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Healthcare Utilisation and Healthcare Costs for patients with Hypermobile Spectrum Disorders and coexisting Functional Dyspepsia and/or Irritable Bowel Syndrome

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CONFLICTS OF INTEREST

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WHAT IS ALREADY KNOWN ON THIS TOPIC:

- Healthcare utilisation and healthcare costs are significant in patients with one or more Disorder of Gut-Brain Interaction (DGBI) and are increased in patients with multimorbidity, polypharmacy and foregut disorders.
- Patients with Hypermobile Ehlers-Danlos Syndrome/Hypermobile Spectrum Disorder (hEDS/HSD) have a high prevalence of DGBI, including Irritable Bowel Syndrome (IBS) and Functional Dyspepsia (FD), and multiple other co-morbidities.

WHAT THIS STUDY ADDS:

- Healthcare utilisation and healthcare costs are substantial in patients with hEDS/HSD
- Healthcare costs are twice as high in hEDS/HSD patients with FD compared to those with IBS.
- Inpatient admissions and outpatient consultations account for the largest shares of healthcare costs.
- FD, low BMI, positive screen for Avoidant Restrictive Food Intake Disorder (ARFID), number of medications, number of different outpatient vistis, and having one or more of PoTS MCAS, CFS and fibromyalgia are independent predictors of higher healthcare costs inpatients with hEDS/HSD.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY:

- This study highlights the need for a cost-effective, multidisciplinary services to manage patients with hEDS/HSD, particularly those with FD and with multiple comorbidities.

ABBREVIATIONS

ARFID = Avoidant/Restrictive Food Intake Disorder

BMI = Body Mass Index

CFS = Chronic Fatigue Syndrome

CANDI = Comprehensive Assessment of Nutrition & Dietary Intervention in hypermobile Ehlers-Danlos Syndrome

CANH = Clinically Assisted Nutrition and Hydration

CI = Confidence Interval

DGBI = Disorders of Gut Brain Interactions

(h)EDS = (Hypermobile) Ehlers Danlos Syndrome

FD = Functional Dyspepsia

GI = Gastrointestinal

HSD = Hypermobile Spectrum Disorder

HADS = Hospital Anxiety and Depression Scale

IBS = Irritable Bowel Syndrome

IQR = Interquartile Range

MCAS = Mast Cell Activation Syndrome

NIAS = Nine Item Avoidant/Restrictive Food Intake Disorder Screen

PHQ-15 = Patient Health Questionnaire-15

PoTS = Postural Tachycardia Syndrome

PP = per patient

SF6D = Short form 6D version 2

VSI =Visceral Sensitivity Index

ABSTRACT:

Background/Objective: Disorders of Gut-Brain Interactions (DGBI), e.g., Functional Dyspepsia (FD) or Irritable Bowel Syndrome (IBS), are common in patients with Hypermobile Ehlers-Danlos Syndrome/Hypermobile Spectrum Disorder (hEDS/HSD). DGBI is associated with significant healthcare use – how this applies to patients with coexisting hEDS/HSD is unknown.

Design: A cross-sectional study was performed. Patients recruited from tertiary neurogastroenterology clinics and from Ehlers-Danlos Support UK completed questionnaires, characterising their demographic, healthcare data and expenses, over 6 months (July/21-January/22) and their ROME IV diagnoses. NHS unit costs were used. Healthcare use and costs were compared across and between DGBI and non-DGBI subgroups. Regression analysis was performed to determine predictors of costs. $p<0.005$ was considered significant.

Results: Median age of the 660 respondents was 39 (IQR: 29-50) years; 96.1% had a DGBI. 13.6% had IBS, 29.9% had FD, 32.1% had IBS and FD, 24.4% had neither. Patients with DGBI had high healthcare use, and large healthcare costs; £3388.79/6 months, mostly attributed to consultations (36.4%) and admissions (22.7%). Costs per patient (pp) were at least double in any group with FD (£4026.53-£4297.30pp) compared to those without (£1372.49- £1979.36pp), $p<0.001$. The highest costs were in FD patients (>£20,000 pp/6-months). Predictors of rising costs were FD, non-gastrointestinal comorbidities, lower BMI, positive ARFID screen, having an altered diet, polypharmacy, visits to different healthcare professionals and tertiary neurogastroenterology recruitment.

Conclusions: It is imperative to develop cost-effective multidisciplinary services for hEDS/HSD patients with FD, particularly in the current fiscal climate, as they have significant healthcare use and costs.

INTRODUCTION:

Ehlers-Danlos Syndromes (EDS) are an inherited group of connective tissue disorders, characterised by joint hypermobility, skin hyperelasticity, and musculoskeletal symptoms[1]. There are 13 different subtypes, with Hypermobile Ehlers-Danlos Syndrome/Hypermobile Spectrum Disorder (hEDS/HSD) being the most common, with a prevalence of 1:10,000 in the general population[2]. It is the only subtype where a genetic defect has not been identified[3, 4], therefore, diagnosis is made clinically using the 2017 Diagnostic Criteria for Hypermobile Ehlers-Danlos Syndrome[5].

Disorders of Gut-Brain Interaction (DGBI) are very prevalent in hEDS/HSD, present in up to 98% of individuals[6]. DGBI, previously known as functional gastrointestinal disorders, are a highly prevalent group of conditions characterised by chronic gastrointestinal symptoms (e.g. nausea or abdominal pain) with no discernible organic pathology identified upon investigation[7]. Functional Dyspepsia (FD) and Irritable Bowel Syndrome (IBS) are the commonest DGBIs in hEDS/HSD. FD is a foregut disorder characterised by epigastric pain or discomfort, early satiety and postprandial fullness[8], whereas IBS is a hindgut disorder characterised by abdominal pain and altered bowel habits[9].

DGBI are associated with high healthcare use and costs. It is estimated that the direct healthcare costs associated with IBS in the United Kingdom are £1.27 billion per annum[10] whereas the costs associated with FD are estimated to be £1.55 billion per annum[11]. However, the true costs are thought to be considerably more due to indirect costs such as sick days, early retirement, unemployment and the subsequent loss of productivity[12]. Factors associated with higher healthcare use and costs in DGBI include polypharmacy, multimorbidity, chronic conditions, functional impairment, psychopathology and somatisation[13]. Studies in patients with FD have shown a higher healthcare burden than patients with IBS due to increased imaging, clinically assisted nutrition and hydration (CANH) and visits to healthcare professionals[14, 15].

Polypharmacy, multimorbidity, functional impairment, psychopathology and somatisation are common in hEDS/HSD[16]. Patients with hEDS/HSD have numerous chronic conditions including Fibromyalgia, Chronic Fatigue Syndrome, Anxiety, Depression, Genitourinary problems[17], Postural Tachycardia Syndrome (PoTS, characterised by autonomic dysregulation[18]) and allergic type reactions sometimes referred to as Mast Cell Activation Syndrome (MCAS, a multi-systemic condition characterised by aberrant mast cell degranulation causing not only systemic allergy type symptoms but gastrointestinal symptoms such as abdominal pain,

diarrhoea/constipation and nausea as well[19]). The objective confirmation and the nature of these frequently self-reported allergic associations remain to be established.

As such, we expect high healthcare use and costs in patients with hEDS/HSD and DGBI. Additionally, we hypothesise that those with FD will have higher healthcare use and costs than those with IBS, reflecting what is known in previous studies. No study to date has comprehensively and systematically detailed the healthcare use or characterised the healthcare costs in patients with hEDS/HSD who have comorbid DGBI, despite these being common comorbidities. Furthermore, no study has compared the healthcare use and costs between hEDS/HSD patients with IBS versus FD. We therefore aimed to investigate this and to determine predictors of healthcare costs.

The aims of the study were to investigate this and specifically:

- Assess the healthcare use and costs of patients with hEDS/HSD and coexisting DGBI.
- Compare the healthcare use and costs in hEDS/HSD patients with and without FD+/-IBS.
- Determine predictors of healthcare costs in hEDS/HSD patients with DGBI.

METHODOLOGY:

Study Design

A cross-sectional survey was performed on patients with hEDS/HSD who were recruited as part of the CANDI-hEDS study (Comprehensive Assessment of Nutrition and Dietary Intervention in Patients with hEDS) between July 2021 and January 2022 [20]. This included a group of hEDS/HSD patients from tertiary Neurogastroenterology clinics at 2 London teaching hospitals and a non-tertiary group recruited nationally through an advert via Ehlers Danlos Support UK. Patients were included if aged ≥16 years, had a positive diagnosis of hEDS/HSD and had completed the requisite questionnaires. The study was approved by London - Westminster Research Ethics Committee (REC reference: 21/PR/0916)

Questionnaires

Demographic information and past medical history were collected electronically with a standardised form. The following questionnaires were administered electronically.

1) An EDS healthcare use questionnaire. This was specifically developed for this study and was based on the resource use questionnaire used in the 'IBD-BOOST' study[21]. It was adapted by health economists with input from a Patient and Public Involvement group of hEDS/HSD patients. This questionnaire collected information about consultations, admissions, investigations, CANH, medications and personal expenses over 6 months.
2) The ROME IV questionnaire was used to diagnose those with and without DGBI, and to further stratify the entire cohort into 4 subgroups[22]: *IBS only*, *FD only*, FD and IBS (*FD+IBS+)* and neither FD nor IBS (*FD-IBS-*). The *FD-IBS-* group could include patients with other ROME IV DGBI.
3) The Short Form 6D version 2 6D version 2 (SF6D) questionnaire was used to measure the quality of life utility score, with higher scores suggesting a better quality of life[23].
4) The Patient Health Questionnaire-15 (PHQ-15) questionnaire was used to screen for somatic sensitivity[24].
5) The Hospital Anxiety and Depression Scale (HADS) questionnaire was used to screen for anxiety and depression[25].
6) The Visceral Sensitivity Index (VSI) questionnaire screened for gastrointestinal specific anxiety[26].
7) The Nine Item ARFID Screen (NIAS) subscale was used to screen for Avoidant/Restrictive Food Intake Disorders (ARFID)[27].

Costing Resource Uses

The unit costs for primary care services were obtained from '*Unit Costs of Health and Social Care 2021*', which included costs for GP, practice nurse and pharmacist consultations[28]. Unit costs for secondary care, e.g. outpatient visits, diagnostic tests, operations and hospitalisations, were obtained from the '*National Schedule of NHS Costs 2019/20v2*'[29]. Costs were based on the length of average consultation times; 10-20 minutes for primary/secondary/tertiary appointments vs 1 hour for allied health care professional appointments. Similar services were grouped for healthcare use. For example, gastroscopies, colonoscopies and sigmoidoscopies were grouped as 'endoscopic investigations' (**Supplementary Table 1** details the groupings). Unit costs for medication and artificial nutrition were obtained by the NHS Business Services Authority Prescription Cost Analysis[30]. The total costs were made on the assumption that the medications/CANH were taken daily for 6 months (183 days) unless specified otherwise, as this was the specified time frame for the study. Out-of-pocket expenses were directly obtained from the patients in the healthcare use questionnaire, and costs for travelling by car were calculated in accordance with national guidance[31]. For a complete set of costings and assumptions used to cost services, please refer to **Supplementary Tables 2 and 3**.

Data Analysis

For healthcare use, continuous data was expressed as median and interquartile (IQR) range, and categorical data was expressed as number and percentage. Healthcare costs were expressed as mean and 95% Confidence Interval (CI). Healthcare use and costs were calculated in patients with DGBI and summarised by DGBI subgroups (*IBS only*, *FD only*, *FD+IBS+* (both FD and IBS), and *FD-IBS-* (neither IBS nor FD)). Comparisons across groups were made using Kruskal-Wallis tests or Chi-squared for trend as appropriate; subsequently, pair-wise comparisons were performed for differences between groups. Given multiple comparisons, a p-value of <0.005 was deemed significant

To ensure normality, Box-Cox transformation was used for variables that were linearly distributed. Univariate analysis was used to determine factors associated with increasing healthcare costs. Where there was collinearity, one variable was chosen to represent the others. Multivariate regression analysis was then performed using variables from the univariate analysis that were significantly associated with increasing costs, to determine factors which

were independently associated with higher healthcare costs. For the regression analysis, a p value <0.05 was considered significant. Data was analysed using SPSS® version 28.0[32].

RESULTS:

Study Population

From the 683 initially consented participants in the CANDI-hEDS study, 20 did not complete all of the questionnaires and 3 patients did not meet the new diagnostic criteria for hEDS/HSD, leaving 660 patients eligible for the study; 110 (16.7%) were from tertiary clinics and 550 (83.3%) recruited nationally via the Ehlers Danlos Charity, 632 (95.8%) female, median age 39 (IQR:29.0 – 50.0) years, and median BMI was 24.7kg/m^2 (21.2-30.1) – **Table 1.** The majority did not drink alcohol (n=465, 70.5%), nor smoke (n=599, 90.8%). Multimorbidity was high in our cohort - with 96.1% having a ROME IV diagnosis of at least 1 DGBI, and 63.0% had more than 3. 98.9% had at least one other self-reported comorbidity from PoTS, MCAS, migraines, CFS, fibromyalgia, anxiety and depression.

Based on the ROME IV questionnaire, 634 participants had at least one DGBI. Of the total 660 patients eligible for the study, 90 had *IBS only*, 197 had *FD only*, 212 had *FD+IBS+* and 161 had *FD-IBS-* (**Supplementary Figure 1**). Age, BMI, sex and ethnicity were similar across the groups. Patients with both FD and IBS were most likely to be unemployed (n=144, 67.9%) and least likely to be independently mobile (n=112, 52.8%) or drink alcohol (n=166, 78.3%). Patients with *FD only* were more likely to report PoTS (p<0.001) and MCAS (p=0.005) than patients without FD (*IBS only* and *FD-IBS-* groups). However, patients with *FD+IBS+* were significantly more likely to report functional somatic syndromes such as migraines (66.0% vs 46.7% in *IBS only*, p=0.002), fibromyalgia (42.5% vs 23.6% in *FD-IBS-*, p=0.002) and CFS than patients without FD (55.2% vs 35.5% (*IBS only*) and 34.2% (*FD-IBS-*), p<0.001 each). There was no significant difference in the prevalence of anxiety (p=0.800) or depression (p=0.466) across the groups (see **Supplementary Table 4** for a full list of co-morbidities).

Healthcare use in hEDS/HSD with any DGBI

Healthcare use over the previous 6 months was assessed in hEDS/HSD patients with DGBI (**Table 2**). Patients with DGBI had a median of 8.0 (range: 0.0-135.0) consultations with a healthcare professional and saw a median of 3.5 (IQR: 1.0-5.0) different specialists over the 6-months. 405 (63.9%) patients with DGBI had consulted with primary care and 392 (61.8%) with secondary care specialists; most commonly rheumatologists (n=192 (30.3%)) and

gastroenterologists (n=166 (26.2%)). 316 (49.5%), consulted with an allied health care professional.

In the prior 6 months, 10.7% of hEDS/HSD patients with a DGBI had an inpatient stay with a median length of stay of 7.0 days (IQR: 3.0-20.5 days).

79.3% of patients with DGBI (n=503) had an investigation with a median of 2 different investigations (IQR: 0.5-3.5), including bedside (n=452, 71.3%), radiology (n=280, 44.2%), endoscopy (n=70, 11.0%) and gastrointestinal physiology (n=41, 6.5%) investigations.

Polypharmacy was common across the cohort; patients with DGBI were on a median of 6.0 medications (IQR: 4.0-9.0, maximum 23.0). 73.2% (n=464) were on ≥5, 34.9% (n=221) were on ≥8, and 3.3% (n=21) were on ≥15 medications. The commonest class of medications were those with an anticholinergic burden (75.2%). Following this, analgesic-type medications were the most common class of drug used. This included simple analgesic medication (e.g., paracetamol and ibuprofen) (64.5%), neuromodulators (47.5%) and opioids (39.8%). 30.2% were on more than one opioid, with 5.8% being on more than 2. Other commonly used medications include proton pump inhibitors (44.3%) and H1 blockers (42.1%).

There were significantly more patients with DGBI using parenteral nutrition (9.2%, n=58) than enteral nutrition (6.6%, n=42), p=0.030. 21 patients (3.3%) were on both enteral and parenteral nutrition at least once over the preceding 6 months. Oral nutritional supplements were used in 21.4% of patients.

287 (43.5%) patients were employed at the time of the study; of these, 63.8% reported having to take sick leave with a median of 11.5 days (IQR: 4.5-19.0) off work in the past 6 months. Of the 645 patients of working age, 41.2% were medically retired. Among them, the median number of years out of work was 6.0 years (IQR: 4.0-11.0, maximum: 28 years).

Patients with a DGBI had high PHQ15 scores (18.7) and VSI scores (36.5).

<u>Healthcare costs in hEDS/HSD patients with any DGBI</u>

The mean healthcare costs over the previous 6 months for a patient with hEDS/HSD and DGBI were £3388.79. In patients with DGBI, 36.4% of the total costs were due to outpatient consultations, 22.7% were due to inpatient admissions, 16.8% were due to out-of-pocket expenses, 11.6% were medications, 6.7% due to CANH and 5.7% due to investigations (**Supplementary Figure 2**).

The total outpatient healthcare costs in patients with DGBI were £1198.56 per patient (pp). In patients with DGBI, the highest outpatient costs were for allied healthcare professional consultations (£423.05 pp), higher than for secondary/tertiary consultations (£327.65 pp) and primary care consultations (£192.27 pp). The costs for patients recruited from

neurogastroenterology clinics were significantly higher than for those from EDS UK (£5507.96 pp vs £2958.52 pp, p<0.001)

The mean total cost of an admission over the 6 months, for those who were admitted and had a DGBI, was £7581.44 pp).

The total costs for investigations for a patient with DGBI were £118.07 pp. Endoscopic and physiological investigations appeared to be the costliest investigations in patients with DGBI; £411.93 per endoscopic investigation per patient and £327.13 per physiological investigation per patient.

The mean medication costs in patients with DGBIs were £390.61 pp. Anticholinergics (£81.47 pp), laxatives (£66.12), PoTS-type medications (£60.03) and opioids (£55.04) accounted for the highest medication costs per patient with a DGBI.

The mean CANH costs across the patients with DGBI per patient, for those who needed CANH, were £1065.07 pp over 6 months (maximum £10,107.70).

Out-of-pocket spending were very high, costing a mean of £571.21 per DGBI patient over the preceding 6 months (**Table 3**).

<u>Healthcare use and costs in patients with and without FD and IBS</u>

Patients in the *FD only* and *FD+IBS+* groups had significantly more outpatient consultations over 6 months (median 9, IQR: 2.0-17.0) than *IBS only* (5, p<0.001) and *FD-IBS-* (4, p<0.001) groups. Patients in the *FD only* and *FD+IBS+* groups had significantly greater outpatient costs (£1353.63 pp and £1390.19 pp, respectively) than those with *IBS only* (£1007.05 pp, p<0.001) and *FD-IBS-* (£863.53 pp, p<0.001).

Patients with *FD only* were seven times as likely to have an admission (16.8%) as those with *IBS only* (2.2%, p<0.001). Of the patients who were admitted to a hospital (n=69), the *IBS+FD+* group had the longest length of stay (21.0 days (IQR: 2.4-29.3)), and the *IBS only* group had the shortest (1.0 day (IQR: 0.0-1.0), p<0.001). The longest admission lasted 150 days, and this was in an *FD only* patient. In the 69 patients who were admitted, inpatient costs were significantly higher in *FD only* (£6413.67 pp) and *FD+IBS+* (£10525.56 pp) compared to *FD-IBS-* (£1283.85 pp), p<0.001.

The prevalence and cost of investigations were similar across all groups.

Medication use was broadly similar however, patients with IBS were more likely to require neuromodulators (p=0.003) and opioids (p=0.004) than patients without IBS. However, opioids were significantly more costly in patients with FD compared to those without (*FD only*: £79.55 pp and *FD+IBS+*: £68.59 pp vs *IBS only:* £29.99 pp and *FD-IBS-*: £19.58 pp, p<0.001). Patients in the *FD-IBS-* group were less likely to be on a medication with an anticholinergic burden (67.1%)

compared to the *IBS only* (77.8%), *FD only* (77.7%) and *FD+IBS+* (78.8%) groups, all p<0.005. The medication cost per patient in the *FD only* (£491.16) and *FD+IBS+* (£465.56) groups were twice as much as that in the *IBS only* (£280.49, p<0.001) and the *FD-IBS-* (£196.80, p<0.001) groups.

There was significantly more CANH use in the *FD only* (37.6%) and *FD+IBS+* (29.3%) groups compared to the *IBS only* (8.9%, p<0.001) and the *FD-IBS-* (9.9%, p<0.001) groups, None of *the IBS only* patients were on enteral or parenteral nutrition. Similarly, CANH costs (in the 160 patients who received CANH) were significantly higher in the *FD only* (£1434.37 pp) and *FD+IBS+* group (£885.79 pp, p=0.210), compared with *IBS* (£3.09 pp, p<0.001) and *IBS-FD-* (£118.12 pp, p<0.001) groups (**Supplementary Table 5**).

Patients with FD spent significantly more on transport costs (*FD+IBS+*: £171.70 pp and *FD only*: £104.42 pp) than patients with *IBS only* (£52.39 pp, p<0.001) and *FD-IBS-* patients (£48.09 pp, p<0.001). Most time off work was taken in *FD+IBS+* patients (11.50 days pp) compared with *FD-IBS-* patients (6.5 days pp, p<0.001) over 6 months.

The total mean healthcare costs per patient were doubled in patients with *FD only* (£4297.30) and *FD+IBS+* (£4026.53) compared to the *IBS only* (£1979.36, p<0.001) and *IBS-FD-* (£1736.11, p<0.001) (**Figure 1**). The 10 costliest patients all had FD (>£20,000), were admitted and were on CANH. The highest inpatient cost over 6 months was £99,983.91 pp.

<u>Predictors of higher healthcare costs</u>

In univariate analysis, higher healthcare costs were associated with lower age and BMI, alcohol use, altered diet, recruitment from tertiary care, employment status, higher somatic sensitivity (PHQ15), positive ARFID screen (NIAS), number of visits to different healthcare professionals, number of medications, the presence of reported comorbidities (PoTS, MCAS, fibromyalgia, CFS, migraines, bladder problems) and FD. Anxiety, depression (HADS questionnaires) and IBS were not associated with higher healthcare costs (**Table 3**). IBS was included in the multivariate analysis. Age, BMI, PHQ15, NIAS, number of visits to different healthcare professionals, number of medications, and PoTS, MCAS, CFS and fibromyalgia were Box-Cox transformed because their distributions were far from normality. After adjusting for all other factors, FD, the presence of PoTS, MCAS, CFS and fibromyalgia, lower BMI, altered diet, attendance at tertiary clinics, positive ARFID screen, alcohol intake, visits to different healthcare professionals and the number of medications were independently associated with higher healthcare costs (p<0.05). The adjusted *R*-squared value was calculated as 0.154. The *F*-test of the model was 9.503, p<0.001. The variance inflation factors for the 7 variables were less than 2, highlighting that they did not exhibit multicollinearity with each other .

DISCUSSION:

Our study is the first to quantify healthcare use and costs for patients with hEDS/HSD with or without FD and/or IBS. Healthcare use and costs were high, mainly accounted for by outpatient consultations. Polypharmacy within as well as across drug classes was highly prevalent and associated with higher healthcare costs; these patients had large anticholinergic and opiate burdens. FD was an independent predictor of increased healthcare costs, and patients with FD were twice as costly as those with IBS. Patients with FD were more likely to be admitted to the hospital and to be on CANH; this accounted for higher healthcare costs. Low BMI and bladder problems were strongly associated with higher healthcare costs. Out-of-pocket expenses were high, mostly attributable to over-the-counter analgesia.

Our study mirrors the findings by *Lam et al.,* which showed that patients with hEDS/HSD and DGBI have high healthcare utilisation, mostly accounted for by consultations and admissions[6]. In our study, outpatient consultations accounted for most of the costs; this is in contrast with other studies of DGBI, wherein the majority of costs were attributable to inpatient admissions[33, 34]. This suggests that our patients had a higher outpatient burden compared to other patients with DGBI. Indeed, patients had a median of 8 consultations over the past 6 months, which likely reflects the striking number of comorbidities they have. Gastroenterology, rheumatology, dietetics and psychology were the most commonly accessed outpatient services, which reflects our clinical experience in this cohort of patients. The NHS does not currently have a multidisciplinary service for these patients, which may contribute to higher healthcare use.

Polypharmacy within and across drug classes in our cohort was striking and comparable to that of an elderly population (despite the median age of 39 years)[35]. The large anticholinergic and opioid burden is concerning in this cohort due to the significant gastrointestinal side effects of these drug classes and the fact that current guidelines in the British Society of Gastroenterology advocate for the avoidance of these medications in the management of FD and/or IBS[36, 37] and furthermore general guidelines advocate for the avoidance of opioids for chronic non-cancer pain[38]. Medication burden was associated with higher healthcare costs, which supports studies in other patient groups. In addition to the costs, polypharmacy is associated with negative health outcomes[39]. Prescribing practices should therefore be reviewed, and guidelines created regarding appropriate prescribing and indeed deprescribing in this group of patients, with a move towards more holistic-based treatments such as psychotherapy, which is highly effective in the management of DGBI[40]. This can also address the coexistence of pain disorders and psychopathology in this patient group[7]. Unfortunately, in

spite of current recommendations for the implementation of biopsychosocial care there are few patients with access to psychological interventions.

Extrapolating from healthcare costs over 6 months, the mean annual healthcare costs for hEDS/HSD patients with DGBI (£6777.58) was higher than the reported mean annual spending pp in the UK between 2017-2018 (£1915–£2665)[41] and higher than the annual costs associated with Ulcerative Colitis: (£3084) and Crohn's disease: (£1800)[42]. This is likely to be an underestimation considering that the study took part during the COVID pandemic, when healthcare access was relatively limited. Despite the high healthcare use and costs in patients with DGBI, it is pertinent that neither a bespoke multidisciplinary service nor a specially commissioned service exists for them. *Jones et al.* suggested that a multi-disciplinary approach involving (neuro)gastroenterologists, rheumatologists and allied healthcare for patients with hEDS/HSD improved patient outcomes and could be more cost-effective compared to discrete services, as shown for other chronic conditions[43]. This approach could be piloted in the UK and healthcare use/costs before and after this change in service provision should be compared.

Multimorbidity is a well-known contributor to high healthcare costs [44, 45], and the high levels of comorbidity (>98%) in hEDS/HSD patients may account for the high healthcare costs. Indeed, the presence of FD and any of PoTS, MCAS, CFS and Fibromyalgia were independently associated with higher healthcare costs. The former is in line with other studies which demonstrate that FD costs more than IBS[14, 15, 46].

Lower BMI was also a predictor of higher healthcare costs. In a previous study, we have demonstrated that patients with a lower BMI were more likely to screen positive for ARFID, to have micro and macronutrient deficiencies and to receive CANH[20]. Therefore, this association between BMI and higher healthcare costs likely reflects the greater nutritional demands of these patients. Indeed, 9% and 6% of patients in this study had been on parenteral or enteral nutrition respectively, over the last 6 months. Furthermore, the 10 highest healthcare costs in this study were in patients with FD who were admitted to a hospital and were on CANH. The appropriateness of enteral and parenteral nutrition in patients with hEDS/HSD and/or DGBI is debatable and has been highlighted in the recent guidance[15, 47]. Taking the above points into account, practices revolving around prescribing CANH should be reviewed in patients with hEDS/HSD and concomitant DGBI.

Over 95% of patients incurred out-of-pocket expenses, with over-the-counter analgesia being the most common, highlighting the high prevalence of pain conditions among these patients[6]. The need for out-of-pocket expenditure suggests that this cohort of patients is not having their

healthcare needs met - a theme commonly voiced by hEDS/HSD patients, especially due to disjointed care resulting in (patient-reported) unsatisfactory management[48-50]. With a high incidence of mobility issues and the significant transport costs in this cohort, the development of more local services or telemedicine services for hEDS/HSD shown to reduce treatment burden and improve the quality of life in patients with hEDS/HSD[51] should be considered. Future studies should be performed to see what products/therapies are needed by these patients to not only improve symptoms but also improve accessibility to healthcare services, therefore allowing more healthcare needs to be met.

There were several limitations of the study. Firstly, the healthcare use questionnaire was adapted from the IBD BOOST study[21] and not formally validated. On the questionnaire, patients were given a set of options to choose from, and when these were not selected, assumptions were made to calculate costs (**Supplementary Table 2**), introducing the potential misrepresentation of healthcare usage/costs. Nonetheless, whilst the absolute values will be underestimated, the same rules of costing analysis were used for all patients, allowing for relative comparisons between groups. Secondly, the study was a retrospective questionnaire-based study and therefore prone to recall bias, particularly when it came to healthcare use. We could not clinically corroborate self-reported comorbidities and the clinician appropriateness or otherwise of interventions such as opioids and CANH. Having access to participants' health records could have mitigated this. Thirdly, there was a selection bias as patients were recruited from tertiary clinics and the EDS UK website as opposed to from a range of primary care services, which may have given a better reflection of the hEDS cohort. However, it was assumed that those recruited from the EDS-UK charity would represent those patients attending primary and secondary care and therefore would be distinct from those attending tertiary care. The final limitation of this study was that it was conducted during the COVID-19 pandemic, which may have affected healthcare utilisation and therefore the generalisability of our findings[52].

CONCLUSIONS:

This study is the first to investigate the healthcare utilisation and costs of patients with hEDS/HSD and concomitant FD and IBS. hEDS/HSD patients with FD and, to a lesser degree, IBS have greater healthcare utilisation and higher healthcare costs compared to those who do not have FD or IBS. Despite the high healthcare costs, this group of patients is largely under-represented in literature, and so more research into their symptoms and further cost-effective management strategies is needed. With a limited NHS budget, better targeting of resources may not only improve their quality of life but may also reduce healthcare costs. The cost and clinical effectiveness of developing a novel unified service tailored to patients with hEDS/HSD and concomitant FD and/or IBS merits further exploration.

TABLES AND FIGURES:

Table 1: Demographics, Commonest Co-morbidities and Questionnaire results

		Any DGBI (n=634)	*FD-IBS-* (n=161)	*IBS only* (n=90)	*FD only* (n=197)	*FD+IBS+* (n=212)	p value[+]
Age/years (median (Q1-Q3))		39.5 (29.0-50.8)	43.0 (33.0-52.5)	39.5 (30.5-48.5)	38.0 (27.0-49.0)	39.5 (27.0-50.0)	0.030
BMI/kg/m^2 (median (Q1-Q3))		24.7 (21.2-30.1)	24.6 (20.5-28.8)	25.3 (21.3-29.4)	23.9 (19.23-28.5)	25.0 (20.5-29.6)	0.010
		n (%)	n (%)	n (%)	n (%)	n (%)	
Sex	Female	607 (95.7)	148 (91.9)	89 (98.9)	191 (97.0)	204 (96.2)	0.118
Ethnicity - Caucasian	Caucasian	602 (94.9)	155 (96.3)	86 (95.6)	185 (93.9)	199 (93.9)	0.691
Recruitment	Clinic	107 (16.9)	12 (7.5)^{C}	16 (17.8)	48 (24.4)^{A}	34 (16.0)	**<0.001**
Alcohol Intake	Rarely Drink	450 (71.0)	102 (63.4)^{CD}	52 (57.8)^{D}	145 (73.6)^{A}	166 (78.3)^{AB}	**<0.001**
Smoking Status	Current-Smoker	60 (9.5)	12 (7.5)	3 (3.3)	24 (12.2)	22 (10.4)	0.081
Mobility Status	Independently mobile	401 (63.3)	130 (80.8)^{CD}	65 (72.2)^{CD}	112 (56.9)^{AB}	112 (52.8)^{AB}	**<0.001**
Employment Status	Unemployed	411 (64.8)	65 (40.4)^{CD}	40 (44.2)^{CD}	124 (62.9)^{AB}	144 (67.9)^{AB}	**<0.001**
Exercise Levels	Light Exercise*	601 (94.8)	154 (95.7)	88 (97.8)	182 (92.4)	202 (95.3)	0.100
	Moderate Exercise*	447 (70.5)	123 (76.4)	64 (71.1)	141 (71.6)	140 (66.0)	0.339
	Vigorous Exercise*	130 (20.5)	41 (25.5)	19 (21.1)	39 (19.8)	39 (18.4)	0.605
n (%) of self-reported Comorbidities (aside from DGBIs)		653 (98.9)	158 (98.1)	90 (100.0)	195 (99.0)	99.1 (210)	0.588
Postural Orthostatic Tachycardia Syndrome		314 (49.6)	56 (34.8)^{CD}	40 (44.4)^{CD}	111 (56.4)^{AB}	116 (54.7)^{AB}	**<0.001**
Chronic Fatigue Syndrome		278 (43.9)	55 (34.2)^{CD}	32 (35.6)^{CD}	84 (42.6)	117 (55.2)^{AB}	**<0.001**
Mast Cell Activation Syndrome/Multiple Allergies		218 (34.4)	41 (25.5)^{C}	26 (28.9)^{C}	84 (42.6)^{AB}	73 (34.4)	**0.005**
Migraines		367 (57.9)	81 (50.3)	42 (46.7)^{D}	117 (59.4)	140 (66.0)^{B}	**0.002**
Fibromyalgia		216 (34.1)	38 (23.6)^{D}	30 (33.3)	67 (34.0)	90 (42.5)^{A}	**0.002**
Depression		351 (55.4)	85 (52.8)	49 (54.4)	105 (53.3)	127 (59.9)	0.466
Anxiety		404 (63.7)	99 (61.5)	58 (64.4)	115 (58.4)	149 (70.3)	0.800
Questionnaires		Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	p value[+]
SF6D		0.66 (0.65-0.66)	0.66 (0.64-0.67)	0.65 (0.64-0.66)	0.67 (0.65-0.68)	0.66 (0.65-0.67)	0.172
PHQ 15		18.74 (18.38-19.11)	15.96^{BCD} (15.26-16.66)	18.02^{A} (17.27-18.77)	18.92^{A} (18.30-19.53)	20.52^{A} (19.91-21.15)	**<0.001**
HADS-A		6.06 (5.78-6.34)	0.66 (0.64-0.67)	0.65 (0.64-0.66)	0.67 (0.65-0.68)	0.66 (0.65-0.67)	0.011
HADS-D		9.97 (9.57-10.36)	9.36^{D} (8.62-10.10)	9.59 (8.69-10.49)	9.42 (8.70-10.15)	10.90^{A} (10.20-11.60)	**0.005**
VSI		36.48 (35.16-37.80)	27.06^{BCD} (24.63-29.48)	33.90^{A} (30.90-36.90)	36.96^{A} (34.55-39.37)	43.50^{A} (41.43- 45.57)	**<0.001**
NIAS		18.55 (17.80-19.30)	13.43^{CD} (12.13-14.73)	13.47^{CD} (11.84-15.09)	21.32^{AB} (20.04-22.60)	21.40^{AB} (20.13-22.66)	**<0.001**

Table 1: p-values in **bold** are statistically significant (p<0.005). [+] p value is based on a Chi-Squared across all 4 groups. *any amount of exercise (light/moderate/heavy) per week. IBS = Irritable Bowel Syndrome. FD = Functional Dyspepsia. BMI = Body Mass Index. [A] Significant difference as compared to *FD-IBS-*. [B] Significant difference as compared to *IBS only*. [C] Significant difference as compared to *FD only*. [D] Significant difference as compared to *FD+IBS+*.

Table 2: Comprehensive list the percentage of patients who have utilised or required at least one healthcare service, medication or investigation.

	Any DGBI (n=634) n (%)	*FD-IBS-* (n=161) n (%)	*IBS only* (n=90) n (%)	*FD only* (n=197) n (%)	*FD+IBS+* (n=212) n (%)	p value
n (%) with Outpatient Consultations						
Primary Care	405 (63.9)	86 (53.4)^{CD}	129 (50.6)^{CD}	50 (65.5)^{AB}	151 (71.2)^{AB}	**0.002**
Secondary/Tertiary Care	392 (61.8)	77 (47.8)	47 (52.2)	133 (67.5)^{AB}	147 (69.3)^{AB}	**<0.001**
Allied Healthcare	316 (49.5)	59 (36.7)^{BCD}	45 (50.0)^{A}	98 (49.8)^{A}	124 (58.5)^{A}	**<0.001**
Number of consultations (median Q1-Q3)	8.0 (2.0-17.0)	4.0 (0.0-10.0)^{CD}	5.0 (1.0-13.0)^{CD}	9.0 (1.0-16.0)^{AB}	9.0 (2.0-17.0)^{AB}	**<0.001**
n (%) with Inpatient Admissions	68 (10.7)	8 (5.0)^{CD}	2 (2.2)^{CD}	33 (16.8)^{AB}	26 (12.3)^{AB}	**<0.001**
n (%) undergoing investigations						
Blood, urine and stool tests	71.29 (452)	111 (68.9)	68 (75.6)	139 (70.6)	152 (71.7)	0.729
Radiology	44.16 (280)	67 (41.6)	47 (52.2)	78 (39.6)	98 (46.2)	0.186
Endoscopy	11.04 (70)	21 (13.0)	11 (12.2)	26 (13.2)	16 (7.6)	0.233
GI Physiology	6.47 (41)	17 (20.6)	4 (4.4)	11 (5.6)	11 (5.2)	0.120
n (%) Medication use^{+}						
Anticholinergics	477 (75.2)	108 (67.1)^{BD}	70 (77.8)^{A}	153 (77.7)^{A}	167 (78.8)^{A}	**0.002**
Neuromodulators	301 (47.5)	74 (46.0)^{BD}	49 (54.4)^{AC}	94 (47.7)^{BD}	121 (57.1)^{AC}	**0.003**
Opioids	252 (39.8)	50 (31.1)^{BD}	39 (43.3)^{A}	77 (39.1)	96 (45.3)^{A}	**0.004**
Simple analgesics$^{\&}$	409 (64.5)	108 (67.1)	50 (55.6)	126 (64.0)	123 (58.0)	0.168
H1 Blockers	267 (42.1)	72 (44.7)	33 (36.7)	70 (35.5)	94 (44.3)	0.649
H2 Blockers	65 (10.3)	16 (9.9)	9 (10.0)	22 (11.2)	28 (13.2)	0.754
Prokinetics	83 (13.1)	17 (10.6)	8 (8.9)	26 (13.2)	35 (16.5)	0.214
Anti-emetics	104 (16.4)	27 (16.8)	13 (14.4)	28 (14.2)	38 (17.9)	0.738
Anti-Spasmodic	122 (19.2)	28 (17.4)	18 (20.0)	35 (17.8)	44 (20.8)	0.811
Proton Pump Inhibitors	281 (44.3)	58 (36.0)	44 (48.9)^{A}	86 (43.7)^{A}	90 (42.5)	0.740
Alginates	140 (22.1)	35 (21.7)	10 (11.1)	52 (26.4)	50 (23.6)	0.034
Laxatives	230 (36.3)	55 (34.2)	34 (37.8)	73 (37.1)	76 (35.9)	0.927
Anti-diarrhoeal Medications	16 (2.5)	3 (1.9)	2 (2.2)	5 (2.5)	7 (3.3)	0.859
Autonomic Agents	202 (31.9)	47 (29.2)	29 (22.2)	60 (20.5)	65 (30.7)	0.967
Mast Cell Stabilisers	66 (10.4)	12 (7.5)	8 (8.9)	20 (10.2)	23 (10.9)	0.852
Opioid Antagonists	19 (3.0)	2 (1.2)	7 (7.8)	4 (2.0)	6 (2.8)	0.019
Vitamins and Mineral Supplements	507 (80.0)	132 (82.0)	73 (81.1)	155 (78.7)	168 (79.3)	0.860
n(%) with Out-of-Pocket Expenses						
Symptom Management	556 (87.7)	147 (91.3)	80 (88.9)	163 (82.7)	188 (88.7)	0.082
Products	499 (78.7)	125 (77.6)	66 (73.3)	154 (78.2)	172 (81.1)	0.506
Complementary and Alternative Therapies	452 (71.3)	114 (70.8)	60 (66.7)	136 (69.0)	157 (74.1)	0.548
n(%)receiving CANH						
Supplemental nutritional shakes or drinks	136 (21.5)	14 (8.7)^{CD}	8 (8.9)^{CD}	67 (34.0)^{AB}	54 (25.5)^{AB}	**<0.001**
Enteral Feeding	42 (6.6)	0 (0.0)^{CD}	0 (0.0)^{CD}	26 (13.2)^{AB}	16 (7.56)^{AB}	**<0.001**
Parenteral Nutrition	58 (9.2)	3 (1.9)^{CD}	0 (0.0)^{CD}	29 (14.7)^{AB}	26 (12.3)^{AB}	**<0.001**

Table 2: p-values in **bold** are statistically significant (p<0.005).$^{+}$ Percentage of patients on the specific medication class. $^{\&}$Paracetamol and Ibuprofen. ^{A} Significant difference as compared to *FD-IBS-*. ^{B} Significant difference as compared to *IBS*. ^{C} Significant difference as compared to *FD*. ^{D} Significant difference as compared to *FD+IBS+*. CANH = Clinically Assisted Nutrition and Hydration. IBS = Irritable Bowel Syndrome. FD = Functional Dyspepsia.

Table 3: Table showing Univariate and Multivariate Regression analysis investigating the factors associated with higher Healthcare Costs

	Univariate Linear Regression				Multivariate Linear Regression			
	Unstandardized Coefficients (95% CI)	Standardised Coefficient	t-value	p-value	Unstandardized Coefficients (95% CI)	Standardised Coefficient	t-value	p-value
(Constant)								
Demographics								
Age	-27.30 (-49.26 - -5.33)	-0.10	-2.44	**0.015**	1.68 (-20.08 - 23.44)	0.01	0.151	0.880
BMI	-48.89 (-71.44 - -26.35)	-0.16	-4.26	**<0.001**	-35.53 (-57.52 - -13.51)	-0.12	-3.169	**0.002**
Gender	-287.74 (-1713.26 - 1137.78)	-0.02	-0.40	0.692				
Ethnicity	329.43 (-970.14 - 1609.01)	0.02	0.49	0.627				
Alcohol Intake	-689.53 (-1320.84 - -58.22)	-0.08	-2.15	**0.032**	-565.15 (-1272.02 - -36.72)	-0.01	-0.176	0.861
Smoking Status	1036.81 (41.99 - 2031.62)	0.08	2.05	0.052				
Altered Diet	1021.40 (432.97 - 1609.84)	0.13	3.41	**<0.001**	210.50 (-374.70 – 795.71)	0.27	1.706	**0.048**
Recruitment	681.91 (-91.90 - 1455.72)	0.07	1.73	**0.044**	296.04 (-445.56 – 1037.63)	0.29	1.784	**0.043**
Independently Mobile	-603.04 (-1201.58 - -4.50)	-0.08	-1.98	0.068				
Employment Status	-688.58 (-1286.58 - -90.58)	-0.09	-2.26	**0.024**	-775.41 (-1176.46 – -225.64)	-0.01	-0.246	0.805
Questionnaires								
HADS	18.97 (-19.74 - 57.68)	0.04	0.96	0.336				
VSI	12.35 (-4.72 - 29.42)	0.06	1.42	0.156				
PHQ15	88.43 (26.18 - 150.67)	0.11	2.79	**0.005**	29.90 (-37.65 – 97.44)	0.04	0.869	0.385
NIAS	70.95 (41.27 - 100.64)	0.18	4.69	**<0.001**	21.96 (-10.01 – 54.00)	0.06	2.749	**0.018**
SF6D	-1398.75 (-5386.32 - 2588.81)	-0.03	-0.69	0.491				
Number of Visits to different Healthcare Professionals	483.09 (385.35 - 580.82)	0.35	9.71	**<0.001**	434.11 (328.10 – 540.12)	0.32	8.041	**<0.001**
Number of Medications	118.02 (33.76 - 202.28)	0.11	2.75	**0.006**	70.07 (-10.34 – 150.48)	0.26	2.711	**0.038**
ROME IV Diagnoses								
Functional Dyspepsia	1361.84 (775.66 - 1948.02)	0.18	4.56	**<0.001**	574.44 (328.10 – 540.12)	0.28	1.253	**0.021**
IBS	347.16 (-226.72 - 532.40)	0.05	-1.18	0.240	187.96 (-10.34 – 150.48)	0.07	1.747	0.081
Self-reported Comorbidities								
PoTS, MCAS, Fibromyalgia, CFS	250.81 (-15.02 - 516.64)	0.07	2.12	**0.034**	174.17 (-47.03 – 298.69)	0.10	2.435	**0.015**
Migraines	629.92 (47.08 - 1212.75)	0.08	1.85	0.064				
Depression	-74.44 (-655.96 - 507.08)	-0.01	-0.25	0.802				
Anxiety	-79.08 (-680.45 - 522.28)	-0.01	-0.26	0.796				
Bladder Problems	604.96 (5.37 - 1204.58)	0.08	1.98	**0.048**	111.60 (-415.11 – 591.92)	0.014	0.363	0.717
Gynaecological Problems	-190.23 (-884.75 - 504.30)	-0.02	-0.54	0.591				
Eating Disorder	-20.93 (-793.70 - 751.84)	0.00	-0.05	0.958				

Table 3: Greyed boxes in the multivariate table are factors which were not statistically significant in the univariate analysis and were not included in the multivariate analysis. Box Cox transformation was used for variables that were linearly distributed which were not normally distributed. For the multivariate regression r^2 value = 0.172 and adjusted r^2 value = 0.154. F-value = 9.503, p<0.001. p-values in **bold** are significant (p<0.050). **Supplementary Table 6** shows multicollinearity figures.

Figure 1: Bar Graph to show contribution of costs to total healthcare costs per patient.

Figure 1: * denotes p<0.001. IBS = Irritable Bowel Syndrome. FD = Functional Dyspepsia. CANH = Clinically Assisted Nutrition and Hydration

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