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A survey of functional dyspepsia in 361,360 individuals: Phenotypic and genetic cross-disease analyses

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Abstract

Background: Functional dyspepsia (FD) is a common gastrointestinal condition of poorly understood pathophysiology. While symptoms' overlap with other conditions may indicate common pathogenetic mechanisms, genetic predisposition is suspected but has not been adequately investigated.

Methods: Using healthcare, questionnaire, and genetic data from three large population-based biobanks (UK Biobank, EGCUT, and MGI), we surveyed FD comorbidities, heritability, and genetic correlations across a wide spectrum of conditions and traits in 10,078 cases and 351,282 non-FD controls of European ancestry.

Key Results: In UK Biobank, 281 diagnoses were detected at increased prevalence in FD, based on healthcare records. Among these, gastrointestinal conditions (OR = 4.0, $p < 1.0 \times 10^{-300}$), anxiety disorders (OR = 2.3, $p < 1.4 \times 10^{-27}$), ischemic heart disease (OR = 2.2, $p < 2.3 \times 10^{-76}$), and infectious and parasitic diseases (OR = 2.1, $p = 1.5 \times 10^{-73}$) showed strongest association with FD. Similar results were obtained in an analysis of self-reported conditions and use of medications from questionnaire

Abbreviations: EGCUT, Estonian Genome Center of the University of Tartu; FD, functional dyspepsia; FGID, functional gastrointestinal disorder; GWAS, genome-wide association study; ICD10, International Classification of Diseases 10th Revision; ICD9, International Classification of Diseases 9th Revision; MGI, Michigan Genome Initiative; UKBB, UK Biobank.

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data. Based on a genome-wide association meta-analysis of genotypes across all cohorts, FD heritability was estimated close to 5% ($h^2_{SNP} = 0.047$, $p = 0.014$). Genetic correlations indicate FD predisposition is shared with several other diseases and traits ($r_g > 0.344$), mostly overlapping with those also enriched in FD patients. Suggestive ($p < 5.0 \times 10^{-6}$) association with FD risk was detected for 13 loci, with 2 showing nominal replication ($p < 0.05$) in an independent cohort of 192 FD patients.

Conclusions & Inferences: FD has a weak heritable component that shows commonalities with multiple conditions across a wide spectrum of pathophysiological domains. This new knowledge contributes to a better understanding of FD etiology and may have implications for improving its treatment.

KEYWORDS
biobank studies, comorbidities, functional dyspepsia, genetics, genome-wide association study

1 | INTRODUCTION

Functional dyspepsia (FD) is a functional gastrointestinal disorder (FGID) estimated to affect approximately 10% of the adult population worldwide, with symptoms including postprandial fullness, early satiation, and epigastric pain or burning in the absence of detectable organic disease.[1,2] FD is often associated with symptoms overlapping with other FGIDs, such as irritable bowel syndrome (IBS), and strongly impacts patients' quality of life.[1,3] This is particularly true in the important portion of FD patients (20%) also experiencing psychosocial conditions such as anxiety, depression, or somatization, and who are therefore often referred to advanced care because of severely impaired daily functioning.[4,5] Overall, FD is associated with major substantial direct (healthcare) and indirect (work loss) cost, thus posing a considerable burden to society.[6,7] Current treatment options for FD have shown limited efficacy, and the development of novel therapeutic approaches is hampered by the heterogeneity of symptoms, the observed large placebo response in clinical trials (30%–40%), and the intrinsic difficulty in establishing the underlying pathophysiology in individual patients.[8–10]

The etiology of FD is heterogeneous and not fully elucidated. Several candidate mechanisms have been implicated in symptom generation, such as altered visceral sensitivity and motility, mucosal perturbations (low-grade duodenal inflammation, impaired mucosal duodenal integrity), and abnormal processing in the brain (visceral specific anxiety, somatization).[11–14] Genetic predisposition to FD is suspected from the observation of familial clustering, though genetic studies have been very scarce and limited to candidate genes in small sample sets of cases and controls, and hence, no unequivocal FD risk gene has been proposed.[15,16]

In the study of human complex conditions, cross-disease analyses are useful approaches to unearth similar etiology and common pathophysiological mechanisms, including those eventually accounted for by shared genetic factors. This may be particularly relevant in FD and other FGIDs, whereby studying commonalities may improve disease understanding and eventually inform the development of novel or alternative preventive and therapeutic strategies. Here, we leveraged data from UK Biobank (UKBB) and two smaller population-based cohorts (Michigan Genome Initiative—MGI, and the Biobank of the Estonian Genome Center, University of Tartu—EGCUT) for large-scale cross-disease analyses in order to study (i) the co-occurrence of FD and other conditions, based on participants' healthcare records and questionnaire data, and (ii) genetic correlation between FD and other traits and diseases, based on previous and newly generated FD GWAS data. We report the results obtained from such surveys conducted on a total of 361,360 individuals of European ancestry.

2 | MATERIALS AND METHODS

2.1 | Definition of functional dyspepsia cases

A similar protocol was adopted in all cohorts for the identification of FD cases based on respective participants' healthcare data and diagnoses classified according to the International Classification of Diseases 10th Revision (ICD10) for UKBB and EGCUT, and/or 9th revision (ICD9) for MGI. Cases were selected as those with a FD diagnosis (ICD9 536.8 or ICD10 K30) in their medical records, while the remainder of the cohorts served as control group. Exclusion criteria included *diseases of esophagus* (ICD9 530.*), *gastroesophageal reflux disease* (ICD10 K21, except K21.9 in cases), *other diseases of esophagus* (ICD10 K22), *gastric ulcer* (ICD9 531.* or ICD10 K25), *duodenal ulcer* (ICD9 532* or ICD10 K26), *peptic ulcer* (ICD9 533* or ICD10 K27), *gastrojejunal ulcer* (ICD9 534* or ICD10 K28), *inflammatory bowel disease* (IBD; ICD9 555.*, 556*, or ICD10 K50), *IBS* (ICD9 564.1 or ICD10 K58), and *coeliac disease* (CD; ICD9 579.0 or ICD10 K90.0).

2.2 | Study cohorts

2.2.1 | UKBB

UK Biobank is a longitudinal cohort including approximately 500,000 individuals (aged 40–69 years), recruited between 2006 and 2010 in the UK.[17] Together with genotypes (Affymetrix Biobank Axiom and UK BiLEVE Axiom arrays), participants' health-related information is available and spans questionnaire data on general health and lifestyle, self-reported conditions, and use of medications. In the informed consent participants gave "permission for access to my medical and other health-related records, and for long-term storage and use of this and other information about me, for health-related research purposes (even after my incapacity or death)." For the purpose of this study, genotypes and the following phenotypic data have been used in relation to UKBB participants' self-reporting British ancestry (as from UK Biobank data field 21000): main and secondary ICD10 diagnoses (respectively, UK Biobank data fields 41202 and 41024); doctor's diagnosis of non-cancer illnesses, self-reported (UK Biobank data field 20002), and use of medications (UK Biobank data fields 6153, 6154, 6177). The study was approved by the regional Ethics Committee of the Basque Country (CEIm-E ref PI2020167) and performed with UKBB data accessed under UKBB registration nr 30537. The demographics of UKBB individuals is reported in Table 1.

2.2.2 | EGCUT

EGCUT is a volunteer-based sample of the Estonian adult population, which comprises more than 52,000 participants aged >18 years, and previously described eslsewhere.[18] In the informed consent, the participants were made aware that "The Gene Bank enables scientific and applied gene and health research to be carried out in order to determine genes that influence the development of diseases." For the purpose of this study, among EGCUT participants with genotype data available (Illumina 370K, OmniExpress, CoreExome and Global Screening arrays—GSA), cases were selected as those with a K30 ICD10 record in their healthcare data, while unrelated individuals were randomly drawn from the remainder of the cohort as population controls. The study was approved by the local ethics committee at the Estonian eHealth Foundation. EGCUT demographics is reported in Table 1.

TABLE 1 Demographics of cohorts included in the study

	FD cases	CTRLS
UKB	5950	294,202
Age (SD)	58.6 (7.4)	56.6 (8.0)
% Female	64.4	53.6
EGCUT	3383	23,054
Age (SD)	42.3 (18.2)	42.3 (17.2)
% Female	72.3	64.2
MGI	745	34,026
Age (SD)	57.6 (14.8)	56.0 (16.2)
% Female	61.7	52.1
TARGID	192	442
Age (SD)	43.0 (14.2)	55.8 (14.3)
% Female	81.2	53.4

2.2.3 | MGI

MGI is a longitudinal cohort that includes participants recruited via the Michigan Medicine healthcare system, who provided consent for linking medical records to genetic data (Illumina HumanCoreExome v12.1 arrays).[19] With their informed consent, participants gave "*permission for researchers to use your samples and health information to study any disease or health condition.*" We used a data freeze containing 40,000 individuals of PCA-derived European ancestry for the study, which was reviewed and approved by the Michigan University Institutional Review Board. The demographics of MGI individuals is reported in Table 1.

2.2.4 | FD patients from TARGID

Consecutive FD patients ($N = 192$) were recruited at the Translational Research Center for Gastrointestinal Disorder (TARGID), University Hospital Leuven, Belgium, according to Rome III criteria. Individuals were excluded if they showed abnormal findings on upper GI endoscopy, and/or if they had a history of former upper digestive surgery, diabetes, IBS, CD, IBD, or other predominant symptoms typically associated with perturbed upper GI motility. FD patients' genotypes were extracted from available Illumina GSA data. Patients provided written informed consent, and the study was approved by the local ethics committee (S52032). Belgian population control genotype data (Illumina HumanOmni 5M Exome) were obtained from a dataset previously described ($N = 442$).[20] The demographics is reported in Table 1.

2.3 | Cross-disease phenotype analysis

Associations between FD and other ICD10 common diagnoses (≥1% prevalence), self-reported conditions, and use of medications from UKBB data were tested in a logistic regression model adjusting for sex and age using base functions implemented in R (v3.6.1). A false discovery rate (Benjamini & Hochberg) correction for multiple tests (corrected $\alpha = 0.05$) was included in the calculation of statistical significance, in order to control for type I error. Results obtained for ICD10 diagnoses were visualized with circular plots using the Circlize (v0.4.8) package (http://cran.r-project.org/web/packages/circlize/) implemented in R (v3.6.1).

2.4 | Genotype quality control, imputation, and individual GWAS

A common pipeline with minor modifications was applied to all cohorts for quality control (QC) of genotype data, imputation, and FD GWAS tests. Briefly, genotype QC filters were applied per sample (missing rate <95%–99%; heterozygosity rate >3*SD) and per marker (call rate >95%–99%; Hardy-Weinberg equilibrium $p < 1 \times 10^{-4}$), and individuals of non-European ancestry (detected from principal component analysis [PCA]), with excessive relatedness (KING kinship coefficient > 0.0663), or with genotype-phenotype sex discrepancy were excluded from the analyses. Missing genotypes were imputed using the Haplotype Reference Consortium (HRC), UK10K, 1KG, or Estonian reference panels, and only high-quality (INFO > 0.8) common (MAF > 0.01) markers were included in downstream analyses. GWAS association tests were performed with a mixed linear model using SAIGE (v0.29.4.2),[21] in order to control for low case:control ratio and population stratification in UKBB and MGI, and logistic regression implemented in the Epacts software (https://genome.sph.umich.edu/wiki/EPACTS) for EGCUT. Association testing included sex, age, genotyping array, and the first 4–10 principal components as covariates in the analyses.

2.5 | GWAS meta-analysis

Individual GWAS results were brought forward into the meta-analysis pipeline, with the absence of population stratification (inflation factor λ range 0.97–1.03). Prior to meta-analysis, individual GWAS association results were inspected with the R package EasyQC (v9.2),[22] in order to check for data integrity, remove invalid or unmapped markers, and harmonize SNP rsIDs and allele strand coding across datasets. A total of 7,347,476 high-quality SNP markers passing QC, with available summary statistics from at least 2 datasets, and the absence of heterogeneity across studies (Cochran's Q > 0.05) were brought forward into a meta-analysis performed with METAL (v2011-03-25)[23] and the fixed-effect model weighted by *p*-value (showing no population stratification based on a Lambda inflation factor = 1.0195).

2.6 | Downstream annotation of GWAS meta-analysis results

Annotation of suggestive ($p < 5.0 \times 10^{-6}$) FD risk loci was done with Functional Annotation of GWAS (FUMA) v1.3.5 (https://fuma.ctglab.nl/).[24] The 13 association signals were identified based on SNP *p*-value and linkage disequilibrium between markers (LD; $r^2 < 0.4$) and lead SNPs defined as those with the lowest *p*-values in each region. Gene content at FD loci was annotated based on positional, expression quantitative trait loci (eQTL) and 3D chromatin interactions also using FUMA with default parameters. Gene-set enrichment analysis for biological pathways, functions, or tissues was performed using FUMA, and false discovery rate was used for multiple testing correction.

2.7 | PheWAS and genetic correlation analyses

A phenome-wide association study (PheWAS) approach was used to identify known associations ($p < 5 \times 10^{-8}$) of other traits at FD GWAS-suggestive loci using PhenoScanner2.[25,26] Partitioned FD heritability (h^2_{SNP}) on the liability scale was calculated as described (https://nealelab.github.io/UKBB_ldsc/methods.html). Genetic correlation (r_g) with other traits was computed using linkage disequilibrium score regression (LDSC)[27] implemented in the online platform CTG-VL (https://vl.genoma.io/). False discovery rate (FDR) correction was adopted in order to control for type I error.

2.8 | Pilot replication in a case-control cohort

Genotypes of lead SNPs (or best LD proxies with minimum $r^2 > 0.5$) from FD GWAS-suggestive loci were extracted from QC'ed imputed genotype data available for TARGID patients and Belgian controls. GWAS effect alleles were tested for replication using 1-tailed *p* under an additive model with logistic regression adjusting for sex, age, and first 10 principal components from PCA analysis in Plink (v1.9, www.cog-genomics.org/plink/1.9/).[28]

2.9 | Data availability

FD GWAS meta-analysis results have been deposited in the GWAS Catalog (https://www.ebi.ac.uk/gwas/) and are publicly available under accession nr GCST90010719.

3 | RESULTS

3.1 | UK Biobank participants with FD

After excluding potentially confounding diagnoses, participants of non-European ancestry and population outliers, related individuals, and participants with poor phenotype or genotype data, a total of 300,152 UKBB participants were included in the study (Table 1). This subset of UKBB was selected for all analyses described below, in order to be able to compare phenotype and genetic cross-disease results. Among these, 5950 had a K30 diagnosis of functional dyspepsia in their medical records and were therefore selected as FD cases, while the remainder of the population ($N = 294{,}202$) were assigned to the control group. FD cases were more likely to be female and older than controls (respectively, OR = 1.6; $p = 5 \times 10^{-62}$ and OR = 1.03; $p = 9.99 \times 10^{-88}$).

3.2 | Cross-disease analyses I: ICD10 diagnoses

We tested common (≥1% occurrence in UKBB) medical conditions for their differential prevalence in FD cases and controls, based on logistic regression adjusting for sex and age. UKBB diagnoses were studied at various ICD10 code levels (Chapters to four-digit codes), for a total of 99,350,312 data points (331 common ICD10 codes in 300,152 individuals). In these analyses, we observed 284 codes differentially distributed in FD cases and controls (Figure 1 and Table S1). Most ICD10 codes showed a significant increase in FD cases at the Chapter level, including higher risk of *diseases of the digestive system* (K00-K93; OR = 4.0 [95% CI 3.8–4.2], $p < 1.0 \times 10^{-300}$), *symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified* (R00-R99; OR = 3.2 [95% CI 3.0–3.4], $p < 1.0 \times 10^{-300}$), and *certain infectious and parasitic diseases* (A00-B99; OR = 2.1 [95% CI 2.0–2.3], $p = 1.5 \times 10^{-73}$). Expectedly, while reflux-related diagnoses were among the exclusion criteria (see Section 2), *diseases of esophagus, stomach, and duodenum* (K20-K31) still showed the strongest association and most pronounced risk effects (OR = 8.2 [95% CI 7.7–8.7], $p < 1.0 \times 10^{-300}$). At the four-digit level (ie, most informative, detailed diagnosis code) *gastritis, unspecified* (K29.7) and *hernia without obstruction or gangrene* (K44.9) accounted for the strongest risk effects (respectively, OR = 5.4 [95% CI 5.0–5.9] and OR = 5.9 [95% CI 5.5–6.4], both with *p*-values $< 1 \times 10^{-100}$) within the digestive disease domain. A high association was also observed for *cholelithiasis* (K80, OR = 3.1 [95% CI 2.8–3.4], $p < 4.5 \times 10^{-129}$) among the digestive *disorders of gallbladder, biliary tract, and pancreas* (K80-K87). Similarly, most prominent R00-R99 differences were observed for *symptoms and signs involving the digestive system and abdomen* (R10-R19) such as *dysphagia* (R13) and *nausea and vomiting* (R11) (respectively, OR = 6.0 [95% CI 5.3–6.7] and OR = 3.2 [95% CI 2.9–3.5], both *p*-values $< 1 \times 10^{-100}$), together with a series of codes related to pain and the circulatory system such as *abdominal pain* (R10.1, R10.4) and *chest pain* (R07.3 and R07.4) (ORs > 2, *p*-values $< 1 \times 10^{-11}$). Of interest, other notable associations (ORs > 2, *p*-values $< 1 \times 10^{-2}$) were detected for *neurotic, stress-related and somatoform disorders* (F40-F48) including *anxiety disorders* (F41); *ischemic heart diseases* (I20-I25) including *chronic ischemic heart disease* (I25.8 and I25.9), *angina* (I20.0 and I20.9), and *myocardial infarction* (I25.2), and finally *diseases of the musculoskeletal system and connective tissue* (M00-M99) such as *osteoporosis* (M81) and *spondylosis* (M47) (Figure 1 and Table S1).

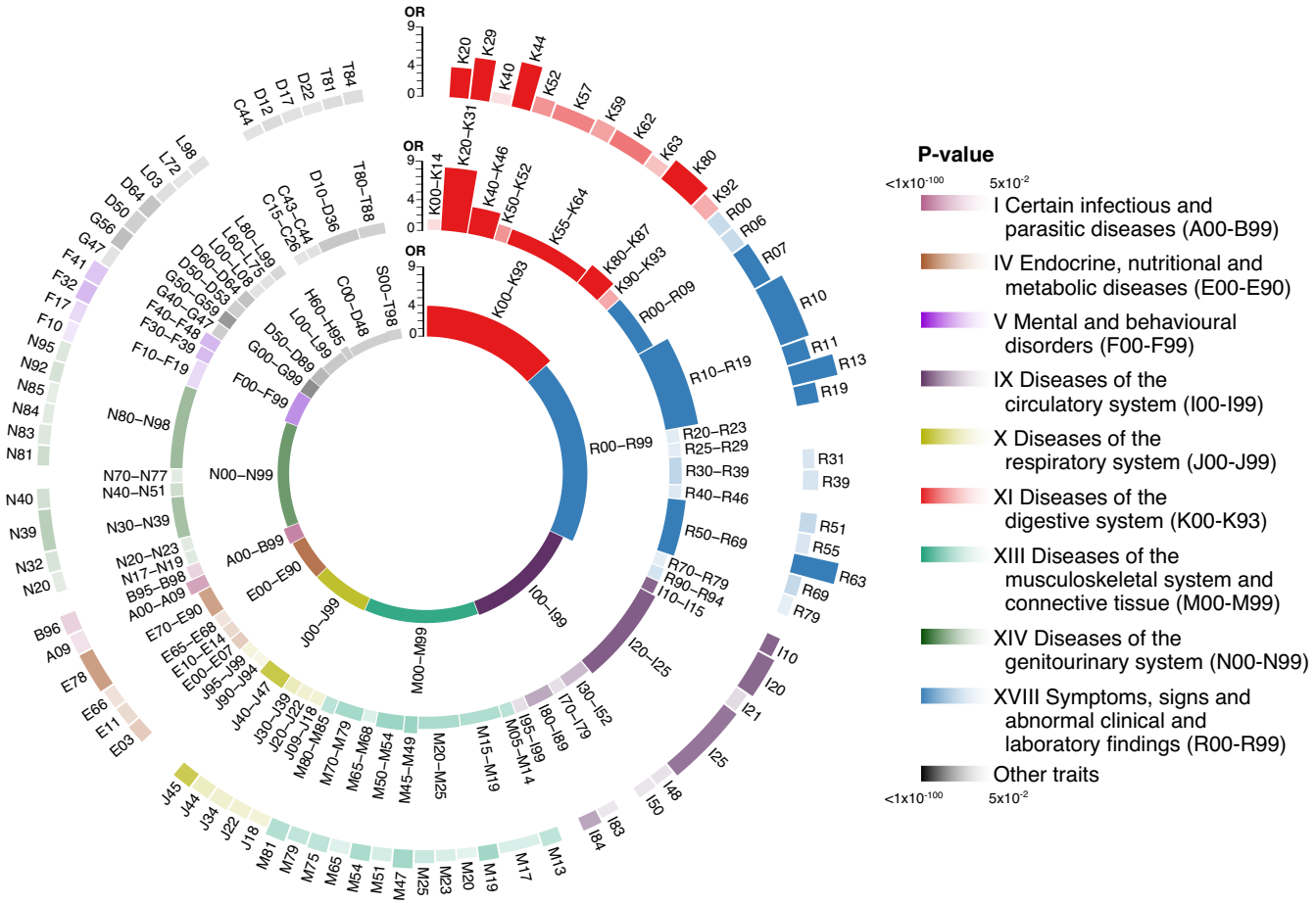

FIGURE 1 Results of cross-disease analysis of selected ICD10 diagnoses in UK Biobank. The results are schematically represented with a circos plot, where each circle represents a level of ICD10 coding (chapter, block, and three-digit levels, respectively, from inner to outer circles). Odds ratios (OR) are reported on the *Y*-axis at each level, while statistical significance is expressed across a color gradient of *p*-values

3.3 | Cross-disease analyses II: conditions and medications, self-reported

We also studied UKBB data collected via touchscreen questionnaire at UKBB participants' enrollment, in relation to common (occurrence ≥1%, $N = 55$) self-reported non-cancer illnesses and use of medications. We detected significant FD association for 15/55 self-reported conditions (Table 2), notably often from disease domains similar to those highlighted in the ICD10 analyses. Expectedly, strongest association was observed for self-reported *gastroesophageal reflux* (OR = 4.3 [95% CI 3.9–4.6], $p = 3.8 \times 10^{-296}$). In addition, *hiatus hernia*, *IBS*, *anxiety/panic attacks*, *angina*, *heart attack/myocardial infarction*, and *osteoporosis/spondylitis* were also markedly increased (Table 2), similar to what observed for diagnoses directly accessed from healthcare records (ICD10). As expected, the use of *medication for pain relief, constipation, or heartburn* was more common in FD patients (OR = 0.55 [95% CI 0.5–0.6], $p = 2.7 \times 10^{-113}$ when testing *none of the above* from questionnaire data; Table 2), with the PPI *omeprazole* (OR = 4.4 [95% CI 4.1–4.7], $p < 1.0 \times 10^{-300}$) and the H2 receptor blocker *ranitidine* (OR = 3.1 [95% CI 2.7–3.5], $p = 6.2 \times 10^{-71}$) showing strongest associations.

3.4 | Genetic analyses: GWAS and follow-up

For the purpose of genetic analyses, we produced GWAS data from UKBB, MGI, and EGCUT (see Section 2). Harmonization and QC filtering of individual datasets allowed GWAS association results to be included in a meta-analysis spanning 7,347,476 high-quality SNP markers in 10,078 FD cases and 351,282 non-FD controls. Due to its larger size, UKB had a more pronounced weight in the meta-analysis (effective size, $N_e = 11{,}664.10$) compared with EGCUT ($N_e = 5900.16$) and MGI ($N_e = 1458.08$). We detected no genome-wide significant association ($p < 5 \times 10^{-8}$), though 28 markers gave rise to suggestive ($p < 5 \times 10^{-6}$) signals mapped to 13 independent loci using FUMA (see Section 2) (Table 3). Computational annotation of suggestive FD risk loci based on FUMA positional, eQTL, and chromatin interaction mapping (Section 2) resulted in the identification of 80 candidate genes (Table 3). Among these were genes related to neuronal development (*NFASC*, *CNTN2*, or *NXPH1*), ion channels (*KCNE4*), adherens junctions (*PTPRK*), cell apoptosis (*DIDO1*), and cell migration (*GID8*). However, tissue-specific and gene-set enrichment analyses did not disclose any significant associations with specific biological pathways, functions, or tissues after correction for multiple testing (not shown). In a pilot experiment of replication, we tested lead SNPs (or their best LD proxies, see Section 2) from the 13 GWAS risk loci in a small cohort of 192 well-characterized FD patients and 442 population controls from Belgium (Table S2). We detected nominal significance for two loci tagged by markers rs2093045 on chromosome 20 and rs2189730 (a weak proxy for rs6463848, see Section 2) on chromosome 9, with concordant genetic risk effects across all tested cohorts (Figure 2).

3.5 | Cross-disease analyses III: PheWAS lookup and genetic correlations

We studied FD-suggestive GWAS loci for their eventual relevance to other traits and conditions, by inspecting public repositories of GWAS data using PhenoScanner2 (see Section 2). This highlighted 3/13 loci to be relevant to other diseases and traits, namely mean platelet counts (locus rs2595968), impedance measures, C-reactive protein and white blood cell counts (rs6719560), and B-cell lymphoma (rs184132620). Broader evidence of genetic correlation with other conditions and traits was obtained from larger analyses of FD GWAS summary statistics using LDSC (implemented in CTG-VL, see Section 2). Although weak, FD showed detectable heritability (FD $h^2_{SNP} = 0.047$, $p = 0.014$) and significant genetic correlation with other upper GI diseases (*diaphragmatic hernia*, *gastritis* and *duodenitis*, *use of omeprazole*, *self-reported reflux*), several pain-related traits (*pain in throat and chest*, *stomach*, *abdominal and pelvic pain*, *back pain*), personality traits (neuroticism), mood/anxiety disorders (*anxiety*, *depression*), and joint disorders (*osteoarthritis*) (Figure 3, Table S3). Thus, once again, these observations were similar to those made in cross-disease phenotypic analyses of UKBB ICD10 and self-reported diagnoses, suggesting shared genetic predisposition.

4 | DISCUSSION

FD is one of the most common functional gastrointestinal disorders, as also highlighted by a recent global epidemiological study from the Rome Foundation.[2] In spite of its large prevalence, FD has received less attention than its lower-bowel counterpart, IBS, and many aspects of its pathogenesis remain poorly understood. In this study, we have used complementary approaches to gain insight into FD pathophysiology through a large-scale investigation of cross-disease overlap at the epidemiological and genetic levels. We extracted FD and other diagnoses from UK Biobank participants' healthcare records and self-reported questionnaires, and we produced and exploited GWAS results for genetic correlation analyses. Hence, with the limitation that ICD10 and self-reported diagnoses could not be formally verified by inspection of individual medical notes, we hereby report the largest population-based survey of FD to date.

The overlap between FD, other GI conditions and, to a lesser extent, personality traits and mood/anxiety disorders has been studied in a few surveys, while the analysis of other conditions has been scarce. The most comprehensive survey, where several disease domains were investigated, included 1669 FD cases and 83,450 matched controls, with clinical data retrieved from paid health insurance claims.[29] In the current report, we studied >300,000 UK Biobank participants including 5950 FD cases ascertained via their healthcare records and interrogated 335 diagnostic codes at four ICD10 classification levels, making it the largest and most comprehensive survey of FD comorbidities.

TABLE 2 Prevalence of self-reported conditions, diagnoses, traits, and medications in UKB patients and controls

	FD %	CTRL %	p_{FDR}	OR (95% CI)
Self-reported conditions, diagnoses, or traits				
Gastroesophageal reflux (gord)/gastric reflux	16.3	4.3	3.8E-296	4.3 (3.9–4.6)
Hiatus hernia	6.3	2.0	6.3E-73	3.0 (2.6–3.3)
Irritable bowel syndrome	5.6	2.7	4.1E-29	2.0 (1.8–2.3)
Angina	6.6	3.7	5.2E-26	1.9 (1.7–2.1)
Cholelithiasis/gall stones	4.4	2.0	2.1E-20	1.9 (1.7–2.2)
Heart attack/myocardial infarction	3.9	2.8	2.1E-08	1.6 (1.3–1.8)
Anxiety/panic attacks	3.0	1.9	2.6E-08	1.6 (1.4–1.9)
Back problem	3.3	2.3	4.6E-06	1.5 (1.3–1.7)
Osteoporosis	3.7	2.0	6.2E-06	1.5 (1.3–1.7)
Osteoarthritis	14.8	11.1	1.4E-05	1.2 (1.1–1.3)
Spine arthritis/spondylitis	1.8	1.1	2.7E-04	1.5 (1.2–1.9)
Asthma	16.5	15.0	3.1E-04	1.2 (1.1–1.3)
Migraine	5.5	4.2	4.0E-04	1.3 (1.1–1.4)
Emphysema/chronic bronchitis	2.3	1.6	1.4E-03	1.4 (1.2–1.7)
Diverticular disease/diverticulitis	2.2	1.4	2.7E-03	1.4 (1.1–1.7)
Prolapsed disk/slipped disk	2.9	2.3	3.7E-03	1.3 (1.1–1.6)
Depression	8.8	7.7	5.9E-03	1.2 (1.1–1.3)
Ovarian cyst or cysts	1.8	1.1	5.9E-03	1.4 (1.1–1.7)
Enlarged prostate	2.1	2.0	8.3E-03	1.4 (1.1–1.6)
pulmonary embolism +/− dvt	1.5	1.0	2.0E-02	1.4 (1.1–1.7)
Self-reported medications				
Omeprazole (eg, Zanprol)	18.2	4.4	<1.0E-300	4.4 (4.1–4.7)
None of the above (Medication for pain relief, constipation, heartburn)	41.9	58.1	2.7E-113	0.5 (0.5–0.6)
Ranitidine (eg, Zantac)	4.8	16	6.2E-71	3.1 (2.7–3.5)
Paracetamol	29.6	21.2	9.9E-50	1.5 (1.5–1.6)
Laxatives (eg, Dulcolax, Senokot)	5.5	2.7	1.5E-23	1.8 (1.6–2.0)
None of the above (Medication for cholesterol, blood pressure, diabetes, or exogenous hormones) (female)	62.2	70.4	9.3E-14	0.8 (0.7–0.8)
Hormone replacement therapy (female)	10.1	7.3	4.4E-10	1.4 (1.3–1.6)
Cholesterol-lowering medication (female)	17.5	12.0	8.6E-09	1.3 (1.2–1.4)
None of the above (Medication for cholesterol, blood pressure or diabetes) (male)	59.1	67.6	1.6E-07	0.8 (0.7–0.8)
Cholesterol-lowering medication (male)	30.0	22.8	4.6E-07	1.3 (1.2–1.4)
Blood pressure medication (female)	22.0	16.8	1.8E-04	1.2 (1.1–1.3)
Aspirin	15.4	13.7	2.3E-02	1.1 (1.0–1.2)
Blood pressure medication (male)	29.2	24.4	2.5E-02	1.1 (1.0–1.3)

A first important observation from these analyses is the large number of conditions (N = 281) whose prevalence is significantly higher in FD patients compared with controls. This is consistent with previous reports on insurance claims,[29] as well as studies looking at FD patients' self-evaluation of their health status.[30] Overall, therefore, there appears to be compelling evidence that FD patients generally experience worse health conditions than the rest of the population, a notion that may have implication for the clinical management of this common disorder and the pressure it poses on the healthcare system; also noteworthy, cross-disease analyses gave rise to remarkably consistent results across ICD10 diagnoses identified via linkage to healthcare records, self-reported conditions from questionnaire data, and genetic correlation using GWAS summary statistics. This suggests that FD and comorbid conditions co-manifest because of shared genetic architecture and the contribution of genes and pathways with multiple (pleiotropic) disease risk effects on a spectrum of ailments.

TABLE 3 GWAS meta-analysis association results and annotation of suggestive loci

Lead SNP	Chr	EA	OA	EAF	*Z*-score	*p*	Nearest gene	Mapped genes
rs2595968	1q32.1	A	G	0.283	4.8	2.0E-06	NFASC	NFASC[p,c], CNTN2[e,c], TMEM81[e,c], CDK18[e], MDM4[c], LRRN2[c], DSTYK[c], TMCC2[c], KLHDC8A[c]
rs6719560	2q36.1	T	C	0.108	4.9	8.4E-07	KCNE4	KCNE4[p,e,c], FARSB[e,c], PAX3[c], CCDC140[c], MOGAT1[c], SCG2[c], AP1S3[c], WDFY1[c], MRPL44[c], FAM124B[c], CUL3[c]
rs144885331	3p24.3	C	T	0.027	4.9	8.2E-07	ZNF385D	ZNF385D[p]
rs9868674	3q22.1	T	C	0.410	4.7	2.5E-06	CPNE4	CPNE4[p,e], ASTE1[c], NEK11[c], MRPL3[c]
rs80062354	3q26.31	T	C	0.194	−4.8	1.7E-06	SPATA16	SPATA16[p,c], NLGN1[c], NAALADL2[c]
rs961136	5p15.33	T	C	0.014	4.6	4.7E-06	IRX2	ADAMTS16[c]
rs67375755	5q34	T	C	0.065	−4.9	1.0E-06		HMMR[c], MAT2B[c], TENM2[c]
rs17245411	6q22.33	C	T	0.040	−4.6	3.3E-06	PTPRK	PTPRK[p,e],THEMIS[c], LAMA2[c], TMEM244[c], L3MBTL3[c]
rs6463848	7p21.3	T	C	0.404	−5	5.2E-07		NXPH1[c], NDUFA4[c], PHF14[c], THSD7A[c]
rs9696092	9p21.3	C	T	0.459	−4.6	4.7E-06	CDKN2B	MTAP[c], RP11-145E5.5[c], C9orf53[c], CDKN2A[c], CDKN2B[c]
rs184132620	15q21.2	C	A	0.014	−4.6	3.5E-06	ARPP19	ARPP19[p,c], FAM214A[p,c], LYSMD2[e], SCG3[c], TMOD3[c], LEO1[c], MAPK6[c], BCL2L10[c], GNB5[c], MYO5C[c], UNC13C[c], RSL24D1[c], RAB27A[c], PIGB[c], DYX1C1[c], UQCRFS1[c]
rs17597505	19q13.11	T	C	0.051	4.6	3.8E-06	–	VSTM2B[c], POP4[c], C19orf12[c], CCNE1[c], URI1[c], ZNF536[c], TSHZ3[c], DPY19L3[c], PDCD[c], SLC7A9[c]
rs2093045	20q13.33	C	T	0.323	−4.8	1.8E-06	SLC17A9	DIDO1[p,e,c], GID8[p,e,c], SLC17A9[p,e,c], COL9A3[e], TCFL5[e,c], BHLHE23[c]

EA, effect allele; OA, other allele; EAF, effect allele frequency; Nearest gene, nearest gene within 100 kb from lead SNP (if any). Mapped genes include protein-coding genes mapped by FUMA, [p]genes physically mapped; [e]genes mapped by eQTLs; [c]genes mapped by chromatin interactions.

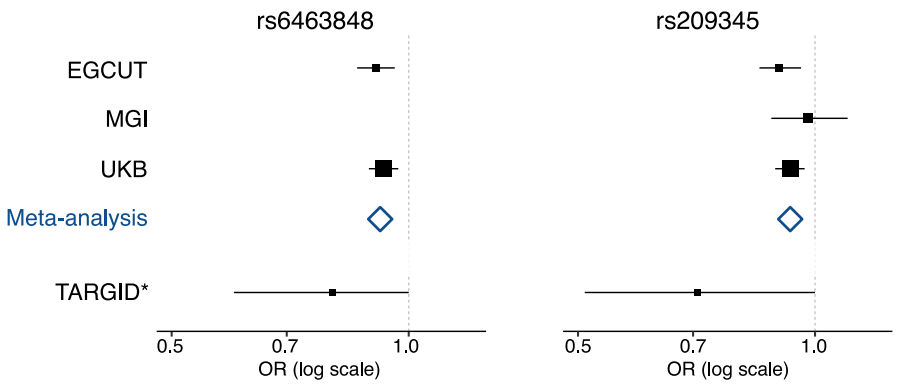

FIGURE 2 GWAS and replication results for selected markers. The Forest plots show association results for SNPs rs6463848 and rs2093045, reported for each with respective odds ratio (OR) and 95% confidence intervals, according to sample size (size of the symbol). (*) For the TARGID case/ctrl analysis, data for the rs6463848 locus correspond to marker rs2189730, which is the best LD proxy ($r^2 = 0.5$) with genotype data available in this cohort

A series of conditions from the digestive disease domain were expectedly found to occur more often in FD patients than controls, either as ICD10 codes from healthcare records or as self-reported traits. For instance, while excluded in the ICD10 analyses (see Section 2), IBS and reflux (including its prescriptions drugs omeprazole and ranitidine) were among the conditions most often self-reported by FD patients and are notoriously associated with dyspepsia.[31–34] Similarly, gastritis, hiatus hernia, and eventually chest pain and angina, which were all linked to FD in UK Biobank (as ICD10 and self-reported diagnoses as well as related medications), may represent proxies for reflux due to heartburn and/or other overlapping symptoms. At the same time, upper abdominal pain is a key feature of FD patients with epigastric pain syndrome,[35] but can also occur postprandially in the postprandial distress syndrome group.[36]

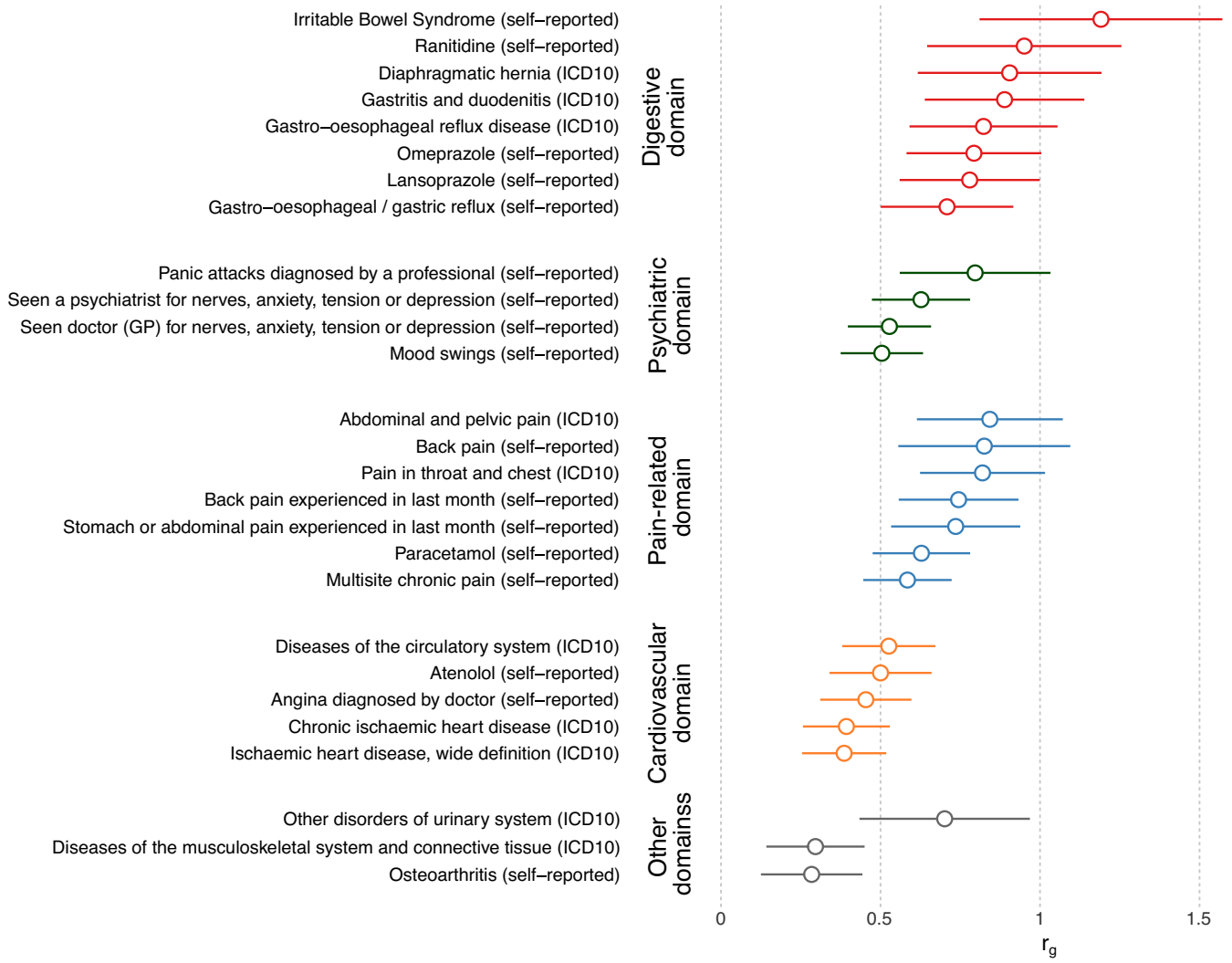

FIGURE 3 Results of LDSC analyses and genetic overlap with selected traits. Genetic overlap is reported as regression score (r_g) with standard error, for selected conditions, diagnoses, or traits from different disease domains. ICD10: conditions, diagnoses, or traits based on healthcare records; self-reported: conditions, diagnoses, or traits based on questionnaire data

Finally among digestive diseases, gallstone prevalence was much higher in FD patients, who in fact represent 6.3% of cholelithiasis cases among the selected UK Biobank participants, an observation that may be relevant to studying the source of symptoms and avoiding the risk of ineffective cholecystectomies.[37] We also detected increased prevalence of personality traits and mood/anxiety disorders among FD patients (both as ICD10 and self-reported conditions), which is consistent with previous reports and the fact that FD individuals tend to show a higher degree of somatization.[38,39] In particular, the prevalence of anxiety and depression has been shown to correlate with the number and severity of comorbid FGIDs,[40] again an observation made here in relation to the high number of co-manifestations detected in FD cases compared with the rest of UK Biobank. Finally, several other associations were detected that represent novel observations, including the associations with osteoarthropathies and, to a lesser extent, diseases of the circulatory system. Association with osteoporosis was detected in the analysis of ICD10 and self-reported diagnoses but not among the significant genetic correlations, which could be interpreted as a possible consequence of long-term PPI use and its known effect on bone density.[41] Spondylosis, spondylitis, and other diseases of the bone and joints were linked to FD both in the survey of ICD10 and self-reported diagnoses and in the genetic correlations with other conditions and traits, suggesting a possible common pathogenetic denominator. Increased prevalence of rheumatological disorders has been previously reported in FGIDs,[42,43] while spondylosis has not been studied in FD. Of interest, cervical spondylosis has been recently proposed to induce FGIDs in an experimental rat model.[44] Heart disease has been studied in relation to upper gastrointestinal symptoms, and FD patients appear to more often suffer from circulatory system disease, myocardial infarction, angina, and chest pain.[45] While some risk factors (smoking, obesity, high blood pressure) are known to be common to FD and heart disease, the explanation for the observed comorbidity has often been sought in the side effects of respective pharmacological treatments. However, the LDSC results reported here, where significant genetic correlation is detected for FD and

other heart conditions, suggest commonalities exist in the genetic architecture of these traits, which may thus arise from similar, partially overlapping pathophysiological mechanisms.

We also report here the first GWAS and meta-analysis of FD, performed exploiting genotype data and information on ICD10 diagnoses from healthcare records in three large population-based cohorts. Although more than 360,000 individuals were included in the analyses, the total number of FD cases was limited to 10,078 and likely not enough to identify robust association signals at the genome-wide level of significance ($p < 5 \times 10^{-8}$). This is not surprising given that FD shows detectable but only weak heritability (5%), and, similar to other common FGIDs such as IBS, this represents a challenge for gene hunting efforts requiring massive sample size. However, genetic correlation analyses (which do not solely rely on genome-wide significant signals) suggest that the genetic factors predisposing to FD also contribute to risk of several other conditions, indeed many of which often co-manifesting in FD, as reported in this and previous surveys. Hence, genetic liability in FD may extend across a much wider spectrum of conditions and traits, with potential implications for a better understanding of its pathophysiology and the identification of therapeutically actionable pathways from the study of genetically overlapping diseases.

Finally, while the thirteen GWAS-suggestive signals identified here may represent best candidates for investigation in future studies, we report preliminary replication for 2 loci in a pilot case/control analysis of 192 FD patients defined according to gold standard Rome III Criteria. This is for markers rs2189730 and rs2093045, respectively, tagging FD-suggestive risk loci on chromosomes 7 and 20. Among four genes mapped via chromatin interactions to the risk locus on chromosome 7, *NXPH1* likely represents the best candidate to play a role in FD, since polymorphisms in this gene have been previously reported to also affect risk of IBS.[46] *NXPH1* codes for neurexophilin-1, a glycoprotein ligand of the α-neurexin receptors involved in synaptic neurotransmission and plasticity in the brain.[47] Neurexophilin-1 is primarily expressed in inhibitory neurons where it modulates γ-aminobutyric acid (GABA) receptor-mediated signaling, thus possibly affecting FD-relevant motor functions and GI motility similar to what has been shown for other members of the neurexophilin family.[48] Several genes map to the chromosome 20 risk loci, including *GID8*, *DIDO1*, *SLC17A9*, and *TCFL5*, whose expression is detected in human esophagus and is affected by eQTLs for the rs2093045 lead SNP. Among these, *GID8* may be of particular interest as it codes for TWA1, a nuclear protein that is an important member of the CTLH complex regulating cell migration,[49] hence potentially relevant to upper GI development and integrity.

In summary, we report here a large-scale survey of FD comorbidity and genetic predisposition, which highlights considerable clinical and genetic overlap with several other conditions. This novel knowledge contributes to a better understanding of FD pathophysiology and may be relevant to the identification of actionable pathways from the study of common disease mechanisms.

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CONFLICT OF INTEREST

No competing interests declared.

AUTHORS' CONTRIBUTION

JT and MD conceptualized and designed the study; FC, MTL, AP, LH, VT, RL, AF, SZ, MB, MZ, TE, JT, and MD involved in cohorts, patient characterization, and data collection; KGE, MTL, AP, and MZ carried out statistical analyses; KGE, FC, MTL, LB, MZ, TE, JT, and MD analyzed and interpreted the data; MD obtained funding, administrative and technical support, and supervised the study; KGE, FC, JT, and MD drafted the manuscript, with input and critical revision from all other authors.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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