.e. an incompletely relaxing LOS. One of these patients had a high basal LOS pressure and the other had a borderline high basal LOS pressure.

Oesophageal motility

Although 2 patients had a high IRP and should have been classified as GOJ outflow obstruction (Table 5.1), it was clear from the barium swallow that there was no obstruction and hence they were categorised as per their motility pattern - Table 5.1.

Of the 25 patients with JHS and dysphagia, 11 had normal oesophageal motility, 3 had weak peristalsis with small defects, 7 had weak peristalsis with large defects and 4 had frequent failed peristalsis - Figure 5.9. Thus, a total of 14 patients (56%) had oesophageal hypomotility.

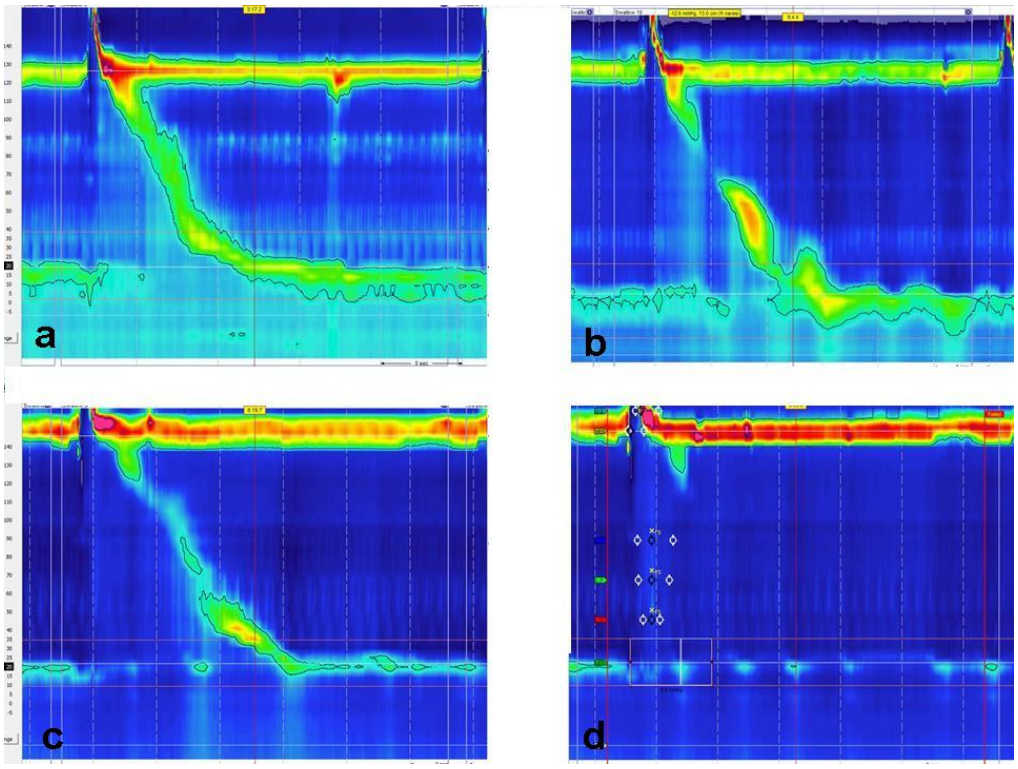


Figure 5.9: HRM motility patterns in JHS patients with dysphagia.
a- Normal motility (44%), b- weak peristalsis with small breaks (12%), c-weak peristalsis with large breaks (28%), d- frequent failed peristalsis (16%). Oesophageal hypomotility was present in 56%.

Consistent with the high prevalence of fragmented or failed swallows, the mean DCI, a measure of total contractile force, was low in 10 patients (40%), and in the remaining patients it was in the lower end of the normal range - Figure 5.10.

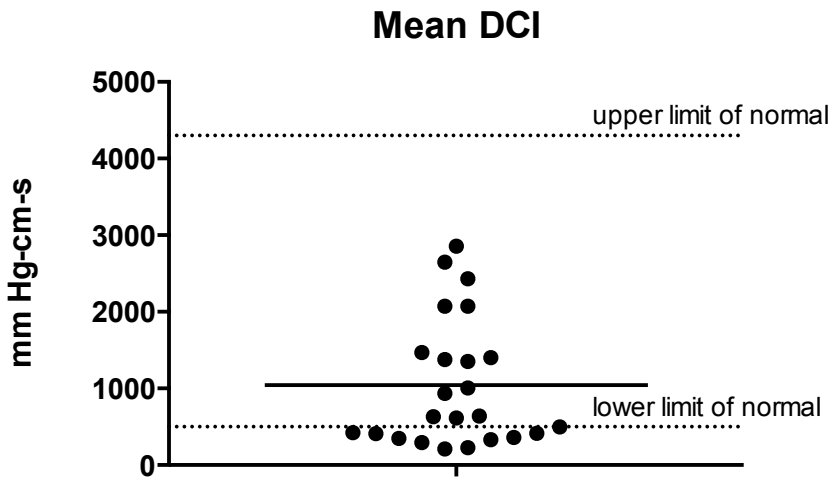


Figure 5.10: **Mean DCI in patients with JHS and dysphagia.**
Dotted lines represent the upper and lower limit of normal. None of the JHS patients had a high DCI, or hypertensive oesophageal contractions. 10 of the 25 patients had a very low DCI, consistent with oesophageal hypomotility.

To further characterise the oesophageal hypomotility the multiple rapid swallow (MRS) traces were examined. A normal MRS involves the complete relaxation of the LOS, inhibition of oesophageal contractions during the MRS and a high amplitude after-MRS contraction (Figure 5.11a). All patients with normal motility had a normal MRS response. Out of the 14 patients with hypomotility, 6 (43%) had an abnormal MRS response, with weak, fragmented after-contractions (Figure 5.11b). This suggested that in 43% of the patients with oesophageal hypomotility, there was a problem with the neuromuscular apparatus.

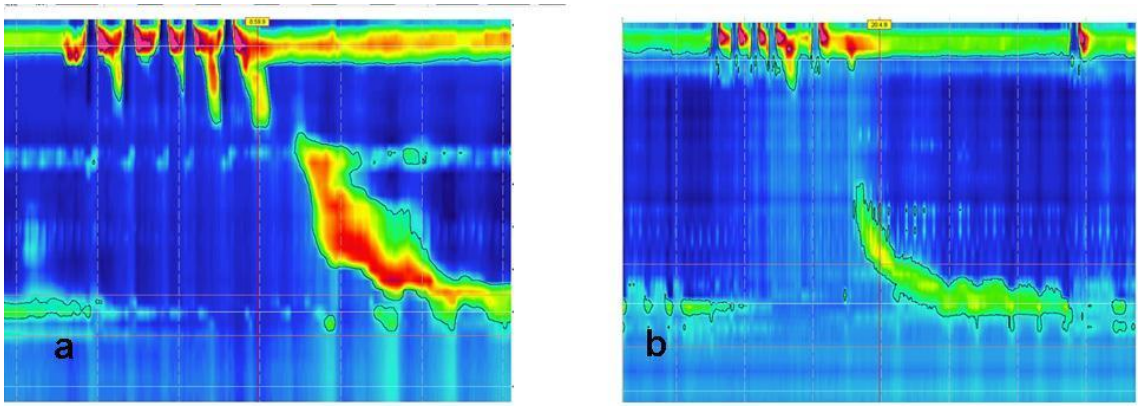


Figure 5.11: MRS responses in JHS patients with oesophageal hypomotility.
a- Normal MRS present in 8 (57%) patients, b- abnormal MRS with weak or fragmented after-MRS contractions in 6 (43%).

5.5.2.2 Comparison of motility patterns in JHS and non-hypermobile controls with dysphagia

In the 98 control patients with dysphagia, 47 had normal motility, 18 had hypomotility, 5 had absent peristalsis, 15 had achalasia, 10 had diffuse oesophageal spasm, 2 had hypertensive contractions and 1 had functional GOJ obstruction – Figure 5.12. The prevalence of normal oesophageal motility was similar in both groups, but the controls had a much larger range of motility patterns. Oesophageal hypomotility was significantly more common in the JHS patients (56% vs 18%, $p<0.001$). None of the JHS patients had achalasia and this was significant compared to the controls (0% vs 15%, $p=0.04$).

Of the 23 control patients with oesophageal hypomotility, 9 (39%) had an abnormal MRS response, which was no different to the prevalence in the JHS patients (43%, $p=1.0$).

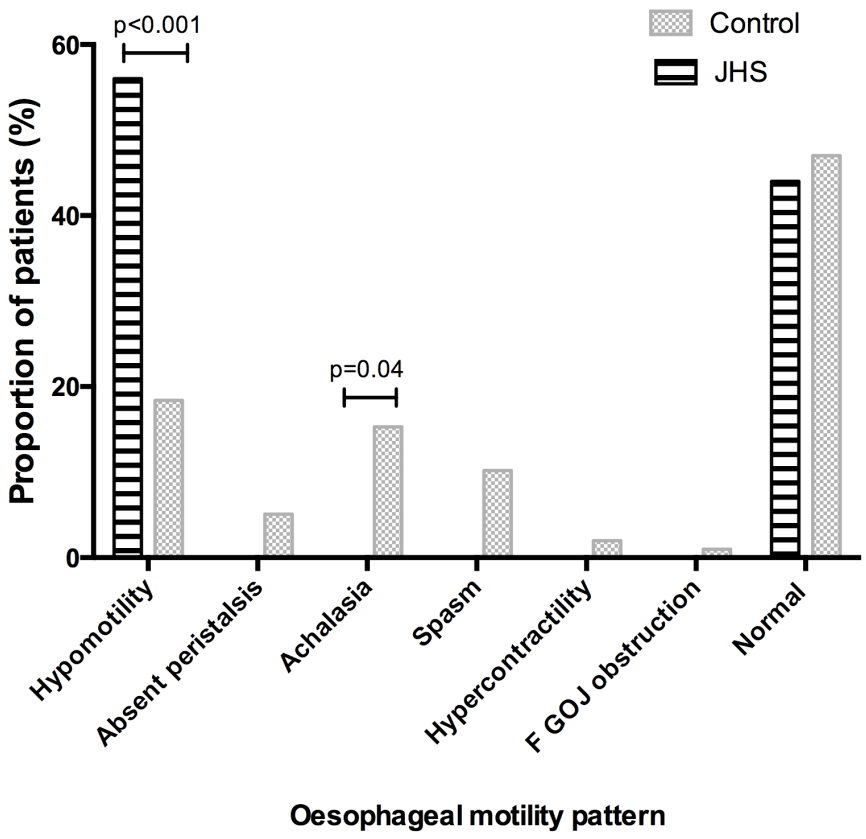


Figure 5.12: Comparison of HRM motility patterns in JHS and control patients with dysphagia.
There was significantly more hypomotility, and significantly less achalasia in JHS patients.

5.5.3 Reflux in JHS

The JHS patients had a range of reflux symptom scores - Figure 5.13. In general scores for regurgitation (12.3 ± 1.0) were higher than those for heartburn (9.1 ± 1.2). 26 patients had reflux symptoms (score>9), 1 of these did not have MII testing because of a latex allergy. Hence 25 patients were included in the analysis (92% female, age range: 18-62).

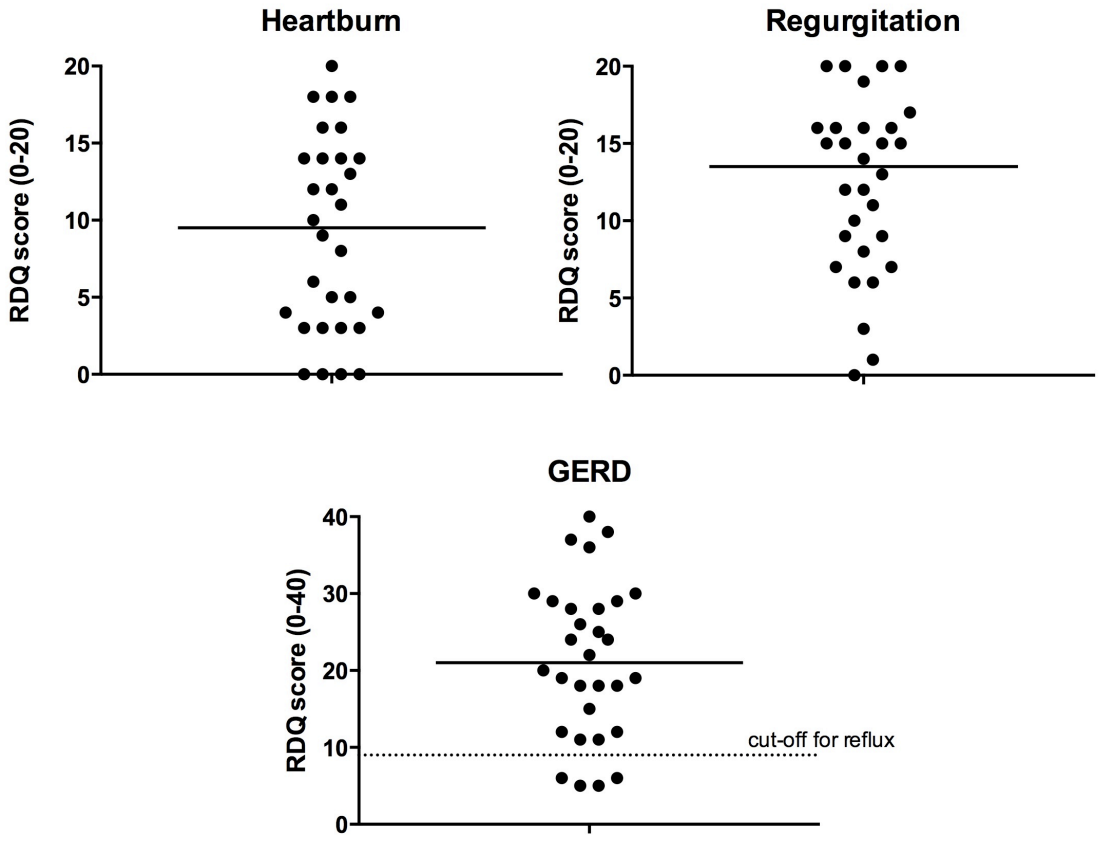


Figure 5.13: Symptom scores for heartburn, regurgitation and overall reflux (GORD) in JHS patients.
Bar represents the median score. The dotted line represents the cut-off score of 9 which is sensitive and specific for identifying the presence of reflux symptoms.

5.5.3.1 Reflux diagnoses in JHS and control patients

None of the 25 JHS patients had erosive reflux disease. 21 (84%) had NERD: 15 (60%) with high acid exposure, and 6 (24%) with hypersensitive oesophagus. The remaining 4 (16%) patients had functional heartburn. JHS patients with pathological reflux were more likely to have to have increased number of non-acid reflux episodes (53%) compared to acid reflux episodes (27%). In those with increased acid exposure, this was more likely to occur in the recumbent position (67%) compared to the upright position (40%).

Of the 108 control patients with reflux symptoms, 11 (10.2%) had erosive disease on endoscopy, 55 (50.9%) had increased acid exposure with no erosions (non erosive pathological GOR), 5 (4.6%) had hypersensitive oesophagus, and 37 (34.3%) had functional heartburn.

The prevalence of non-erosive pathological GOR was comparable in both groups (60% vs 51%, p=0.4). The prevalence of hypersensitive oesophagus was significantly increased in JHS (24% vs 5%, p=0.006). The prevalence of functional heartburn in JHS was low but this was not significant (12% vs 34%, p=0.07) - Figure 5.14.

9 (60%) JHS patients had isolated nocturnal reflux compared to 19 (35%) control patients but this was not significant (p=0.1).

HRM parameters in patients with non-erosive pathological GOR

To determine if there were differences in anatomical factors predisposing to reflux in JHS compared to the control patients, the presence of hiatus hernias, hypotensive LOS and hypomotility was compared in patients with non-erosive pathological reflux.

Only 3 (20%) JHS patients had a hiatus hernia compared to 25 (45%) control patients (p=0.08). 2 (13%) of JHS patients had a hypotensive LOS and this was no different to controls (29%, p=0.3). Although there was a higher prevalence of hypomotility in the JHS group compared to the controls (60% vs 34%, p=0.07) this only showed a trend.

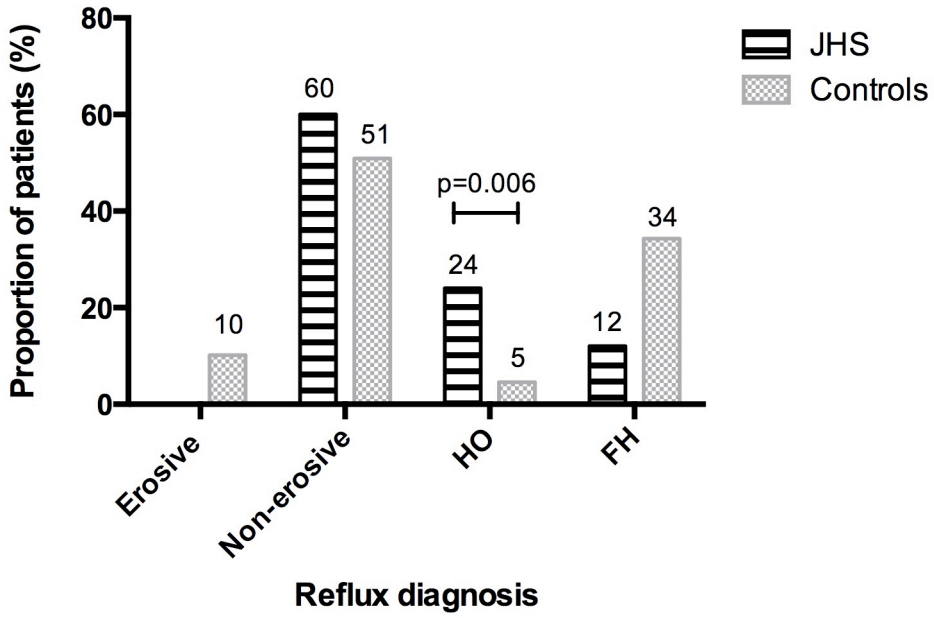


Figure 5.14: Reflux diagnoses in JHS and control patients.
JHS patients had significantly more hypersensitive oesophagus. The prevalence of NERD was high (>50%) in both groups. HO: Hypersensitive oesophagus, FH: Functional heartburn

5.5.4 Gastric emptying in JHS patients

16 JHS patients had gastric emptying testing as requested by their physician. The range of dyspepsia scores in these patients is shown in Figure 5.15. 2 patients (12.5%) had normal gastric emptying, and 14 patients (87.5%) had delayed gastric emptying.

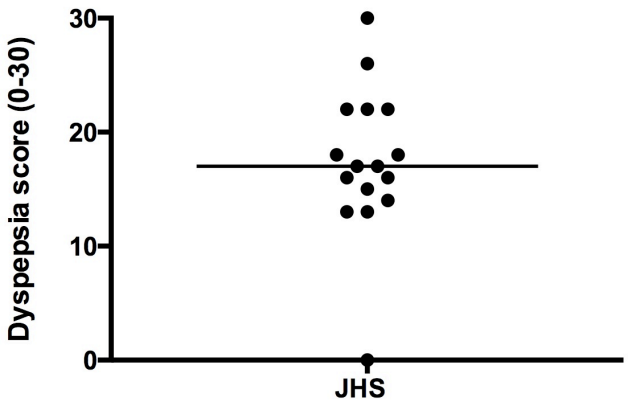


Figure 5.15: Dyspepsia scores in JHS patients undergoing gastric emptying testing.

In view of the association between orthostatic symptoms and postprandial distress syndrome demonstrated in Chapter 5, the prevalence of PoTS was compared in JHS patients with and without gastroparesis. PoTS was present in 10 (71%) of the JHS patients with delayed gastric emptying and 1 (50%) of the JHS patients with normal gastric emptying (p=0.5).

Gastric emptying in JHS patients with NERD

The prevalence of gastroparesis was also assessed in the subgroup of JHS patients with reflux. Of the 15 JHS patients with non-erosive pathological reflux, 7 had gastric emptying testing and all had delayed gastric emptying.

5.5.5 Distensibility testing of the GOJ

8 patients with reflux symptoms and NERD (7 female, age range 18-44) underwent endoflip testing of the GOJ - Figure 5.16. CSA - Pressure curves were plotted for each patient - Figure 5.17 - the slope of the curves represents GOJ distensibility. Control data from healthy subjects was obtained from another study as described in the methods section. This was plotted as a reference (Rohof, Hirsch et al. 2012).

GOJ distensibility appeared to be lower in JHS compared to healthy controls. Only 5 patients tolerated the full distension protocol to 50ml, so values of CSA, pressure and distensibility were compared at the 40ml distension volume. There was no difference in the CSA of the GOJ in JHS or controls (114.4 ± 15.71 vs 124.8 ± 26.5, p=0.5). However patients with JHS had higher intraballoon pressures (34.8 ± 2.4 vs 26.5 ± 1.3, p=0.01) and lower GOJ distensibility (3.5 ± 0.6 vs 5.0 ± 0.6, p=0.048).

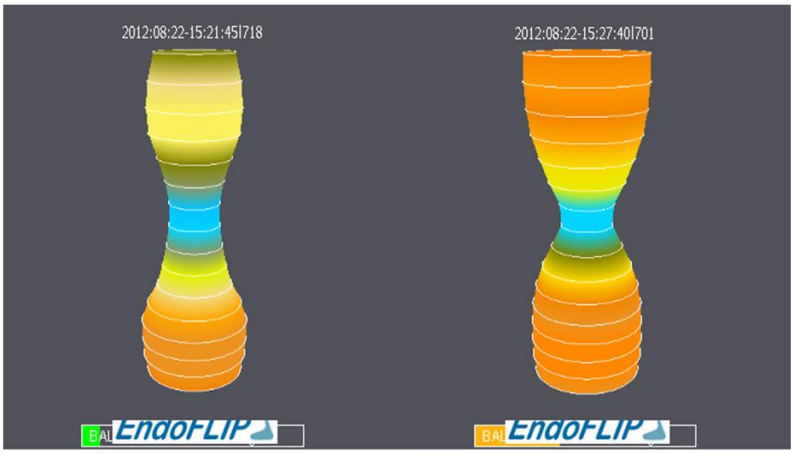


Figure 5.16: Appearances of endoflip testing of GOJ in a patient with JHS. Left: distension with 30ml water. Right: distension with 50ml water.

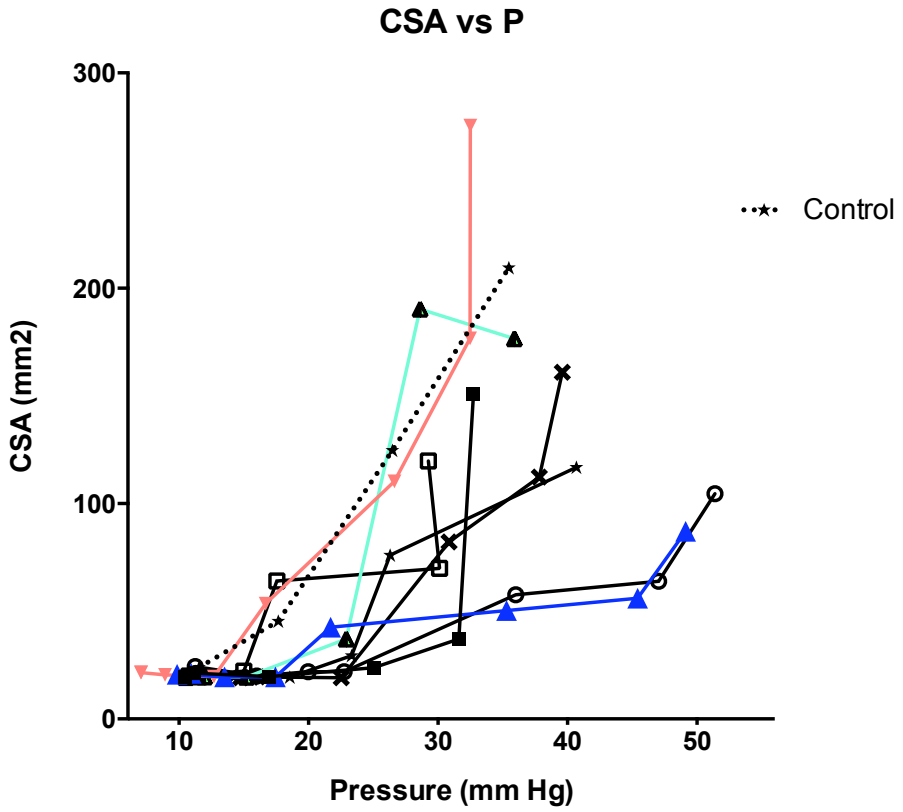


Figure 5.17: CSA Pressure curves representing GOJ distensibility for each patient.

The dotted line represents the CSA-Pressure curve for healthy subjects. JHS patients have lower GOJ distensibility compared to healthy subjects.

5.6 Discussion

The aim of this pilot study was to determine if physiological abnormalities were present in the stomach and oesophagus of JHS patients with symptoms of dysphagia and reflux. We discovered that (1) there was a high prevalence of oesophageal and gastric dysmotility in symptomatic patients, (2) most patients had true non-erosive reflux (NERD), as opposed to functional heartburn, and (3) there was no evidence of increased GOJ compliance in patients with JHS and reflux.

5.6.1 Dysphagia in JHS

Dysphagia in the JHS patients referred to the GI physiology unit was non-obstructive and none of the patients had radiographic or endoscopic evidence of obstruction. 2 patients had an incompletely relaxing LOS but even they had no evidence of true or functional obstruction on barium swallow.

56% of JHS patients with dysphagia had oesophageal hypomotility, and the prevalence of this motility pattern was significantly increased compared to the non-hypermobile controls with dysphagia in our study. It was also increased compared to a published study of 113 patients with dysphagia attending a GI physiology unit (Roman, Lin et al. 2011). In that study, 14% of the patients had weak peristalsis with large breaks, whereas in our JHS patients 7 of the 25 patients (28%) had this motility pattern (section 5.5.2.1). This suggests that the JHS patients with dysphagia do indeed have relatively more hypomotility compared to other patients with dysphagia.

Weak peristalsis, particularly in the presence of large breaks, and frequent failed peristalsis, as well as DCI values of less than 450 are associated with incomplete bolus clearance (Bulsiewicz, Kahrilas et al. 2009; Xiao, Kahrilas et al. 2012). In our study, 44% of patients had weak peristalsis with large breaks or frequent failed peristalsis, and 36% had DCI values less than 450mmHg-cm-s. Thus it is likely that incomplete bolus clearance may be present in about 40% of JHS patients with dysphagia, and may account for symptoms.

The cause of the oesophageal hypomotility in the JHS patients is unknown. The presence of hypomotility is known to be associated with erosive reflux disease, particularly Barrett's oesophagus (Porter, Kumar et al. 2012). However, none of the JHS patients in our study had erosive reflux disease and therefore this is not a potential explanation for the dysmotility. Another potential explanation comes from studies of the peripheral neuromusculature in JHS patients. These demonstrate that myopathic features of skeletal muscle can be present in JHS patients with myalgia and muscle weakness (Voermans, van Alfen et al. 2009). It is therefore possible that the oesophageal dysmotility is secondary to a primary myopathy or neuropathy of the smooth muscle of the oesophagus. From our study, it is not possible to determine if this is indeed the case. The presence of a normal MRS response on HRM in the majority of patients with oesophageal hypomotility would suggest that most patients have an intact neuromuscular apparatus (Fornari, Bravi et al. 2009). Future studies in those patients with abnormal MRS may help shed further light on the matter.

11 JHS patients with dysphagia had normal motility, and no manometric cause of dysphagia was found, thus in these patients the dysphagia was unexplained. As shown in Figure 5.14 hypersensitive oesophagus was relatively more common in JHS patients compared to controls. The presence of oesophageal hypersensitivity may provide an explanation for the dysphagia in a proportion of patients with normal oesophageal motility. Another possibility is that the dysphagia is more proximal and arises secondary to problems in the proximal striated muscle of the oesophagus or in the transition zone. In one study these type of abnormalities were present in 6% of patients undergoing HRM and in half of these patients it was associated with unexplained dysphagia (Ghosh, Janiak et al. 2008). This was not investigated in our study, but pharyngeal dysphagia in JHS, requiring referral to ENT specialists, has been documented in the literature (Rombaut, Malfait et al. 2011).

Thus it would appear that majority of JHS patients with dysphagia have associated oesophageal hypomotility, and that other factors such as oesophageal hypersensitivity or oropharyngeal dysphagia, may be important in the patients with normal HRM motility patterns, and these deserve further study.

5.6.2 Reflux in JHS

The majority of JHS patients with reflux symptoms had true reflux (NERD) and this is consistent with the association between JHS and NERD demonstrated in Chapter 4. Only 4 (16%) patients had functional heartburn, suggesting that most JHS patients with reflux symptoms do have physiological abnormalities which can account for symptoms. The majority of patients with NERD had increased acid exposure, and this was more likely to occur when patients were

recumbent (67% of patients) compared to when they were upright (40%). Furthermore, in those with pathological acid exposure, only 27% had a high number of reflux episodes, suggesting that most episodes were long lasting to account for the high acid exposure. In terms of possible mechanisms for the reflux, a small hiatus hernia and a hypotensive LOS were only present in a small proportion of patients (3 and 2 patients out of 15 respectively). Oesophageal hypomotility was present in 60% of these patients and gastroparesis in 7 out of the 7 patients studied, and these may have contributed to decreased clearance of acid from the oesophagus, and increased volume of potential refluxate respectively. Putting this all together it would appear that in a significant proportion of JHS patients, pathological reflux may be due to long-lasting nocturnal episodes, exacerbated by incomplete acid clearance secondary to oesophageal hypomotility, and by the presence of gastroparesis, particularly in the presence of a hypotensive LOS.

Compared to non-hypermobile controls, JHS patients were significantly more likely to have hypersensitive oesophagus (24% vs 5%, p=0.006), though this finding may be a consequence of the surprisingly low prevalence of hypersensitive oesophagus in our control patients. In a published study of 200 patients with endoscopy negative reflux, 32% had hypersensitive oesophagus (Savarino, Pohl et al. 2009), which suggests that the prevalence of hypersensitive oesophagus seen in the JHS patients is no different to that in other patients with reflux symptoms.

The prevalence of hiatus hernias in JHS patients was surprisingly low, being present in only 6 out of the 25 JHS patients with reflux symptoms. Most of these

hernias were very small, and often disappeared halfway through the HRM study. This low prevalence was contrary to our expectations, partly because the presence of hernias form part of the Brighton criteria for diagnosis of JHS, and because an association between hypermobility and hiatus hernias has previously been demonstrated (Al-Rawi, Al-Dubaikel et al. 2004). However in that study, the diagnosis of hiatus hernias was made on endoscopy and not manometry, and the term 'hypermobility' referred to a high beighton score, which is simply a measure of joint hyperflexibility and not necessarily synonymous with JHS.

The last section of the results included preliminary pilot data relating to GOJ distensibility in the JHS patients. This was simply an observation in a very small sample using a newly acquired tool, and was designed to assess for any gross differences in visceral compliance in the JHS patients compared to healthy controls. GOJ distensibility at a 40ml distension volume was significantly lower than that in healthy controls and more comparable to the GOJ distensibility observed in successfully treated achalasics (Rohof, Hirsch et al. 2012). This was a surprising finding and contrary to our assumed hypothesis, and suggests that pathological GOR in JHS is not due to increased GOJ distensibility.

5.6.3 Limitations

The main limitation of the study was the small size of the JHS group, which made comparisons difficult, particularly for the endoflip testing. However, the study was designed to be pragmatic and to simply provide initial observations that may help tailor future studies in a larger number of patients.

6.1.1 Clinical implications.

The findings in his study have implications for the clinical management of JHS patients with dysphagia and reflux symptoms. In the absence of obstructive causes for dysphagia, the need for oesophageal dilatation in these patients can be excluded, leaving treatment to pharmacological agents. In view of the hypomotility, prokinetics such as domperidone may be useful, particularly for those patients with a normal MRS response.

For the patients with reflux, the absence of large hiatus hernias and the high prevalence of hypomotility make anti-reflux surgery a less attractive option than pharmacological measures, particularly in patients with poor MRS response. A combination of prokinetics for the dysmotility, neuromodulators for the hypersensitivity, and lifestyle changes, is likely to be more efficacious.

6.1.2 Patho-aetiological implications

The high prevalence of GI dysmotility in these patients has implications for the underlying aetiology of JHS, which is as yet unknown. The dysmotility, in the absence of gross differences in compliance, would suggest an underlying myopathy or neuropathy. As described before, such features have been observed in skeletal muscle and it is possible that a similar process is taking place in the smooth muscle. In view of our observations in Chapter 2 that upper GI symptoms are mediated by autonomic and somatic factors, it is possible that the mechanism for the dysmotility involves abnormalities in autonomic nerves or in sensory afferents. The possibility of autonomic involvement is supported by

the fact that 10/14 (70%) patients with oesophageal dysmotility and with gastroparesis had POTS. This requires future study.

6.2 Conclusion

It is thus clear, that the majority of patients with JHS and upper GI symptoms do have abnormal GI physiology, particularly dysmotility in the stomach and oesophagus, and that this is not too dissimilar to the physiological patterns found in other connective tissue disorders such as scleroderma and Sjogren's syndrome. Future studies will need to explore the possible mechanisms for this, focussing on autonomic and sensorimotor aetiologies. In this small group of patients, compliance of the GOJ did not seem to be increased. However, compliance of visceral tissue at other locations will need to be assessed before the possibility of biomechanical abnormalities in these patients can be discounted.

Chapter 6

General Discussion

Research to discover the aetiology of FGID has so far not been fruitful, and this is thought to be due to the heterogeneous nature of the condition and that attempts to divide FGIDs into symptom-based ROME subcategories may not have resulted in aetiologically meaningful subgroups. Preliminary observations from previous studies suggest an overlap between JHS, a non-inflammatory connective tissue disorder, and FGID. Confirmation of this overlap would provide an identifiable and homogenous phenotype of patients who are predisposed to FGID, and will thus facilitate progress in understanding the aetiology of FGID, at least in a subgroup of patients.

My aim in this thesis was to determine if an association exists between JHS and FGID. Furthermore, I aimed to fully characterise the range and prevalence of GI symptoms in JHS in health and in disease, to determine the influence of various aetiological factors on these symptoms, and to determine if physiological abnormalities were associated with GI symptoms in these patients.

I have addressed all these aims through a systematic series of epidemiology studies in 3 groups of JHS patients: patients with established JHS which represented a forme fruste of the condition (JHS-Rh); healthy students who were previously unaware that they had JHS (a blinded non-patient sample); and new patients attending GI clinics who were previously unaware that they had

JHS (JHS-G: blinded unselected patient sample). For each of these JHS groups, an appropriately matched control group without JHS was selected.

6.1 JHS and GI symptoms

6.1.1 JHS and Dyspepsia

The most conclusive finding was an association between postprandial dyspeptic symptoms and JHS. In Chapter 2, I demonstrated that in tertiary care patients with established JHS and GI symptoms, the prevalence of postprandial distress symptoms (i.e. early satiety and postprandial fullness) is significantly increased compared to that in other patients with GI symptoms, but without JHS. In Chapter 3 I further demonstrated that these dyspeptic symptoms are also significantly increased in healthy students with JHS compared to those without JHS, suggesting that the association is related to JHS and not to factors associated with being a tertiary care patient. Furthermore, in Chapter 4 I have shown in a large case control study of over 600 new patients attending GI clinics that JHS is associated with postprandial distress syndrome (PDS). The validity of these findings is strengthened by the fact that they have been reproduced in different groups of patients as well as in non-patients. Moreover, as most studies have been performed in subjects unaware of their JHS status, these results are less likely to be influenced by response bias. Furthermore they are consistent with the preliminary observations in the literature in patients attending non-GI clinics, adding further support to the validity of these findings.

6.1.2 JHS and Gastro-Oesophageal Reflux Disease

Other GI associations that were demonstrated for JHS were not as clear-cut. There appears to be an association between JHS and reflux disease,

particularly with non-erosive reflux disease (NERD). In Chapter 2, I demonstrated that patients with established JHS have significantly increased regurgitation compared to other GI patients, and in Chapter 4 I demonstrated that in patients newly referred to GI clinics there was a significant and independent association between JHS and NERD. This association was not however demonstrated in healthy students so it is difficult to conclude whether the association between JHS and gastro-oesophageal reflux is to do with all JHS groups, or only to those individuals who become patients.

6.1.3 JHS and IBS symptoms

Lastly, I demonstrated in Chapter 2 that patients with established JHS also had significantly increased IBS-type symptoms with increased abdominal pain, bloating and alternating bowel habit compared to other GI patients. However no such association between JHS and these symptoms was demonstrated in the non-patient sample in Chapter 3, nor was an association between JHS and IBS disorders demonstrated in Chapter 4. This suggests that either this association is only relevant to those JHS patients who have previously consulted a rheumatologist i.e. those with severe symptoms and musculoskeletal involvement, or that the association of JHS with these symptoms is due to another confounding factor. However, in Chapter 2 I demonstrated that the association between JHS and alternating bowel habit, abdominal pain and bloating was independent of all other measured factors including medication use, psychopathology, autonomic and somatosensory factors, suggesting that these factors were not confounding the association. A final explanation is that the association with IBS symptoms is only present in tertiary JHS patients, and indeed the presence of IBS-type symptoms has been reported in several

tertiary JHS patient groups including those attending rheumatology, urology and genetics clinics (Manning, Korda et al. 2003; Hakim and Grahame 2004; Castori, Camerota et al. 2010; Rombaut, Malfait et al. 2011). Hence it would seem that these IBS symptoms are only relevant in a subgroup of JHS patients, possibly those with a more severe presentation with musculoskeletal involvement, and attending tertiary care.

6.2 Factors mediating the association between JHS and GI symptoms

One of the aims of the research was to explore, using epidemiology techniques, what factors might be involved in the association between JHS and GI dysfunction. Previous studies have postulated that GI and extra-articular symptoms in JHS are due to either medication use, deconditioning, genetic factors or autonomic factors (De Wandele, Rombaut et al. 2013). In addition, somatisation and psychopathology are strongly linked to both JHS and to FGID (Table 1.6) and therefore also have to be considered as a possible explanation for the GI symptom association in JHS. By demonstrating excess GI symptoms in JHS students, none of whom were on opiates and all of whom were active and healthy, medication and deconditioning can be excluded as main reasons for the association between JHS and GI symptoms. Using multiple logistic regression analysis in the epidemiology studies in Chapters 2-4, it was evident that anxiety was not involved in the association between JHS and GI symptoms in any of the JHS groups. This suggests that despite the fact that anxiety is strongly linked to JHS (Bulbena, Gago et al. 2011) and that anxiety is known to be associated with several FGID, anxiety is not the explanation for the GI

manifestations in JHS. This leaves the possibility of autonomic, genetic or somatisation factors.

It was clearly demonstrated that autonomic symptom scores, number of positive tender points and somatisation scores (PHQ15) were significantly increased in the JHS subjects in all the different groups, including the healthy students, confirming previous observations that these symptoms are inherently associated with JHS (Gazit, Nahir et al. 2003; Baeza-Velasco, Gely-Nargeot et al. 2011; Castori 2012), and suggesting that they were potentially responsible for the GI association seen. This was explored further using multiple logistic regression analyses which demonstrated that autonomic factors, and to a lesser extent somatisation factors were involved in the association between JHS and postprandial symptoms. The degree of involvement varied depending on the JHS group. In the rheumatology patients with established JHS, the presence of autonomic and somatic symptoms completely accounted for the association seen with postprandial symptoms. In the unselected GI patient group (Chapter 4), autonomic factors completely accounted for the association between JHS and PDS, but somatic factors did not. In the student study in Chapter 3, the presence of postprandial satiety was partly accounted for by autonomic factors (particularly orthostatic factors) but somatic factors were not involved (Table 3.6).

6.2.1 Autonomic factors and GI symptoms in JHS

Putting this all together, it would appear that autonomic factors are consistently involved in the association between JHS and postprandial symptoms, and that this involvement is very significant in established JHS patients with severe

disease, and that it is less important in healthy students who have milder disease and who are non-patients. Interestingly, out of all the autonomic domains it was the orthostatic domains which were most important in mediating the postprandial symptoms in all three studies (Chapter 2-4). Evidence from the literature on PoTS supports this finding. Orthostatic symptoms are the hallmark of PoTS and in these patients, postprandial symptoms are common (Mathias, Low et al. 2011), regardless of whether or not they have coexistent JHS. Furthermore, it has been demonstrated that PoTS is associated with increased variability of the gastric pacemaker rhythm pre and post-prandially, and that in patients with GI symptoms, the postprandial changes are more marked (Seligman, Low et al. 2012). In view of the fact that gastric pacemaker activity is integral to the coordinated motor activity of the stomach, it is possible that the presence of this altered pacemaker variability leads to gastric dysmotility, particularly postprandially. Indeed, as demonstrated in Chapter 5, gastroparesis is present in a large proportion of JHS patients with postprandial symptoms and that the majority of patients with gastroparesis had PoTS.

Therefore it is possible that as JHS severity increases and the presence of PoTS increases, this will be associated with altered pacemaker activity, gastroparesis and therefore postprandial symptoms, and eventually a diagnosis of postprandial distress syndrome. This is simply a hypothesis and will need to be tested in much larger studies of JHS patients and suitable control groups.

6.2.2 Somatic factors and GI symptoms in JHS

The partial involvement of somatic sensitivity factors (somatisation) in the association between JHS and GI symptoms was interesting, as it was much

less important than initially expected to be. Although the definition of somatisation is vague, there is consensus that it refers to the presence of multiple somatic symptoms, and that this can be measured by various questionnaires such as the PHQ15 questionnaire which was used in our study. It is clear from our study and previous studies (Baeza-Velasco, Gely-Nargeot et al. 2011) that the presence of JHS is associated with higher levels of 'somatisation' or higher somatic symptom scores than in non-JHS patients, and that it is associated with several functional somatic syndromes, such as fibromyalgia, chronic fatigue syndrome and FGID. What is less clear, and perhaps more interesting, is what somatisation really refers to. In fact, the definition of somatisation is currently undergoing dramatic change. Somatisation was initially considered a psychiatric condition, characterised by the presence of multiple clinically significant complaints about gastrointestinal, sexual, pseudoneurological and pain symptoms in the absence of clear organic pathology, and it was considered a manifestation of emotional distress. According to this psychological definition of 'somatisation', it was thought that the presence of multiple somatic symptoms, and functional somatic disorders e.g. FGID, were 'psychosomatic'. That is, they were simply psychological with no physiological basis.

Applying this psychological explanation of somatisation to the association between JHS and FGID would suggest that the presence of FGID in JHS would be strongly associated with psychopathology and not with demonstrable physiological abnormalities on testing. This is clearly not the case. Firstly, it is evident that the association between JHS and GI symptoms are present even in healthy students, who do not have anxiety and depression. Secondly, in patient

studies (Chapter 2 and 4) the association between JHS and GI symptoms and disorders was independent of psychopathology. Thirdly, physiological abnormalities were in fact demonstrated in the majority of symptomatic JHS patients in our physiology study (Chapter 5). Hence, the psychosomatic explanation for the higher somatic symptom scores and for increased prevalence of functional somatic syndromes does not appear to hold true, at least for FGID.

More recent explanations for 'somatisation' suggest that these disorders are not all 'in the mind', but rather that some yet undiscovered common aetiology underlies them all (White 2012). Various factors had been put forward, and these include pain hypersensitivity and changes in autonomic processing, both of which have been documented in association with symptoms in patients with functional somatic syndromes. As an example, patients with FM have abnormal autonomic responses to exercise (da Cunha Ribeiro, Roschel et al. 2011) and that in both patients with IBS and those with FM, these abnormal autonomic responses are associated with somatic hyperalgesia (Chalaye, Goffaux et al. 2012). Thus an alternative explanation for the presence of multiple somatic symptoms in JHS may be that these patients have abnormal or altered pain processing and that this itself may be secondary to autonomic dysfunction. This proposed explanation for the high prevalence of functional somatic syndromes in JHS has been put forward by other authors (Castori, Celletti et al. 2011), but has not yet been proven. Investigating this further, and exploring the link between pain processing, dysautonomia and functional somatic syndromes in JHS may further our understanding of the mechanisms underlying FGID in the subgroup of patients who suffer with multiple unexplained syndromes.

6.2.3 Biomechanics and altered sensori-motor function

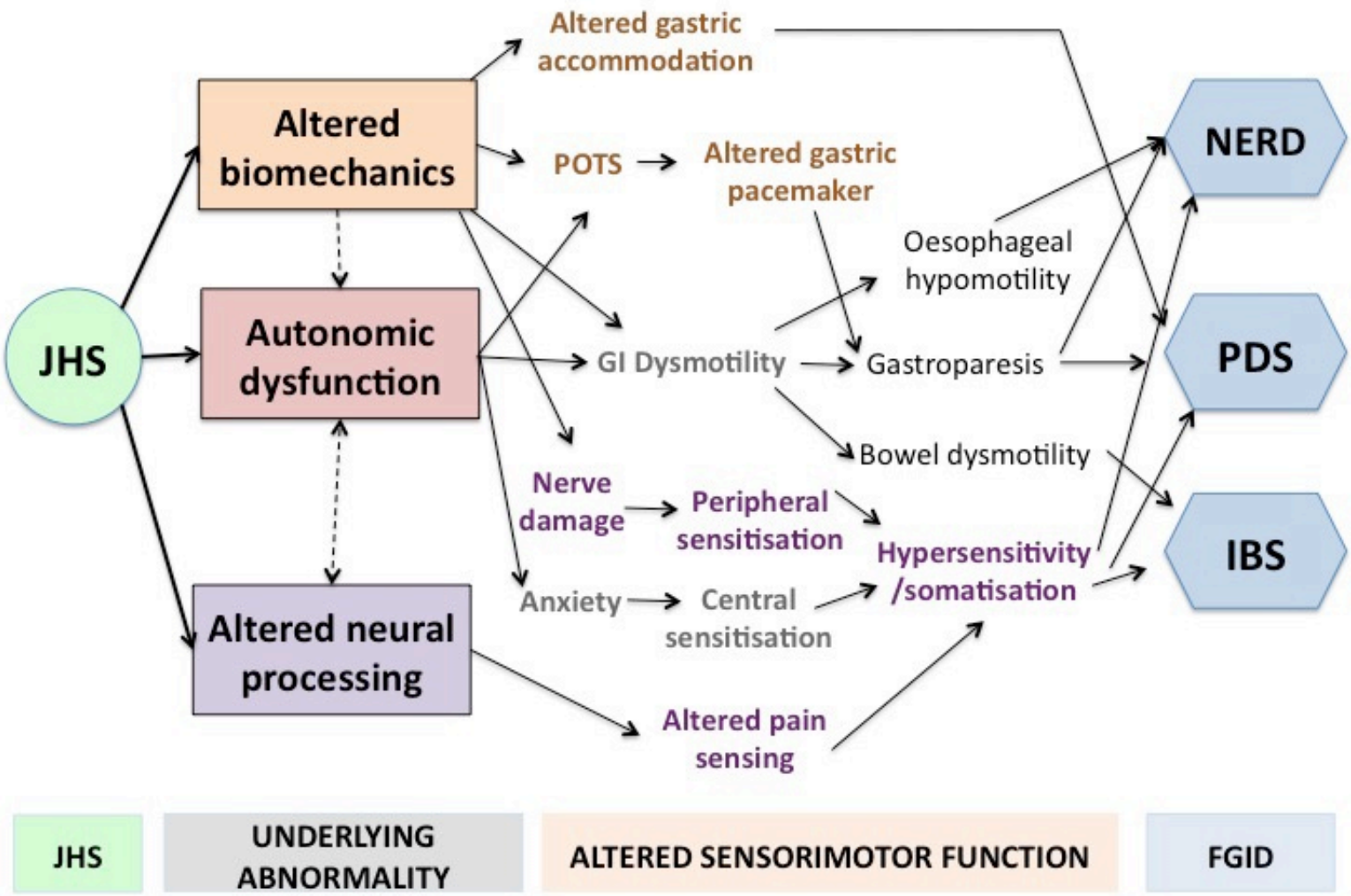
In the case of functional dyspepsia, somatic and autonomic factors seem to be important, and may be working via a shared pathway. In contrast, these factors do not seem to be responsible for the association seen with NERD and with IBS-type symptoms. In the case of NERD, one possibility includes altered compliance of the gastro-oesophageal junction, which has previously been shown to be associated with reflux (Kwiatek, Pandolfino et al. 2010). However in our limited study of 8 patients, we did not find this to be the case. This study will need to be repeated in a larger number of patients and at other locations in the GI tract before the biomechanical theory can be discounted. For the IBS-type symptoms, one possible mechanism is altered sensori-motor function. This was clearly associated with upper GI symptoms in the JHS patients in Chapter 5, but has not been studied in relation to the lower GI tract.

6.3 Schematic for mechanism of GI symptoms in JHS

It would appear therefore that the aetiology of GI symptoms in JHS is multifactorial, and involves at least the following 3 underlying processes: autonomic dysfunction, altered pain sensitivity, and altered biomechanics, either working alone or in combination with each other. It would also appear that the relative contribution of each of these factors varies depending on the type of symptoms, severity of disease and patient type. All these factors are assumed to result in altered sensori-motor function and therefore a functional, as opposed to organic, GI disorder. It can be postulated that altered sensori-motor function results in the symptoms of heartburn and regurgitation in NERD, nausea and postprandial satiety in PDS and bloating, altered bowel habit and abdominal pain in IBS. A hypothetical mechanism by which these factors lead

to these FGID subtypes is illustrated in Figure 6.1. The individual processes are described below.

Figure 6.1: Schematic for mechanism of GI symptoms and aetiology of FGID in JHS


Altered gastric accommodation
Altered biomechanics
POTS
Altered gastric pacemaker
NERD
Oesophageal hypomotility
JHS
Autonomic dysfunction
GI Dysmotility
Gastroparesis
PDS
Bowel dysmotility
Nerve damage
Peripheral sensitisation
Hypersensitivity /somatisation
IBS
Anxiety
Central sensitisation
Altered neural processing
Altered pain sensing
JHS
UNDERLYING ABNORMALITY
ALTERED SENSORIMOTOR FUNCTION
FGID

6.4 Processes underlying FGID in JHS

6.4.1 Autonomic dysfunction and dysmotility

Autonomic dysfunction would appear to be integral to the whole schema, as it was most important in all the regression analyses presented in this thesis, and appears to be strongly associated with JHS, both in health and disease. The autonomic dysfunction in JHS is likely to be of two types – pure orthostatic dysfunction (PoTS), and generalized autonomic dysfunction. The latter would result in GI dysmotility and would lead to various symptoms depending on which part of the GI tract was involved. Oesophageal dysmotility would result in impaired clearance of acid reflux and predispose JHS individuals to gastro-oesophageal reflux disorders, such as NERD, particularly at night, when swallowing is reduced. Gastroparesis, is implicated in both NERD and PDS, and would result in postprandial symptoms. Small bowel dysmotility predisposes to small bowel bacterial overgrowth, which leads to symptoms of bloating, diarrhoea and abdominal pain, all features of IBS.

In Chapter 5 I demonstrated that oesophageal hypomotility and gastroparesis were common in symptomatic JHS patients, particularly in those with autonomic dysfunction. Although my work did not investigate small bowel motility, there is literature to suggest that small bowel dysmotility is indeed present in patients with JHS and abdominal pain and bloating (Zarate, Farmer et al. 2009). Future work can focus on reproducing and refining these motility findings in larger numbers of patients, and correlating this with autonomic function.

PoTS is associated with increased variability of the gastric pacemaker rhythm (Seligman, Low et al. 2012), and this in turn may lead to gastroparesis which

may consequently explain the postprandial and regurgitation symptoms in JHS. Whereas dyspepsia is associated with delayed gastric emptying in the antrum, regurgitation and NERD is thought to be associated with delayed gastric emptying in the fundus (Karamanolis, Caenepeel et al. 2007). Thus the location of the gastric dysmotility may explain the various upper GI symptoms. To confirm this and to further our understanding of the consequence of the gastric myoelectric changes in PoTS, motility testing in both the proximal and distal stomach, and with both solids and liquids independently, would need to be assessed.

6.4.2 Altered sensory processing and visceral hypersensitivity

It is clear that both patients and healthy individuals with JHS have a higher prevalence of somatic symptoms and chronic pain than their non-JHS counterparts (Chapter 2 and 3); (Baeza-Velasco, Gely-Nargeot et al. 2011; Castori, Morlino et al. 2012). As described earlier, this is suggestive of an underlying hypersensitivity or pain-sensing problem. If this sensory abnormality is generalized, then it would be expected to cause both somatic and visceral hypersensitivity. The latter could explain reflux symptoms (oesophageal hypersensitivity), dyspeptic symptoms (gastric hypersensitivity) and abdominal pain and bloating (visceral hypersensitivity of the bowel).

Hypersensitivity in JHS is likely to arise due to sensitization at both a peripheral and central level. At a peripheral level, alterations in the biomechanical properties of tissue can potentially cause undue stretch and strain, leading to sensitization of the nerves peripherally. Central sensitization can arise secondary to anxiety and hyperarousal states, which themselves can be a

consequence of dysautonomia, which is known to be present in JHS. It is also possible that in JHS, alterations in connective tissue surrounding nerve plexuses, lead to altered neural processing, potentially leading to altered pain sensing or increased pain. These underlying processes are not specific to FGID but can also be implicated in the other functional somatic syndromes characterized by hypersensitivity, such as chronic pelvic pain and fibromyalgia. This common underlying process occurring in various somatic and visceral tissues may represent the common mechanism that links the many functional somatic syndromes, and may explain why individuals can have multiple pain syndromes.

Clearly these are simply hypotheses at present, and will need to be tested in future studies, focusing on sensitivity testing of different parts of the GI tract, and correlating this with sensitivity testing of somatic sites e.g. skin and muscle, and with autonomic function.

6.4.3 Altered biomechanics

It is clear from the regression analysis in Chapter 3 that some GI symptoms (particularly abdominal pain, bloating and alternating bowel habit) are not significantly affected by autonomic or somatic factors. This suggests that some other mechanism may be more important for these symptoms. One possibility relates to altered biomechanics. It has been consistently demonstrated that patients with JHS have altered biomechanics of their skin and joints, and it is not inconceivable that a similar process could occur in the viscera.

It is clear from patients with scleroderma, that alterations in the connective tissue structure of the GI tract leads to alterations in the biomechanical properties of the gut (Gao, Liao et al. 2009), and that this in turn has a direct effect on motility and tone of the gut (Gregersen, Villadsen et al. 2011; Frokjaer, Brock et al. 2012). Furthermore, it is known that in patients with functional dyspepsia, abnormal gastric accommodation is associated with hypersensitivity. Thus there is evidence that biomechanical abnormalities in the GI tract are associated with alterations in both sensation and motility of the gut. Therefore it is possible that if the underlying connective tissue disorder in JHS does indeed affect the biomechanics of the GI tract, then this would provide another explanation for some of the functional GI symptoms in JHS.

Although no such biomechanical abnormalities were detected on preliminary testing of a very small number of subjects in Chapter 5, this would need to be repeated in larger numbers of patients in different parts of the GI tract and in relation to both upper and lower GI symptoms, before it can be completely discounted.

6.5 Investigating the aetiology of FGID in JHS

Now that an association between JHS and FGID has been demonstrated, the focus can shift to elucidating the exact mechanisms by which this occurs at a physiological, biomechanical, molecular and genetic level, and to test the hypothetical mechanisms illustrated in Figure 6.1. This would need to be done systematically, using a translational approach with both human and animal studies.

Firstly, one would need to confirm using physiological studies that GI dysmotility, visceral hypersensitivity and visceral biomechanical abnormalities do indeed exist in individuals with JHS. In addition to the standardised historical techniques that have been developed to test for all these, recent advances in radiology and physiological testing means that less invasive techniques such as functional magnetic resonance imaging for motility, and the use of the smartpill capsule for motility testing, can also be used, thus increasing the willingness of the patients to comply with these tests. It would also be useful to characterise the GI symptoms, FGID subtypes and non-GI characteristics that are associated with the above abnormalities, as this will enable categorisation of a very heterogenous group of JHS individuals into more homogenous phenotypes, which will be useful when doing genetic or molecular studies later on.

Secondly, one would need to demonstrate that the above-mentioned physiological abnormalities are responsible for the symptoms. That is, that they are present in symptomatic JHS individuals and not asymptomatic ones, and that by treating the underlying process, the symptoms improve. To do this would require interventional studies, involving symptomatic JHS patients and asymptomatic JHS controls, all of whom undergo motility, sensitivity and distensibility testing, and then are randomised to treatment or no treatment for the underlying abnormality, all the while making a detailed assessment of symptom severity.

Thirdly, it would be useful to assess the temporal order by which symptoms and physiological abnormalities develop and also to identify risk factors which

predict the development of FGID in JHS individuals. This would require longitudinal cohort studies. It would be important that the cohort be followed up from a very young age, as it is evident from the literature that some of the complications associated with JHS occur very early on in life.

The final step would be the investigation of the aetiology of the above processes. This is perhaps the most difficult step, particularly in view of the fact that the aetiology of JHS itself has not yet been determined. This may, in part, be due to the fact that JHS is heterogeneous in aetiology, that connective tissue biology is extremely complicated and that abnormalities in a whole variety of connective tissue enzymes and proteins can lead to the same endpoint i.e. abnormal connective tissue. This is where stratifying JHS individuals into very homogenous groups may enable more meaningful conclusions to be drawn. This is particularly important for genetic studies, particularly as genome wide association studies have so far failed to find candidate genes which are responsible for JHS. Newer techniques such as exome-sequencing can be used for 'JHS families', however once again, it is important that the affected family members have a similar phenotype, which is generally not the case.

It is important to bear in mind that even if a candidate gene were to be found, this is not necessarily meaningful. Epigenetics suggests that the environment has a huge effect on the expression of genes, and that this is a fairly dynamic process. Thus it may be more useful to look at abnormalities in expressed proteins, as opposed to abnormalities in the genes. This is where translational studies will be very informative.

Animal models of JHS exist, and these can be used to develop our understanding of the macroscopic and microscopic connective tissue and biomechanical abnormalities present in the GI tract in JHS. To ensure that the animal models are sufficiently comparable to humans, motility and autonomic function should be tested first in these animal models to ensure they are similar to findings in humans. Provided that this is the case, in vivo, ex vivo and in vitro biomechanical studies of different parts of the GI tract can be assessed. Using immunohistochemistry, a quantitative and qualitative assessment of the structure of different connective tissue components can be assessed, and their relationship to various neuronal components in the bowel can be determined. 3D electron microscopy can yield further information at an ultrastructural level. Single nerve recordings can be used to determine how the nerves function in response to biomechanical stimuli. These findings can then be compared to that in GI tissue obtained from JHS patients undergoing bowel resections or endoscopic biopsies to enable a fully translational model to be built.

Understanding all this will not only result in a better understanding of the pathological processes underlying GI dysfunction in JHS patients, but more importantly, will further our understanding of the role of connective tissue in the GI tract in health and in disease, something which for many years has remained a relative enigma. This will have implications on our understanding and treatment of the GI aspects of a variety of connective tissue disorders, both inflammatory and non-inflammatory, and hopefully have the potential to lead to the development of new pharmacological agents in the future.

6.6 Clinical implications of the association between JHS and FGID

Aside from the exciting research implications described above, the novel findings in my PhD have several clinical implications.

It is evident from the studies in Chapters 3 and 4 that quality of life in JHS individuals who have not yet seen a rheumatologist and have not had a formal diagnosis of JHS was relatively preserved, even in the presence of GI symptoms. In comparison, patients with an established diagnosis of JHS had very poor general health, and physical and social functioning, compared not only to GI patients without JHS but also to other JHS patients seen at tertiary care centres (Rombaut, Malfait et al. 2010). This suggests that earlier recognition and management of JHS and its associated complications may enable intervention at an earlier stage before the patient becomes moribund from a physical, social and emotional point of view.

The presence of JHS in GI clinics provides gastroenterologists with an ideal opportunity to diagnose this condition early and initiate multidisciplinary management at this early stage. In view of the fact that the prevalence of JHS is very high in PDS and in NERD, the diagnosis of JHS should be considered in patients with these GI disorders, particularly if they have rheumatological symptoms with or without other functional somatic syndromes such as fibromyalgia and chronic fatigue syndrome. If autonomic factors are indeed involved in the aetiology of PDS in JHS patients, then treating the autonomic problem may also help treat the PDS. Although anecdotal evidence suggests that this may be the case, it has not been formally studied. In any case, it is

worth enquiring about the presence of autonomic symptoms in JHS patients with upper GI symptoms, and referring patients to an autonomic specialist if these symptoms are present.

The discovery of this novel link between JHS and FGID is extremely exciting. It is hoped that this will lead to a paradigm shift in our approach to FGID and other medically unexplained disorders. This is absolutely critical if we are to tackle the false preconceptions surrounding the medically unexplained disorders, remove the stigma associated with them and improve lives for the millions of patients who suffer unnecessarily with these.

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