

The overlap of atopy and functional gastrointestinal disorders among 23 471 patients in primary care

M. P. Jones*, M. M. Walker[†], A. C. Ford^{‡,§} & N. J. Talley[†]

*Psychology Department, Macquarie University, North Ryde, NSW, USA.

[†]Faculty of Health and Medicine, University of Newcastle, Callaghan, NSW, USA.

[‡]Leeds Gastroenterology Institute, St. James's University Hospital, Leeds, UK.

[§]Leeds Institute of Biomedical and Clinical Sciences, Leeds University, Leeds, UK.

Correspondence to:

Dr M. P. Jones, Psychology Department, Macquarie University, North Ryde, NSW 2109, Australia.
E-mail: Mike.Jones@mq.edu.au

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SUMMARY

Background

Activation of the immune system has been demonstrated in atopy and functional gastrointestinal disorders (FGIDs). Previous data from our group have suggested a connection between immune dysregulation, FGIDs and mood disorders.

Aim

To investigate if these data translate to clinical practice and examine connections from the perspective of FGIDs to determine whether atopy and FGIDs are connected via mood disorders.

Methods

Evidence of irritable bowel syndrome (IBS), functional dyspepsia (FD) and constipation was sought from the medical records of 30 000 primary care records over a minimum 5 year period. The same records yielded diagnoses of four atopic conditions (asthma, eczema, allergic rhinitis/hay fever and conjunctivitis).

Results

Atopic conditions were found in excess among all FGID groups considered when compared with controls. In the groups with IBS alone (OR = 1.43, 1.29–1.58), FD alone (OR = 1.41, 1.26–1.58) and those with multiple FGIDs (OR = 1.92, 1.75–2.12) there was elevated prevalence of asthma compared with controls without a FGID. Across disorders the excess was generally highest among patients diagnosed with multiple FGIDs (rhinitis/hay fever OR = 3.74, 3.32–4.20; conjunctivitis OR = 3.00, 2.49–3.62) and was only partly explained by a common association between both FGIDs and atopic conditions with mood disorders, although not for every atopic/FGID combination (rhinitis/hay fever OR = 2.60, 2.29–2.96, conjunctivitis OR = 2.34, 1.90–2.87).

Conclusions

Irritable bowel syndrome, functional dyspepsia and constipation share an association with atopy that is only partly explained via a common connection with mood disorders. These data have important implications for understanding both the pathophysiology of functional gastrointestinal disorders and development of new treatments.

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INTRODUCTION

Disease can arise through differing pathways, which include infection, metabolic disturbances, inflammation and immune dysregulation. The latter include immune conditions such as rheumatoid arthritis¹ and psoriasis² which have a predominant T-helper-1 (TH1) type immune response. Other immune diseases have an atopic diathesis, such as asthma³ and atopic dermatitis.⁴ Asthma is characterised by a predominant T-helper-2 (TH2) type immune response. There are anatomical and immunological links with the lung and the gut and common disordered TH2 immune responses occur in atopy (asthma, eczema rhinitis/hay fever in particular) and functional gastrointestinal disorders (FGIDs).⁵ Disordered cellular immunity has been shown to play a role in some FGIDs, particularly irritable bowel syndrome (IBS) with increased mast cell infiltration in the small and large intestine.^{6–8} Eosinophils have also shown to be elevated in the duodenum of functional dyspepsia (FD) patients compared with healthy controls.⁹ A TH2 cytokine profile, as seen in atopy, is also seen in patients with FGIDs.¹⁰

Further, co-morbidity has been demonstrated between a number of these conditions. Focussing on overlap between FGIDs and other conditions, Powell *et al.*¹¹ demonstrated an excess of IBS among patients with general practitioner (GP)-diagnosed allergic conditions, specifically asthma and allergic rhinitis in a United Kingdom primary care setting. The odds ratio (OR) for IBS among asthma patients was twofold that of controls, indicating a substantial association between these conditions. Cole *et al.*¹² found a similar pattern for IBS prevalence in asthmatics that was not apparently due to asthma therapy, although another study has shown an increased risk of IBS in asthma patients alongside a decreased risk for IBS in oral steroid users.¹³ Their findings were replicated by Panicker *et al.*¹⁴ who reported an OR for IBS of almost three in an allergy out-patient sample in Kuwait and Hunskar *et al.* in Norway¹⁵ who also found an association with IBS and asthma. Similar findings have also been made in the upper gastrointestinal tract for FD¹⁶ and chronic idiopathic constipation (CIC) in both adults¹⁷ and children.¹⁸

The observation that there is an overlap with the immune inflammation in FGIDs and atopic conditions, combined with empirical evidence of an association between some FGIDs and atopic conditions suggests, although does not prove, that both types of disease may be expressions of a common underlying immune dysfunction.

The purpose of this study was to build upon available evidence by considering a wider range of FGIDs and atopic conditions than previously studied and to control for potentially confounding variables. The potentially confounding variables are age, gender, anxiety disorder and depressive disorder, chosen as they are known to play a role in several FGIDs. We hypothesised these variables may play a role in explaining any excess in atopic conditions found among individuals with FGIDs.^{19, 20}

METHODS

Data acquisition

Subjects were drawn from general practices across the United Kingdom²¹ with data captured from electronic medical records via the Health Improvement Network (THIN). THIN collects raw data from practices, queries possible data errors and resolves fields pertaining to diagnoses, prescriptions and referrals to a common basis for comparability across practices. It has been shown to be broadly representative of the demographics of the United Kingdom.²¹ The validity of gastrointestinal disorder diagnoses has been undertaken and the diagnostic records in THIN have been shown to be valid.²² THIN follows equivalent methodology to the General Practice Research Database which has also demonstrated diagnostic validity.²³ This procedure has been approved by the National Health Service (UK) South-East Multi-Centre Research Ethics Committee. Funding to obtain access to the data was provided by a grant from the Psychology Department at Macquarie University. Diagnoses are coded according to the Read code system²⁴ and prescriptions are coded according to the British National Formulary system.²⁵ THIN ensures high data quality and engages with practices to correct errors. Data of certified quality are flagged as such. Only data with an explicit quality flag were used for this study.

Subjects

Inclusion criteria were GP diagnosis of IBS, FD or CIC, at least 5 years of medical record follow-up, and an acceptable patient record quality flag. In prospective studies IBS, FD and CIC are usually defined according to the Rome III criteria.²⁶ However, GPs typically do not use such strict criteria.^{27, 28} This is both a strength and a weakness of the study, in that definitions used will not necessarily be consistent across physicians, but as the majority of diagnosis and treatment of FGIDs is undertaken by GPs²⁷ and organic disease is rare in the

community,²⁹ the data are an excellent representation of normal clinical practice.

Gastrointestinal disease definition

As it is possible that GPs will not code diagnoses of IBS and FD in those terms, the Read code term list was searched for additional terms that might be indicative of these disorders. Examples of indicative diagnoses considered are spastic colon in the case of IBS and impaction for CIC. For IBS the Read codes employed were (14CF.00, J521000, J521.00, J521.11, J521.13) all of which explicitly indicate either *irritable bowel* or *spastic colon*. For FD a single occurrence of the codes (1958.00, 8Hg5.00, 8Hl0.00, 9NNK.00, E264400, Eu45318, J16y400) were considered sufficient in themselves to indicate dyspepsia while the codes (J16y412, 195.00, 1954.00) were considered sufficient if multiple diagnoses were identified as they all indicate indigestion. Read codes indicating heartburn or reflux alone were not considered diagnoses of FD. CIC was indicated through codes (7728100, 8138.00, J503.00, J503100, J503y00, J503z00, Jyu5100) indicating constipation explicitly while code (J520000, J520300) were considered indicative of constipation as they refer to intestinal or faecal impaction. Several codes explicitly indicate chronic constipation (E264500, J520.00, J520100, J520200, J520400) and a single record of these codes has been taken as sufficient for membership of the CIC group, whereas more than one medical records was required for the other code specified which are less clearly chronic constipation. While we interpret these disease codes as representing an FGID, due to the low prevalence of organic disease in the community²⁹ there is no explicit indication of cause or aetiology in the medical record. However, the extremely large sample size means that it is likely that the small number of organic cases will be vastly outweighed by the majority of true FGID cases.

Atopic disease definition

Four atopic conditions were identified with sufficient prevalence to yield reliable data. The codes used reflect the retrospective nature of this study and include both direct and indirect indicators of disease. Asthma was defined via codes indicating diagnosis of, treatment for or monitoring of asthma, whereas the codes used for all other diseases represent direct evidence of the disease. The list of individual Read codes is extensive and is provided as an on-line appendix to this paper (Appendix S1).

Anxiety and depression definition

Anxiety was flagged through both direct indications of clinical anxiety such as code E200200 (generalised anxiety disorder) and through indirect indications such as Z4L1.00 (anxiety counselling). Similarly, depression was flagged through both direct indications such as E113.00 (recurrent major depressive episode) and indirect indications such as 9HA0.00 (on depression register). For both anxiety and depression two or more records of diagnoses were required.

Statistical approach

The statistical aim of this study was to determine whether the prevalence of certain atopic conditions was higher in FGIDs than controls without a FGID. We also sought to determine whether any association between atopic disease and FGID groups could, in part, be accounted for by factors known to be involved in FGIDs such as female gender, anxiety or depression. As FGID prevalence is known to decrease with age,^{30, 31} this was also controlled for. We adopted a hierarchical modelling approach fitting three unconditional logistic regression models to each atopic disease outcome; model 1 reports unadjusted ORs comparing individuals with an FGID to controls without an FGID, model 2 controls for age and gender while model 3 controls for age, gender, anxiety, and depression. For each model, ORs were reported along with 95% confidence intervals (CIs). We interpreted a reduction in OR between model 1 and models 2 or 3 as possible explanations for any observed association.

Given the well-documented overlap of FGIDs³² it was decided *a priori* to differentiate single FGID individuals from those with overlapping disorders to form five mutually exclusive study groups; controls without an FGID, IBS alone, FD alone, CIC alone or multiple FGIDs. The prevalence of each atopic disorder within each of the four FGID groups was compared with prevalence among controls without a FGID.

The three-way overlap between FGIDs, mood disorders and atopic conditions has been assessed by classifying individuals as being diagnosed or not diagnosed with (i) any FGID, (ii) either mood disorder and (iii) any atopic disorder and representing the overlap between pairs or all three disorder groupings in a Venn diagram (Figure 3). Percentages reported are of the total sample. It is important to note that the overlaps considered here are only between those FGIDs, mood disorders and atopic conditions investigated in this study.

The sample size available (>23 000) was determined by the number of patients who met the inclusion criteria

but provides statistical power was >0.9 at the 0.01 (two-tailed) level of statistical significance for any OR of 2.0 or greater based on the power function for binary logistic regression assuming a correlation (r^2) of 0.25 for a risk factor of interest.

RESULTS

General practice medical records were supplied from the THIN database for 30 000 patients who met inclusion criteria as far as could be determined from internal mechanisms. Inspection of the data by the authors excluded 6529 individuals on the basis of mortality or failure of quality indication, leaving a total sample of 23 471 subjects, drawn from over 300 general practices across the United Kingdom. Patient groups were controls without an FGID 10 926, IBS alone 4326, FD alone 3477, CIC alone 340 and multiple FGIDs 4402 (Figure 1).

Demographics

The sample was predominantly female, overall ($n = 15\,507$, 66%) with the control ($n = 6960$, 64%) and FD alone ($n = 2043$, 59%) having the lowest female representation and the multiple FGIDs ($n = 3136$, 71%) and IBS alone ($n = 3143$, 73%) groups had the highest female representation. The cohort has records over a prolonged period resulting in patients who are relatively old at the time of analysis. In 2010 overall mean age of the FGID cohorts was 60 years (s.d. = 13) with IBS alone being the youngest (mean age = 55 years, s.d. = 13) and constipation alone being the oldest (mean = 74 years, s.d. = 10).

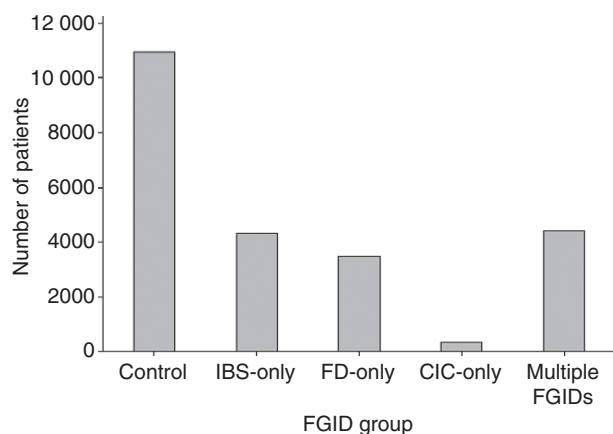


Figure 1 | Number of patients in the control and functional GI disorder (FGID) groupings. IBS, irritable bowel syndrome; FD, functional dyspepsia; CIC, chronic idiopathic constipation.

Mood disturbance

The lifetime prevalence of both anxiety and depression were elevated in all FGID groups compared with controls without a FGID ($P < 0.001$), and among FGID groups mood disorder prevalence was highest in the multiple FGID group (Figure 1). Within disease groups, both anxiety and depression were most prevalent in the multiple FGID group. In terms of anxiety, this difference reached statistical significance for multiple FGIDs compared with IBS alone (OR = 2.53, 95% CI: 2.25–2.84), FD alone (OR = 3.66, 95% CI: 3.19–4.20) and CIC alone (OR = 2.05, 95% CI: 1.50, 2.80). In terms of depression this difference reached statistical significance for multiple FGIDs compared with IBS alone (OR = 1.86, 95% CI: 1.70–2.03), FD alone (OR = 3.44, 95% CI: 3.09–3.83) and CIC alone (OR = 2.10, 95% CI: 1.63, 2.70).

Atopic conditions

Any atopic condition. All disease groups demonstrated a statistically significantly higher prevalence of any atopic condition compared with controls without a FGID (Table 1) with the highest prevalence among the group with multiple FGIDs. After controlling for age, gender and mood disorders the prevalence of any atopic condition in all FGID groups over controls remained statistically significant (Table 1).

Asthma. In the groups with IBS alone, FD alone and those with multiple FGIDs there was a statistically significant elevated prevalence of asthma compared with controls without a FGID (Table 1). The CIC alone group also yielded a higher prevalence of asthma than controls without an FGID but the difference was not statistically significant (Table 1). After controlling for age, gender, and mood disorders the excess among the FD alone (OR = 1.27) and multiple FGID (OR = 1.50) groups compared with controls without an FGID remained statistically significant (Table 1). The highest excess of asthma prevalence over controls without an FGID was found in the multiple FGID group (Table 1).

The change in OR estimate after controlling for demographic and mood factors was most pronounced in the IBS alone group (1.43 down to 1.10). This may suggest some of these factors partly explain the excess of asthma in IBS compared with controls.

Eczema. All disease groups demonstrated a statistically significantly higher prevalence of eczema compared with controls without an FGID (Table 1). After controlling for age, gender, and mood disorders the excess among

Table 1 | Distribution of atopic conditions and mood disorders across functional gastrointestinal disorders

Atopic condition	Prevalence (%)				
	Health (n = 10 926)	IBS (n = 4326)	FD (n = 3477)	Constipation (n = 340)	Overlap FGIDs (n = 4402)
Anxiety, % (n)	4.0 (437)	11.8 (509)	8.4 (293)	14.1 (48)	25.2 (1110)
Depression, % (n)	10.5 (1151)	27.1 (1170)	16.7 (579)	24.7 (84)	40.8 (1794)
Atopy (%)†	32.7 (3575)	44.8 (1938)	41.8 (1454)	50.3 (171)	54.6 (2405)
OR (95% CI) P‡	1.0 (–)	1.66 (1.55, 1.79)***	1.48 (1.37, 1.60)***	2.08 (1.68, 2.58)***	2.48 (2.31, 2.66)***
OR (95% CI) P§	1.0 (–)	1.46 (1.34, 1.59)***	1.41 (1.30, 1.53)***	2.06 (1.65, 2.55)***	2.29 (2.13, 2.47)***
OR (95% CI) P¶	1.0 (–)	1.40 (1.29, 1.52)***	1.38 (1.27, 1.50)***	1.93 (1.55, 2.40)***	2.03 (1.88, 2.19)***
Asthma (%)	11.0 (1202)	15.0 (648)	14.9 (517)	13.2 (45)	19.2 (845)
OR (95% CI) P‡	1.0 (–)	1.43 (1.29, 1.58)***	1.41 (1.26, 1.58)***	1.23 (0.90, 1.70) n	1.92 (1.75, 2.12)***
OR (95% CI) P§	1.0 (–)	1.15 (1.02, 1.30)*	1.30 (1.16, 1.46)***	1.21 (0.88, 1.66) n	1.70 (1.54, 1.88)***
OR (95% CI) P¶	1.0 (–)	1.10 (0.98, 1.24) n	1.27 (1.14, 1.43)***	1.13 (0.82, 1.56) n	1.50 (1.35, 1.67)***
Eczema	21.4 (2334)	28.0 (1211)	27.5 (955)	37.9 (129)	35.2 (1548)
OR (95% CI) P‡	1.0 (–)	1.43 (1.32, 1.55)***	1.39 (1.28, 1.52)***	2.25 (1.80, 2.82)***	2.00 (1.85, 2.16)***
OR (95% CI) P§	1.0 (–)	1.51 (1.31, 1.57)***	1.44 (1.31, 1.57)***	2.26 (1.81, 2.83)***	2.06 (1.90, 2.23)***
OR (95% CI) P¶	1.0 (–)	1.46 (1.33, 1.61)***	1.41 (1.29, 1.55)***	2.16 (1.73, 2.71)***	1.88 (1.72, 2.04)***
Hay fever/rhinitis	5.0 (541)	13.4 (581)	7.8 (270)	7.9 (27)	16.3 (717)
OR (95% CI) P‡	1.0 (–)	2.98 (2.63, 3.37)***	1.62 (1.39, 1.88)***	1.66 (1.11, 2.48)*	3.74 (3.32, 4.20)***
OR (95% CI) P§	1.0 (–)	1.99 (1.73, 2.30)***	1.39 (1.20, 1.63)***	1.59 (1.06, 2.39)*	2.96 (2.62, 3.36)***
OR (95% CI) P¶	1.0 (–)	1.90 (1.65, 2.20)***	1.36 (1.16, 1.58)***	1.48 (0.99, 2.22) ns	2.60 (2.29, 2.96)***
Allergic conjunctivitis	1.9 (212)	4.8 (206)	3.1 (108)	4.1 (14)	5.6 (247)
OR (95% CI) P‡	1.0 (–)	2.53 (2.08, 3.07)***	1.62 (1.28, 2.05)***	2.17 (1.25, 3.77)**	3.00 (2.49, 3.62)***
OR (95% CI) P§	1.0 (–)	2.14 (1.71, 2.68)***	1.57 (1.24, 2.00)***	2.12 (1.22, 3.69)**	2.71 (2.22, 3.30)***
OR (95% CI) P¶	1.0 (–)	2.04 (1.63, 2.55)***	1.53 (1.20, 1.94)***	1.96 (1.13, 3.41)*	2.34 (1.90, 2.87)***

† Atopy = any of the specific conditions listed in Table 1.

‡ Unadjusted.

§ Adjusted for age, gender.

¶ Adjusted for age, gender, anxiety disorder, depressive disorder.

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.0001$.

all disease groups compared with controls without a FGID remained statistically significant (Table 1). The highest excess of eczema prevalence over controls without an FGID was found in the CIC alone group (OR = 2.25), although this was only slightly higher than the multiple FGID group (OR = 2.00, Table 1).

Hay fever/allergic rhinitis. Similarly, all disease groups demonstrated a statistically significantly higher prevalence of hay fever/allergic rhinitis compared with controls without a FGID (Table 1). After controlling for age, gender and mood disorders the excess among all disease groups compared with controls remained statistically significant (Table 1) except for the constipation alone group. The highest excess of hay fever/allergic rhinitis prevalence over controls without a FGID was found in the multiple FGID group (OR = 3.74), although the OR for the IBS alone group was also large (OR = 2.60, Table 1).

The change in OR estimate for hay fever/allergic rhinitis after controlling for demographic and mood factors

was most pronounced in the IBS alone group (2.98 down to 1.90). This suggests these factors could explain some of the excess of hay fever/allergic rhinitis in IBS, compared with controls without a FGID.

Allergic conjunctivitis. All disease groups demonstrated a statistically significant elevation in the prevalence of conjunctivitis compared with controls without an FGID (Table 1). After controlling for age, gender and mood disorders the excess among all disease groups compared with controls remained statistically significant (Table 1). The highest excess of conjunctivitis prevalence over controls without an FGID was found in the multiple FGID group (OR = 3.00, Table 1).

Influence of increasing number of FGIDs

For all atopic conditions except for eczema the prevalence of atopy was highest in the multiple FGID group (Table 1). For eczema, the prevalence was almost identical in the constipation and multiple FGID groups

(Table 1). We also found that among patients with multiple FGIDs the prevalence of atopy was higher in those with all three FGIDs compared with those with only two FGIDs (Figure 2). This finding was consistent across all atopic conditions, although the degree of elevation in those with all three FGIDs compared with those with two FGIDs was most marked for conjunctivitis.

Overlap between FGIDs, atopy and mood disorders

Figure 3 reports the percentage of the sample who met none of the three disorder types, single types, pairs of types and all three types. The figure suggests a strong three-way overlap between FGIDs, atopy and mood disorders. Of overlaps with FGIDs, the overlap with atopy was the most common with 25% of the entire sample ($n = 5968$) yielding both FGID and atopy diagnoses. In contrast 7% of the entire sample ($n = 1555$) yielded both FGID and mood diagnoses. A smaller but non-trivial group comprising 3% of the entire sample ($n = 717$) yielded all three types of disorders.

Order of onset

Of 5968 patients in whom both an FGID and an atopic condition was identified in the medical record the vast majority (78.6%, $n = 4692$) did not have an atopic condition at the time their FGID was first recorded.

DISCUSSION

We sought to examine the overlap between several prevalent FGIDs and a number of atopic conditions. We also considered FGIDs in terms of patients suffering from single conditions or multiple FGIDs to determine whether there was some form of 'dose-response' in individuals suffering from more than one condition. Our rationale for conducting this study was that in a small number of previous studies established a tentative connection between the two conditions.^{9, 33} We also considered a number of factors known to be involved in several FGIDs, including age, gender and mood disorder in order to determine whether these may explain some of the association.

Our data suggest a consistent elevation in the prevalence of all four atopic conditions in IBS alone, FD alone, CIC alone, and multiple FGIDs compared with controls without a FGID in a primary care setting. The degree of excess varied with both the specific atopic condition and the FGID. The most consistent evidence was that individuals diagnosed with multiple FGIDs have the highest excess of atopic conditions. With the exception of eczema, the multiple FGID group always yielded higher ORs than those diagnosed with a single condition (Table 1), although this was less evident for asthma. In the multiple FGID group the odds of hay fever/allergic rhinitis were 3.7-fold higher than controls without an

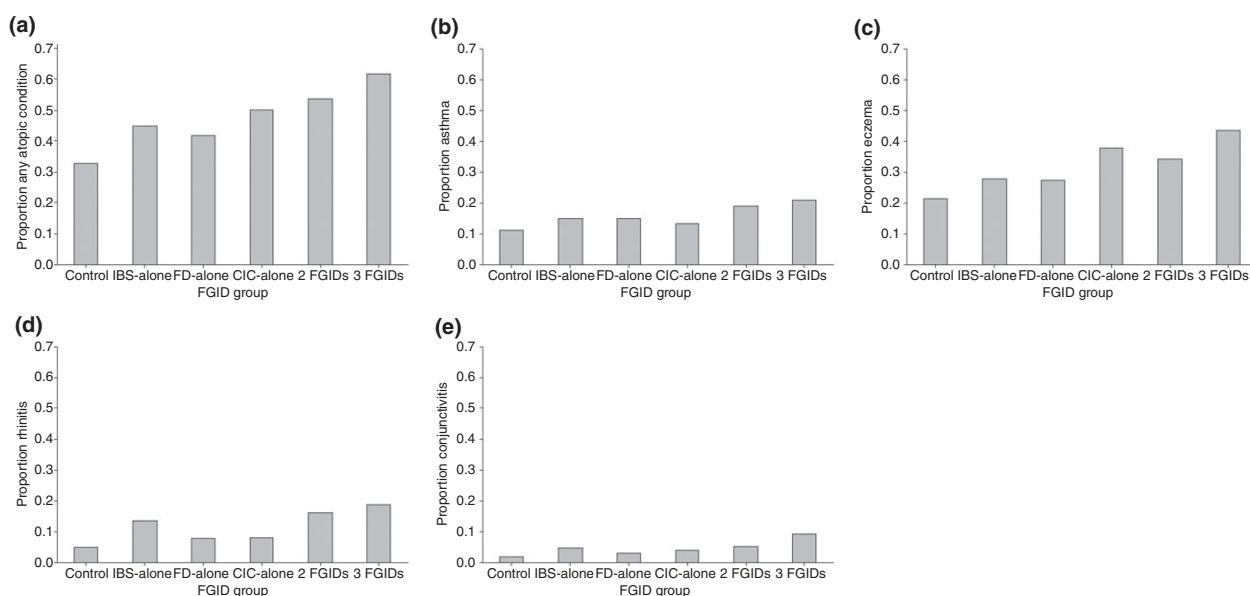


Figure 2 | The proportion of atopy with individual and multiple functional GI disorders (FGIDs). IBS, irritable bowel syndrome; FD, functional dyspepsia; CIC, chronic idiopathic constipation.

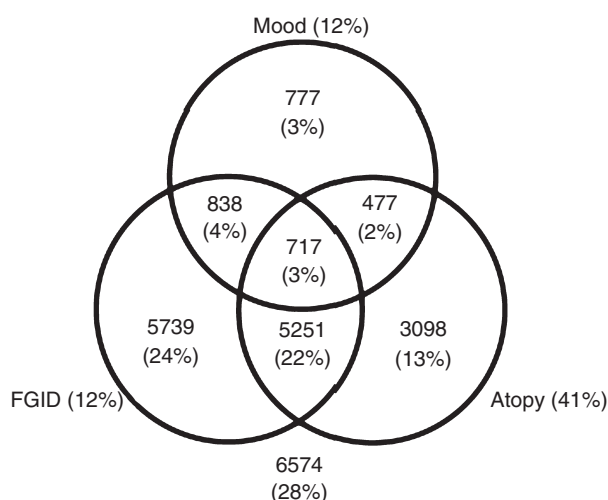


Figure 3 | Overlap between FGIDs, mood disorders and atopy. Circles represent each group of conditions (FGID, mood and atopy) and the percentages quoted outside of each circle are the per cent of the total sample (23 471) for whom diagnostic records of that condition was found. For a total of 6574 patients, no record of FGID, mood disorder or atopy was found, representing 28% of the total sample. The numbers and percentages inside overlapping circles represent the number of patients and percentage of the total sample for whom that combination of conditions was found.

FGID, and for allergic conjunctivitis, the odds were threefold higher (Table 1).

Another consistent finding was that controlling for demographic factors and mood disorders accounted for some of the excess prevalence of atopic conditions seen among FGID groups, with lower ORs seen after controlling for these factors (Table 1). This is in keeping with past literature showing that FGIDs are associated with mood disorders^{19, 34} and gender,²⁰ and that mood disorders have been associated with allergy.^{35, 36} This may suggest a three-way interconnection between FGIDs, mood disorders and atopic conditions. However, in many cases the association between the various FGIDs and atopic conditions remained substantial and statistically significant even after controlling for all these factors which suggests that the common connections between FGIDs and mood disorders on the one hand and atopy and mood disorders on the other do not fully explain the association between FGIDs and atopy. This conclusion is consistent with the theory that FGIDs, atopic conditions and mood disorders all overlap but, due to their inherent heterogeneity, overlap imperfectly, and this interpretation is supported empirically by our data (Figure 3).

Insight into whether the association between an FGID and atopy is via shared connection with demographic factors or mood disorders can be obtained by comparing the unadjusted with adjusted ORs in Table 1. This is most evident for IBS alone and the multiple FGID group where the ORs for asthma, hay fever/allergic rhinitis and conjunctivitis were substantively reduced after controlling for age and gender. While this also occurred for FD alone and CIC alone, the change in OR was more subtle in comparison.

Evidence shows that there are genetic variations that may influence local mucosal immune function in IBS, and in this study the principal genes cited are also linked to atopy.³⁷ At the level of histology, immune alterations in intestinal mucosa akin to those seen in bronchial mucosa in asthma have been described. In FD a duodenal response skewed to eosinophilia has been reported in a subset of patients³⁸ and in IBS increased mast cells, which are also involved in allergic-type responses, have been described in the duodenal⁷ and colonic mucosa.³⁹ While asthma is exacerbated by infection,⁴⁰ similarly IBS⁴¹ and FD^{42, 43} have also been described post-infection, suggesting a two hit hypothesis is required to initiate disease in those with a genetic susceptibility. These mechanisms therefore link this current study with others showing FGIDs and atopy are commonly co-expressed through a genetic/environmental link. Furthermore, atopy is also characterised by imbalance of the stress axis response in which neurogenic inflammation with a cytokine TH2 cytokine bias leads to exacerbation of atopic disease.⁴⁴ Preliminary data by our group⁴⁵ has shown a link with events observed at the cellular level through IBS to anxiety and depression. Using path models to test an *a priori* hypothesised causal path we found that cellular immune activity in the colon is directly linked with depression with a significant contribution of the immune inflammatory load leading to depression via elevated GI symptom burden.⁴⁵ Inflammation in IBS leading to cytokine release (TNF alpha) has also been correlated with mood.⁴⁶ Hence, the data obtained in this study from a clinical perspective support findings obtained at a cellular level, suggesting a three-way relationship between immune dysregulation, mood disturbance and IBS, as well as other FGIDs. Immune mechanisms are complex and while simplistically divided into TH1 and TH2 responses, it is recognised that other pathways are described and this response is a mosaic with a degree of overlap in the TH1/TH2 responses through TH17 and TH22, which may explain incomplete overlap.⁴⁷

This study had a number of strengths and weaknesses that need to be understood to interpret our findings in

context. Weaknesses include non-standard definitions of FGIDs, due to the primary care setting in which it was conducted and the age of the cohort, which was due to the necessity of prolonged follow-up. The general practice, routine medical record setting also opens the possibility of unrecorded FGIDs, atopic conditions, or mood disorders since the medical record only captures those indications that the GP deemed relevant to the patient's care. By the same logic, we were also unable to differentiate an elevated prevalence of atopic conditions from over-reporting among FGID patients compared with non-FGID patients. However, the general practice setting also confers a major strength as patients in the UK are likely to receive lifetime care from their GPs and reporting bias should therefore be minimised. Our data are also likely to be generalisable, given that the majority of health care for FGIDs is provided by GPs and the sample is nationally representative. This study draws together the strengths of previous work into a single manuscript. These include a very large sample size (>20 000), a nationally representative sample and diagnoses made by a physician, rather than patient self-report. The combinations of FGIDs and atopic conditions are wider than previous work, increasing the generalisability of our findings.

This study adds to previous work in three important respects. We consider a wider range of FGIDs and atopic conditions than previous work and therefore are able to comment on the generalisability of the FGID/atopic association with a greater extent than previous studies. Our sample is comprised of both FGID and control subjects as well as atopic and non-atopic subjects and we view the association between these two disease groups as bi-directional. We consider the role of factors known to be important in both FGIDs and atopic conditions, particularly mood disorders and are therefore able to comment on possible aetiological factors.

Our data provide convincing evidence that FGIDs and atopic conditions share a connection that is partly, but not completely, explained via a common association with disordered mood (anxiety and depression). These

data add to the mounting evidence that some FGIDs, particularly IBS, are heterogeneous conditions with respect to aetiology. In addition to post-infectious IBS⁴¹, it has been suggested we could add atopic IBS⁴⁸ although whether these are independent subgroups needs further validation. This heterogeneity may be explained by a genetic- environmental link. The data have practical implications for understanding possible pathophysiologic pathways and treatment options which include manipulation of the atopic pathway and mood disorders.

AUTHORSHIP

Guarantor of the article: None.

Author contributions: Michael Jones: co-conceived study, study design, obtained funding for the data, undertook statistical analysis, interpretation of the results, co-lead manuscript preparation. Marjorie Walker: co-conceived study, study design, interpretation of the results, co-lead manuscript preparation. Alex Ford: co-conceived study, study design, interpretation of the results, co-lead manuscript preparation. Nicholas Talley: co-conceived study, study design, interpretation of the results, co-lead manuscript preparation. All authors have sighted and approved the submitted version of this manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Read codes used to define atopic conditions.

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Appendix 1. Read codes used to define atopic conditions

Asthma		Eczema		Hay fever / allergic rhinitis		Conjunctivitis	
readcode	description	readcode	description	readcode	description	readcode	description
14B4.00	h/o: asthma	14F1.00	h/o: eczema	12D4.00	fh: hay fever	F4C0611	acute allergic conjunctivitis
178..00	asthma trigger	26C4.00	nipple eczema	14B1.00	h/o: hay fever	F4C1400	other chronic allergic conjunctivitis
1O2..00	asthma confirmed	A540.00	eczema herpeticum - kaposi's varicellifo	H170.11	hay fever - pollens	F4C1411	allergic conjunctivitis
2126200	asthma resolved	F4D3000	eczematous eyelid dermatitis	H171.14	hay fever - other allergen		
212G.00	asthma resolved	F4D3112	contact eczema - eyelids	H172.11	hay fever - unspecified allergen		
663..11	asthma monitoring	F502400	acute eczematoid otitis extern	H330.13	hay fever with asthma		
663N.00	asthma disturbing sleep	F502411	eczema of external ear	H330011	hay fever with asthma		
663N000	asthma causing night waking	G831.00	varicose veins of the leg with eczema	H17..00	allergic rhinitis		
663N100	asthma disturbs sleep weekly	G831.11	varicose eczema	H170.00	allergic rhinitis due to pollens		
663N200	asthma disturbs sleep frequently	G832.00	varicose veins of the leg with ulcer and	H171.00	allergic rhinitis due to other allergens		
663O.00	asthma not disturbing sleep	M07y.11	pustular eczema	H172.00	allergic rhinitis due to unspecified allergen		
663O000	asthma never disturbs sleep	M101.12	seborrhoeic eczema	H17z.00	allergic rhinitis nos		
663P.00	asthma limiting activities	M102.00	infectious eczematoid dermatitis				
663Q.00	asthma not limiting activities	M102.11	pustular eczema				
663U.00	asthma management plan given	M111.00	atopic dermatitis/eczema				
663V.00	asthma severity	M112.00	infantile eczema				
663V000	occasional asthma	M113.00	flexural eczema				
663V100	mild asthma	M114.00	allergic (intrinsic) eczema				
663V200	moderate asthma	M119.00	discoïd eczema				
663V300	severe asthma	M12..00	contact dermatitis and other eczemas				
663W.00	asthma prophylactic medication used	M12..12	contact eczema				

663d.00	emergency asthma admission since last ap	M12z100	eczema nos				
663e.00	asthma restricts exercise	M12z111	discoïd eczema				
663e000	asthma sometimes restricts exercise	M12z200	infected eczema				
663e100	asthma severely restricts exercise	M12z300	hand eczema				
663f.00	asthma never restricts exercise	M12z400	erythrodermic eczema				
663h.00	asthma - currently dormant	Myu2.00	[x]dermatitis and eczema				
663j.00	asthma - currently active	Myu2200	[x]exacerbation of eczema				
663n.00	asthma treatment compliance satisfactory						
663p.00	asthma treatment compliance unsatisfacto						
663q.00	asthma daytime symptoms						
663s.00	asthma never causes daytime symptoms						
663t.00	asthma causes daytime symptoms 1 to 2 ti						
663u.00	asthma causes daytime symptoms 1 to 2 ti						
663v.00	asthma causes daytime symptoms most days						
663w.00	asthma limits walking up hills or stairs						
663y.00	number of asthma exacerbations in past y						
66Y5.00	change in asthma management plan						
66Y9.00	step up change in asthma management plan						
66YA.00	step down change in asthma management pl						
66YE.00	asthma monitoring due						
66YJ.00	asthma annual review						
66YK.00	asthma follow-up						
66YP.00	asthma night-time symptoms						
66YQ.00	asthma monitoring by nurse						
66YR.00	asthma monitoring by doctor						
679J.00	health education - asthma						

68C3.00	asthma screening						
8793.00	asthma control step 0						
8794.00	asthma control step 1						
8795.00	asthma control step 2						
8796.00	asthma control step 3						
8797.00	asthma control step 4						
8798.00	asthma control step 5						
8B3j.00	asthma medication review						
8CE2.00	asthma leaflet given						
8CMA000	patient has a written asthma personal ac						
8H2P.00	emergency admission, asthma						
8HTT.00	referral to asthma clinic						
9N1d.00	seen in asthma clinic						
9N4Q.00	dna - did not attend asthma clinic						
9OJ..00	asthma monitoring admin.						
9OJ..11	asthma clinic administration						
9OJ1.00	attends asthma monitoring						
9OJ2.00	refuses asthma monitoring						
9OJ3.00	asthma monitor offer default						
9OJ4.00	asthma monitor 1st letter						
9OJ5.00	asthma monitor 2nd letter						
9OJ6.00	asthma monitor 3rd letter						
9OJ7.00	asthma monitor verbal invite						
9OJ8.00	asthma monitor phone invite						
9OJ9.00	asthma monitoring deleted						
9OJA.00	asthma monitoring check done						
9OJA.11	asthma monitored						
9OJZ.00	asthma monitoring admin.nos						
9Q21.00	patient in asthma study						
9hA..00	exception reporting: asthma quality indi						
9hA1.00	excepted from asthma quality indicators:						
9hA2.00	excepted from asthma quality indicators:						

G581.11	asthma - cardiac						
H312000	chronic asthmatic bronchitis						
H33..00	asthma						
H33..11	bronchial asthma						
H330.00	extrinsic (atopic) asthma						
H330.11	allergic asthma						
H330.12	childhood asthma						
H330.13	hay fever with asthma						
H330.14	pollen asthma						
H330011	hay fever with asthma						
H330111	extrinsic asthma with asthma attack						
H330z00	extrinsic asthma nos						
H331.00	intrinsic asthma						
H331.11	late onset asthma						
H331z00	intrinsic asthma nos						
H332.00	mixed asthma						
H333.00	acute exacerbation of asthma						
H33z.00	asthma unspecified						
H33z000	status asthmaticus nos						
H33z011	severe asthma attack						
H33z100	asthma attack						
H33z111	asthma attack nos						
H33z200	late-onset asthma						
H33zz00	asthma nos						