Evidence for similarity in symptoms and mechanism: the extra-pulmonary symptoms of severe asthma and polysymptomatic presentation of fibromyalgia

*Michael E. Hyland[1,2] ,Joseph W. Lanario[1,2],Yinghui Wei[3] ,Rupert C. Jones[4] , Matthew Masoli[2]

1. School of Psychology, University of Plymouth of Plymouth, Plymouth, UK, 2. University Hospitals Plymouth NHS Trust, Plymouth, UK, 3. School of Computing, Electronics and Mathematics, University of Plymouth, UK, 4.Peninsula School of Medicine and Dentistry, University of Plymouth, UK,

*Correspondence: Prof Michael Hyland, School of Psychology, Plymouth University, Plymouth, PL4 8AA, UK. Email: mhyland@plymouth.ac.uk

Running title: Severe asthma and fibromyalgia

Word count: 3923 words excluding references

3 Tables

2 Figures

Funding support: Non-promotional grant from AstraZeneca.

Abstract

Background

Asthma is a disease of the lung and a systemic disease. Functional disorders are associated with multiple systemic abnormalities that have been explained by complexity models. The aim was to test the similarity in type and aetiology between the extra-pulmonary symptoms of severe asthma and symptoms of fibromyalgia.

Methods

100 patients recruited from a specialist severe asthma clinic and 1751 people reporting different functional disorder diagnoses recruited via the internet completed the same 60-item questionnaire. Symptom patterns were compared between groups using a new measure, the symptom pattern similarity index where 0 = no relationship, 1 = identical patterns between groups.

Results

Severe asthma patients report numerous extra-pulmonary symptoms. The similarity index between the symptom pattern of the asthma patients with other groups was irritable bowel syndrome = 0.54, chronic fatigue syndrome = 0.69, fibromyalgia = 0.75. The index between fibromyalgia and asthma patients with the most and least frequent extra-pulmonary symptoms was 0.81 and 0.55 respectively.

Conclusions

Patients with severe asthma have numerous extra-pulmonary symptoms similar in type and pattern to symptoms of fibromyalgia. The similarity of the symptom pattern between asthma and fibromyalgia increases as the number of extra-pulmonary symptoms increases as predicted by network theory and previously shown to be the

case with other functional disorders. These findings support the hypothesis that functional disorders and extra-pulmonary asthma symptoms have a common complexity or network aetiology. Evidence based, behavioural interventions for fibromyalgia may be helpful for patients with severe asthma reporting extra-pulmonary symptoms.

Keywords: Severe asthma; functional disorder; fibromyalgia; network; complexity; biopsychosocial interaction.

Introduction

Asthma a disease of the lung but also a systemic disease [1 - 3], with well-established co-morbidities [4-6]. Although functional disorders are less commonly cited as co-morbidities of asthma they include fibromyalgia syndrome (FMS) [7-9], chronic fatigue syndrome (CFS) [9, 10] and irritable bowel syndrome (IBS) [11]). Functional disorders are polysymptomatic and have multiple, systemic biological abnormalities. Although they both involve systemic disturbance, the relation between the symptoms of asthma and functional disorders is unknown. Severe asthma patients have a high level of extra-pulmonary symptoms, some of which may relate to side effects of treatment [12], so severe asthma patients provide a useful comparison group with functional disorders.

Despite being described as medically unexplained symptoms, several explanations have been proposed for functional disorders. The first type of explanation is that each of the different syndromes is caused by a specific pathophysiology that is yet to be discovered. This specific pathophysiology may be linked to the immune, neurological and endocrine abnormalities that are associated with functional disorders [13-20]. The second type of explanation is that all the functional disorders are caused by a common psychological mechanism [21], such as somatization (hence, somatoform disorders) or some form of cognitive disturbance [22,23] A third type of explanation, commonly labelled biopsychosocial, combines psychological and biological mechanisms in a single model in order to explain both the biological and psychological abnormalities of functional disorders. These models take a variety of forms, for example, combining neural and psychology[24], neural, gut and psychology [25] and neural, immune, endocrine and psychology [26].

A common theme in the biopsychosocial models is that the body is an adaptive system, and symptoms are the result of some form of adaptation to situational or behavioural events [24,26]. Because complex network structures provide the architecture for learning (i.e., adaptation) in artificial intelligence systems, it has been suggested that complexity theory may provide insights into the underlying mechanisms [27]. The adaptive network theory applies network theory to a biological system with biopsychosocial inputs. The theory assumes that biological pathology causing mechanisms are causally connected in a network, which then adapts according to network learning rules [28,29]. Adaptation results from inputs to the network which include psychological as well as biological inputs, and the resulting biological adaptation is associated with somatic and psychological symptoms.

The symptoms of functional disorders are to some extent shared between different functional disorders [30]. Psychological models of functional disorders explain commonality in symptomatology across functional disorders. Biological explanations explain the specificity of symptoms between functional disorders. Biopsychosocial theories explain both the specificity and commonality that is a feature of functional disorders [30]. The adaptive network theory, however, makes one additional prediction compared to other biopsychosocial theories, namely, that the commonality between functional disorders increases with severity. This prediction stems the assumption of a network structure. In a network of mutually activating nodes, increase in one part of the network activates increases activity across the whole network, such that differentiation between the original activating site and elsewhere becomes lost as severity increases. This prediction has been confirmed using a machine learning form of analysis with the additional finding that the connection

strengths between the outgoing connections also increased with severity, showing that the underlying network structure (and therefore adaptation) varies with severity [29].

If the polysymptomatic presentation of IBS, FMS and CFS is due to a causal network of biological, symptom causing mechanisms, then it is plausible that asthma causing mechanisms as well as systemic effects of treatment could be causally linked to this network to a greater or lesser extent. If the extra-pulmonary symptoms of asthma have the same network aetiology as IBS, FMS and CFS then the symptomatology should exhibit the same properties.

Two predictions stem from the hypothesis that the functional disorder symptoms and the extra-pulmonary symptoms of asthma have the same etiology. First, the relative frequency of the different extra-pulmonary symptoms in a group of patients with severe asthma should be similar to the relative frequency of those symptoms in groups of people diagnosed with IBS, FMS and CFS. Second, the degree of similarity should be greater in those asthma patients with more extra-pulmonary symptoms. Previous research shows that as symptom frequency increases, the pattern of symptoms (i.e., relative frequency of symptoms) in functional disorder groups become more similar to those with fibromyalgia [29]. Therefore, the extra-pulmonary symptoms of people with severe asthma should approximate more to the symptom pattern of fibromyalgia as the number of extra-pulmonary symptoms increases.

The symptom pattern is defined by the *relative* frequency of one symptom to all others symptoms in a group of people, so the symptom pattern is independent of the absolute frequency of symptoms. For example, if symptom A is twice as common as

symptom B in one group of patients, and the same ratio is found in another group, then the two groups have the same symptom pattern even though the absolute frequency of symptoms may be different between the two groups.

This paper has three aims. The first is to compare the type and number of extra-pulmonary symptoms of severe asthma and with the polysymptomatic presentation of IBS, FMS and CFS. A second aim is to use a quantitative method to assess the degree of similarity between the symptom pattern of severe asthma and those of people with IBS, FMS and CFS in order to determine which of these three functional disorders is most similar to severe asthma. A third aim is to test the hypothesis that those severe asthma patients with the more extra-pulmonary symptoms are more similar in symptom pattern to FMS compared to those asthma patients with less extra-pulmonary symptoms – i.e., that the extra-pulmonary symptoms of asthma exhibit the same property of convergence with severity as do functional disorders and predicted by an underlying network mechanism.

Methods

Participants

Asthma sample: Patients aged ≥16 years and attending a specialist severe asthma clinic were invited to participate as part of a questionnaire validation study [31]. All patients were diagnosed with severe asthma as defined by the European Respiratory Society (ERS) and American Thoracic Society (ATS) guidelines [32], and were excluded if they had another condition that could contribute significantly to their respiratory symptoms e.g., lung cancer, heart failure or COPD.

Functional Disorders sample: People over the age of 18 years were recruited through IBS, CFS and FMS patient self-help websites as part of another study [29].

Questionnaire

General symptom questionnaire (GSQ). The questionnaire for assessing extra-pulmonary symptoms in asthma was selected so as to be able to provide a comparison with an existing data set obtained from a separate study [29]. The questionnaire was based on an established general population symptom questionnaire [33] but with items added that are indicative of functional disorders such as FMS and CFS (See online appencix1 for more details). The questionnaire assesses the frequency of somatic and psychological symptoms on a 6 point Likert scale (the value scoring for each response shown in brackets): “Never or almost never” (1), “Less than 3 or 4 times per year” (2), “Every month or so” (3), “Every week or so” (4), “More than once per week” (5) or “Every day” (6). The *GSQ score* was calculated from the mean of all items. The number of *weekly non-respiratory symptoms* reported was calculated by counting the number of items with a score of 4 or more. The number of *daily non-respiratory symptoms* was calculated by counting the number of items with a score of 6. Higher scores indicate more symptoms. There were 60 identical symptoms for which data were obtained from the asthma and functional disorder groups.

Clinic Data

The following clinic data were obtained for the asthma sample: spirometry (%FEV1)), treatment step as defined by Global Initiative for Asthma (GINA) [22] and Body Mass Index (BMI).

Procedure

Asthma Sample: after providing written informed consent, participants either completed the questionnaires at home or during their clinic visit.

Functional disorder sample: These data were collected as part of another study [29]. In an online survey, participants who reported having received a doctor's diagnosis of IBS, CFS or FMS, provided consent and completed an online symptom questionnaire and indicated their age, gender.

Questionnaires from the asthma sample were deemed incomplete if 15 or more items were missing. The online data collection of the functional disorder sample precluded missing items as only complete questionnaires could be submitted.

Ethical approval

Data collection from the asthma sample was approved by the Plymouth Hospitals NHS Trust and REC/HRA, ethical approval number 16/NE/0188, IRAS ID: 207601. All patients provided informed written consent. Ethical approval for data collected the online study [29] was provided by the University of Plymouth, Faculty of Health and Human Science Ethics committee. Participants for this study provided informed consent online.

Analysis

Descriptive statistics of symptoms within groups is provided by the percentage of people reporting a symptom at two levels of frequency: at least once per week and once per day.

The symptom pattern of a group is defined by the means of all the symptom scores of that group. A symptom pattern similarity index was developed to compare the similarity of the symptom patterns between groups, where one = identical pattern and zero = unrelated pattern. In order to calculate this index form, first the mean score for each symptom was calculated for each group (asthma, IBS, FMS, CFS). Each of these symptom means falls along a scale of 0 – 6, and together these

symptoms form the symptom pattern for any group. Two groups were defined as having an identical pattern if the similarity index is 1, in which each of the different symptom means in the two groups are same after adding a constant to all symptoms in one of the groups (the constant can be zero, in which case not only is the pattern identical but so is severity). In order to calculate the symptom pattern similarity index between zero and one, Pearson correlations were calculated where symptoms are treated as cases and groups as variables. We refer to this calculation as a symptom pattern similarity index rather than a correlation coefficient to avoid confusion with the traditional use of correlation. Note that if the correlation were negative this would create a dissimilarity index where -1 = absolute opposite of pattern. Further details about this index are provided in the appendix 1 (why a Pearson rather than a Spearman and the dissimilarity index).

In order to examine to what extent the symptom pattern index of one group was a unique contributor to the symptom pattern of another, multiple regressions were carried out using the means of symptoms scores for each of the groups as predictor and dependent variables.

Funding source

Data collection was supported by a non-promotional grant from AstraZeneca

Results

Participants: Of the 174 patients with severe asthma asked to take part, 20 declined and of the remaining 154 participants, 53 did not return their questionnaires by post, and one participant missed out 20 questions from the GSQ making the data ineligible. Completed questionnaires were received from 100 patients.

Of the 1751 functional disorder participants who completed online questionnaires in a separate study [18], 900 people reporting a single functional disorder diagnosis of whom 370 reported IBS, 384 reported FMS and 146 reported CFS and are included for comparison. The remaining 851 had some combination of IBS, FMS and CFS.

Demographic data and mean questionnaire data of the severe asthma and functional disorder samples (IBS, FMS, CFS) is shown in Table 1. The frequency of weekly and daily extra-pulmonary symptoms (i.e., GSQ items) for all four groups is shown Table 2. Table 2 is limited to the 40 most frequent weekly extra-pulmonary symptoms reported in the asthma sample. The full list of symptoms is shown in the online appendix 2. Figure 1 provides a graphical representation of the same data, in order to show how the pattern of IBS, FMS and CFS groups differs from that of the severe asthma group. The symptom pattern of the severe asthma group forms a decreasing monotonic line because the symptoms have been ordered in terms of their mean values.

The median number of daily extra-pulmonary symptoms reported by the severe asthma sample was 6 and of weekly extra-pulmonary symptoms was 21. Four asthma patients reported zero weekly non-respiratory symptoms and 19 reported zero daily non-respiratory symptoms.

The means of each symptom in the different groups is shown in appendix 2. The symptom pattern similarity index (i.e., the metric of how similar the pattern of symptomatology is between groups) is shown in Table 3. The results show that the symptom pattern of severe asthma is most similar to FMS (the index = 0.75) followed by CFS (0.66) followed by IBS (0.57). The highest symptom pattern similarity index is between FMS and CFS (0.88).

In order to test whether the symptom pattern similarity index varies with severity, the severe asthma sample was dichotomised to two groups based on the patients' mean GSQ scores: Those below the median GSQ score (severe asthma-low) and those above the median GSQ score (severe asthma-high), there being 50 patients in either group. The mean symptom scores for these two asthma groups is shown in appendix 2, a graphical representation is shown in Figure 2 and the correlations in Table 3.

Two multi-variable linear regressions were carried out to assess whether the symptom patterns of FMS and IBS (i.e., the mean symptom scores of the FMS and IBS groups) were predictors of (a) the symptom pattern of the severe asthma-high group and (b) the symptom pattern of the severe asthma-low group (i.e., the mean symptom scores of the dichotomised asthma groups). In these multi-variable regressions, only the pattern of FMS ($p < .001$, beta = .79) but not the pattern of IBS ($p = 0.71$, beta = 0.37) predicted the pattern of severe asthma-high. Both the pattern of FMS ($p = 0.014$, beta = 0.31) and the pattern of IBS ($p = 0.001$, beta = 0.42) predicted the pattern of severe asthma-low.

Discussion

The result of this survey shows that the majority of patients attending a severe asthma clinic report many different extra-pulmonary symptoms. The number of different extra-pulmonary symptoms reported varies between patients with a median of 21 symptoms per week and only a small minority reporting none. Inspection of the type of symptoms reported shows that they are similar to the polysymptomatic presentation of patients with IBS, and CFS, but particularly FMS. For example, 35% of the asthma patients reported, the symptom of 'pain moving from one part of the

body to another on different days' at least once per week. This symptom, reported by 89% of the FMS patients is indicative of central sensitivity syndrome [13] rather than damage. Cognitive disturbance of various kinds were reported by about 50% of the asthma patients, and although this symptom is less common than the FMS patients (where it is about 90%) it is nevertheless a symptom often referred to as 'fibro-fog' [34] by FMS patients but also common in CFS patients. Stomach pain was reported by 20% of the asthma patients weekly, compared to 79% for IBS. The levels of depression (36%) and anxiety (45%) are comparable to those of an international survey of severe asthma [35].

Similarity in symptoms between two groups does not mean similarity of cause. Irritability is a symptom of all four groups but is also a side effect of oral corticosteroids. In order to examine evidence for similarity of cause, we developed a metric, the symptom pattern similarity index, varying between 0 and 1 to express the extent to which the pattern of symptoms is similar between groups, independent of the overall frequency of symptoms (1 = the patterns are identical; 0 = patterns are unrelated). Using this metric, symptom pattern similarity index of the severe asthma sample is most similar to the FMS group (0.75) and least similar to the IBS group (0.57). Figure 1 provides a graphical representation of the difference between symptom similarity and symptom pattern similarity. Of the three groups, the mean symptoms of the IBS are most similar to the severe asthma group. However, the symptom pattern index, however, is defined by the relationship between the means of symptoms within a group, not by the means themselves. The line in Figure 1 formed by the FMS group is almost entirely above that of the severe asthma, but because it approximates more to a line parallel to the severe asthma group, the

correlation between the FMS and severe asthma group is greater than that between the IBS and severe asthma group.

Network theory suggests that similarity between groups should increase with severity because increased severity is associated with increased pathology over the whole network. Therefore symptom patterns within different diagnostic groups should converge as severity increases, consistent with evidence elsewhere that people diagnosed with IBS or CFS become more similar to the more severe group of FMS as the frequency of IBS and CFS symptoms increases [29]. We found that people reporting a diagnosis of FMS report the most frequent symptoms compared with IBS and CFS (see Table 1). We found that those asthma patients who had more extra-pulmonary symptoms were more strongly related to the FMS group using our index (0.81) compared to those with less extra-pulmonary symptoms (0.55). Figure 2 provides a graphical representation of these data. The severe asthma high and severe asthma low lines are approximate mirror images of each other as the mean values of the high and low groups are the same as the means for the total group – and therefore the decreasing line shown in Figure 1. However, in this case, the mean values of the severe asthma-high group are similar to the mean values of the FMS group, and peaks and troughs of the severe asthma-high line tend mirror the peaks and troughs of the FMS line, showing that the FMS and severe asthma-high groups tend to be parallel, though in this case not monotonic. By contrast, the peaks and troughs of the severe asthma-low line tends to oppose the peaks and troughs of the FMS lines. As the correlation shows in Table 3, the pattern index of the severe asthma-high group is more similar to the FMS group than it is to the severe asthma-low group.

This correlation coefficients and graphs show that not only are the extra-pulmonary symptoms of asthma similar (though for most symptoms less frequent) than those reported by FMS, but also that the extra-pulmonary symptoms exhibit the same property of convergence with severity as predicted by network theory. The property of convergence with symptom pattern FMS can be explained by a biopsychosocial model *only* if it includes a network architecture. Models without a network architecture explain symptoms by a combination of biological and psychological mechanisms. In any population, different symptoms have different frequencies such that there is a symptom pattern that characterises for that population. If symptoms have a psychological cause, then, irrespective of whether one or several psychological mechanisms are involved, increase in the severity of one or more psychological mechanisms should increase all symptom reporting by the same proportional amount. The consequence is that as the severity of the psychological cause increases, the symptom pattern for severe and less severe groups should be the same. In the case of biological causes, then increased pathology of a biological cause should increase only the symptoms associated with that biological cause. As our evidence shows that increase in symptom frequency is associated with a convergence towards the FMS symptom pattern, our data are inconsistent with non-network explanations.

The symptom pattern similarity index between CFS and FMS is high (0.87), consistent with clinical observation that the symptoms of these two groups are similar despite different diagnostic procedure. However, this similarity of pattern makes differentiation between CFS and FMS unreliable. The relationship between FMS and IBS is lower (0.57), but still moderately strong. We wished to determine whether the pattern of IBS explained additional variation of the asthma pattern

compared to FMS. In the case of asthma patients with more extra-pulmonary symptoms, only FMS but not IBS was a significant independent predictor of the asthma pattern – i.e., any similarity in pattern between IBS and asthma can be entirely explained by the similarity between FMS and IBS. In the case of asthma patients with less extra-pulmonary symptoms, both FMS and IBS were independent predictors of the asthma pattern. We cannot say whether the latter effect occurs because some of the asthma patients exhibit the IBS and some the FMS pattern, or whether there is a tendency for both patterns to manifest in the same patient, but the results are consistent with the network theory. For patients with less severe pathology in the network, there is greater opportunity for activation at particular nodes in the network (i.e., greater opportunity for localised pathology), and so there is less convergence between symptom patterns between groups when severity is low. These findings are also consistent with a network but not other explanations, including non-network biopsychosocial explanations.

Limitations

All groups are convenience samples. Group membership of the functional disorder groups is based on clinical criteria that may differ from diagnostic criteria. The severe asthma sample was recruited from one centre in the UK. The prevalence of FMS within the asthma group could not be determined because of under diagnosis of FMS in clinical practice exacerbated by significant differences between different diagnostic criteria [36,37]. Statistical bias can arise when correlations are calculated from split groups. There is no statistic available for testing whether differences in the symptom pattern index are significant or not. The reason is explained in the appendix.

Conclusions and clinical relevance

Our results support the hypothesis that the extra-pulmonary symptoms of asthma have a similar aetiology to FMS, and that this aetiology is based on a causal network of symptom causing mechanisms to which the mechanisms of asthma and its treatment are causally linked. This conclusion is supported by existing data showing that asthma, FMS and CFS share several non-diagnostic biological abnormalities, including raised systemic inflammation [38-41], hypothalamic-pituitary-adrenal axis dysregulation [42-44] and low magnesium levels [45,46]. Evidence that fibromyalgia is a risk factor for asthma exacerbations [7] as are non-asthma related visits to the GP [47], is consistent with an inflammatory causal pathway between systemic inflammation and inflammation in the lung.

There are three possible applications of network theory to the management of severe asthma. First, if variation in systemic inflammation interacts with inflammation in the lung, then it is plausible that evidence based interventions for FMS will have a beneficial effect in asthma, but only for those patients with high levels of extra-pulmonary symptoms. Studies on behavioural interventions for severe asthma are needed, and such interventions may also act to prime pharmacological treatments. Second, as asthma treatments affect the immune system in different ways, it is plausible that systemic corticosteroids and biologic treatments have radically different effects on extra-pulmonary symptoms and therefore quality of life. Quality of life scales currently used in severe asthma studies have not been optimised for this patient population [48], and may therefore underestimate the benefit of newer, targeted forms of treatment. A recently developed quality of life scale for severe asthma [31], and the inclusion of measures of extra-pulmonary symptoms will provide a more valid representation of quality of

life and symptoms. Third, patients' reports of the benefit of biologic treatment varies. As these treatments will interact with the existing state of a network of biological mechanisms, it is possible that extra-pulmonary symptom patterns predict benefit pharmacological treatments where outcome varies. Predictor studies for biologic treatments using symptom patterns may help provide a more personalised use of new treatments.

Acknowledgements

RJ and JL were supported by the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care South West Peninsula (NIHR CLAHRC South West Peninsula). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care. The corresponding author acknowledges that all those who contributed significantly to the paper are authors on the paper.

References

1. Holgate ST. Asthma: more than an inflammatory disease. Curr Opin Allergy Cl. 2002; 2):27-9.
2. Wood LG, Baines KJ, Fu J, Scott HA, Gibson PG. The neutrophilic inflammatory phenotype is associated with systemic inflammation in asthma. Chest. 2012;142:86-93.
3. Liang Z, Liu L, Zhao H, Xia Y, Zhang W, Ye Y, Jiang M, Cai S. A systemic inflammatory endotype of asthma with more severe disease identified by unbiased clustering of the serum cytokine profile. Medicine. 2016;95(25) 3E774.
4. Cazzola M, Segreti A, Calzetta L, Rogliani P. Comorbidities of asthma: current knowledge and future research needs. Curr Opin Pulm Med. 2013;19:36-41.
5. Zhang T, Carleton BC, Prosser RJ, Smith AM. The added burden of comorbidity in patients with asthma. J Asthma. 2009;46:1021-6.
6. Gershon AS, Guan J, Wang C, Victor JC, To T. Describing and quantifying asthma comorbidty: a population study. Plos One. 2012;7(5):e34967.
7. Martinez-Moragon E, Plaza V, Torres I, Rosado A, Urrutia I, Casas X, Hinojosa B, Blanco-Aparicio M, Delgado J, Quirce S, Sabadell C. Fibromyalgia as a cause of uncontrolled asthma: a case–control multicenter study. Curr Med Res Opin. 2017;33:2181-6.
8. Queiroz LP. Worldwide epidemiology of fibromyalgia. Curr Pain Headache R. 2013;17:356.

9. Sinaii N, Cleary SD, Ballweg ML, Nieman LK, Stratton P. High rates of autoimmune and endocrine disorders, fibromyalgia, chronic fatigue syndrome and atopic diseases among women with endometriosis: a survey analysis. Hum Reprod. 2002;17:2715-24
10. Kowal K, Schacterele RS, Schur PH, Komaroff AL, DuBuske LM. Prevalence of allergen-specific IgE among patients with chronic fatigue syndrome. Allergy Asthma Proc. 2002 (Vol. 23, No. 1, p. 35). OceanSide Publications.
11. Roussos A, Koursarakos P, Patsopoulos D, Gerogianni I, Philippou N. Increased prevalence of irritable bowel syndrome in patients with bronchial asthma. Resp Med. 2003;97:75-9.
12. Sweeney J, Patterson CC, Menzies-Gow A, Niven RM, Mansur AH, Bucknall C, Chaudhuri R, Price D, Brightling CE, Heaney LG. Comorbidity in severe asthma requiring systemic corticosteroid therapy: cross-sectional data from the Optimum Patient Care Research Database and the British Thoracic Difficult Asthma Registry. Thorax 2016;71:339-346.
13. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. *Pain* 2011;152: S2-15.
14. Cleare AJ. The neuroendocrinology of chronic fatigue syndrome. Endocr Rev 2003;24:236-52.
15. Staud R. Cytokine and immune system abnormalities in fibromyalgia and other central sensitivity syndromes. Current Rheumatology Reviews 2015;11:109-15.
16. Hornig M, Montoya JG, Klimas NG, Levine S, Felsenstein D, Bateman L, Peterson DL, Gottschalk CG, Schultz AF, Che X, Eddy ML. Distinct

plasma immune signatures in ME/CFS are present early in the course of illness. Science Advances 2015:e1400121.

17. Maes M, Leunis JC, Geffard M, Berk M. Evidence for the existence of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) with and without abdominal discomfort (irritable bowel) syndrome. Neuroendocrinology Letters 2014; 35:445-53.
18. Sarzi-Puttini PI, Atzeni F, Diana A, Doria A, Furlan R. Increased neural sympathetic activation in fibromyalgia syndrome. Ann NY Acad Sci. 2006;1069:109-17.
19. Freeman R, Komaroff AL. Does the chronic fatigue syndrome involve the autonomic nervous system? JAMA 1997;102:357-64.
20. Fukudo S. IBS: Autonomic dysregulation in IBS. Nature Reviews Gastroenterology and Hepatology. 2013;10:569-71.
21. Wessely S, Nimnuan C, Sharpe M. Functional somatic syndromes: one or many? Lancet 1999;354:936-9.
22. Häuser W, Henningsen P. Fibromyalgia syndrome: a somatoform disorder?. Eur J Pain. 2014;18:1052-9.
23. Surawy C, Hackmann A, Hawton K, Sharpe M. Chronic fatigue syndrome: a cognitive approach. Behaviour research and therapy. 1995;33(5):535-44.
24. Henningsen P, Gündel H, Kop WJ, Löwe B, Martin A, Rief W, Rosmalen JG, Schröder A, van der Feltz-Cornelis C, Van den Bergh O. Persistent physical symptoms as perceptual dysregulation: a neuropsychobehavioral model and its clinical implications. Psychosomatic medicine. 2018;80(5):422-31.

25. Tanaka Y, Kanazawa M, Fukudo S, Drossman DA. Biopsychosocial model of irritable bowel syndrome. Journal of neurogastroenterology and motility. 2011;17:131-139

26. Chapman CR, Tuckett RP, Song CW. Pain and stress in a systems perspective: reciprocal neural, endocrine, and immune interactions. J Pain. 2008;9:122-45.

27. Martinez-Lavin M, Infante O, Lerma C. Hypothesis: the chaos and complexity theory may help our understanding of fibromyalgia and similar maladies. Semin Arthritis Rheu. 2008 (Vol. 37, No. 4, pp. 260-264). WB Saunders.

28. Hyland ME. The origins of health and disease. Cambridge University Press; 2011.

29. Melidis C, Denham SL, Hyland ME. A test of the adaptive network explanation of functional disorders using a machine learning analysis of symptoms. Biosystems. 2018;165:22-30.

30. Aaron LA, Buchwald D. A review of the evidence for overlap among unexplained clinical conditions. Ann Intern Med. 2001;134:868-81.

31. Hyland ME, Jones RC, Lanario JW, Masoli M. The construction and validation of the Severe Asthma Questionnaire (SAQ). Eur Respir J. 2018; 52:1800618.

32. GINA. 2018 GINA Report, Global Strategy for Asthma Management and Prevention. http://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention/ . Date last updated: March 29 2018. Date last accessed: December 12 2018.

33. Pennebaker JW. The psychology of physical symptoms. Springer Science & Business Media; 2012.

34. Torta RG, Tesio V, Ieraci V, Castelli L, Zizzi FB. Fibro-fog. Clin Exp Rheumatol. 2016 Mar 1;34(2 Suppl 96):S6-8.

35. Katsaounou P, Odemyr M, Spranger O, Hyland ME, Kroegel C, Conde LG, Gore R, Menzella F, Ribas CD, Morais-Almeida M, Gasser M. Still Fighting for Breath: a patient survey of the challenges and impact of severe asthma. ERJ open research. 2018;4(4):00076-2018..

36. Ablin JN, Wolfe F. A Comparative Evaluation of the 2011 and 2016 Criteria for Fibromyalgia. J Rheumatol. 2017:44:1271-1276.

37. Jones GT, Atzeni F, Beasley M, Flüß E, Sarzi-Puttini P, Macfarlane GJ. The prevalence of fibromyalgia in the general population: a comparison of the American College of Rheumatology 1990, 2010, and modified 2010 classification criteria. Arthritis Rheumatol. 2015;67:568-75

38. Ranzolin A, Duarte AL, Bredemeier M, da Costa Neto CA, Ascoli BM, Wollenhaupt-Aguiar B, Kapczinski F, Xavier RM. Evaluation of cytokines, oxidative stress markers and brain-derived neurotrophic factor in patients with fibromyalgia–A controlled cross-sectional study. Cytokine. 2016;84:25-8.

39. Montoya JG, Holmes TH, Anderson JN, Maecker HT, Rosenberg-Hasson Y, Valencia IJ, Chu L, Younger JW, Tato CM, Davis MM. Cytokine signature associated with disease severity in chronic fatigue syndrome patients. P Natl A Sci A. 2017:201710519.

40. Wouters EF, Reynaert NL, Dentener MA, Vernooy JH. Systemic and local inflammation in asthma and chronic obstructive pulmonary disease: is there a connection?. Proc Am Thorac Soc. 2009;6:638-4

41. Ilmarinen P, Tuomisto LE, Niemelä O, Danielsson J, Haanpää J, Kankaanranta T, Kankaanranta H. Comorbidities and elevated IL-6 associate with negative outcome in adult-onset asthma. Eur Respir J. 2016;48:1052-1062.
42. Silverman MN, Sternberg EM. Glucocorticoid regulation of inflammation and its functional correlates: from HPA axis to glucocorticoid receptor dysfunction. Ann Ny Acad Sci. 2012;1261:55-63.
43. Lu Y, Ng TP, Larbi A. Psychological Stress and Asthma: A Mini-reivew of the Neuroendocrine-Immune Responses and the Mediation of Neuropeptide Y. Proc Nat Res Soc. 2018;2:02005.
44. Kempke S, Luyten P, De Coninck S, Van Houdenhove B, Mayes LC, Claes S. Effects of early childhood trauma on hypothalamic–pituitary–adrenal (HPA) axis function in patients with Chronic Fatigue Syndrome. Psychoneuroendocrino. 2015;52:14-21.
45. Lewith GT, Shaw S, Hyland M, Rowe D, Holgate ST. Red cell magnesium in a population of house dust mite sensitive asthmatics. J Nutr Environ Med. 2000;10:305-10.
46. Cox IM, Campbell MJ, Dowson D. Red blood cell magnesium and chronic fatigue syndrome. Lancet. 1991;337:757-60.
47. Hyland ME, Whalley B, Halpin DM, Greaves CJ, Seamark C, Blake S, Pinnuck M, Ward D, Hawkins AL, Seamark D. Frequency of non-asthma GP visits predicts asthma exacerbations: an observational study in general practice. Prim Care Resp J. 2012;21:405-11
48. Hyland ME, Whalley B, Jones RC, Masoli M. A qualitative study of the impact of severe asthma and its treatment showing that treatment burden is

neglected in existing asthma assessment scales. *Qual Life Res* 2015; 24(3):631-639.

Table 1. Characteristics of participants.

	Severe Asthma		IBS		FMS		CFS	
	Mean (SD)	n (%)	Mean (SD)	n (%)	Mean (SD)	n (%)	Mean (SD)	n (%)
Age	52.3 (14.9)	-	50.35(15.66)	-	52.67 (11.49)		44.24(14.01)	
range	17 ~ 79		18 ~ 89		21 ~ 90		17 ~ 76	
Gender								
Female	-	63 (63)		314 (84.9)		362 (94.3)		126 (86.3)
Male		37 (37)		56 (15.1)		22 (5.7)		20 (13.7)
GSQ Average Score (1- 6)	2.94 (1.06)		2.90 (0.78)		3.81(0.73)		3.55(0.70)	
FEV1 percent	69.72(18.26)							
Treatment (GINA step)								
Step 4		61(61)						
Step 5		39(39)						

Table 2. Non-respiratory symptoms limited to the 40 (out of 65) most frequent symptoms occurring weekly in the severe asthma sample. The **percentage** and (number) of participants experiencing each symptom in four groups: severe asthma (n = 100), IBS (n= 370), FMS (n = 382) and CFS (n = 146).

	Weekly Symptom				Daily Symptom			
Symptoms	Severe Asthma	IBS	FMS	CFS	Severe Asthma	IBS	FMS	CFS
Waking up still feeling tired	**73.7**	**75.4**	**96.9**	**95.2**	**45.5**	**36.2**	**78.9**	**78.1**
	73	*279*	*372*	*139*	*45*	*134*	*303*	*114*
Waking up often at night	**69.7**	**62.4**	**89.8**	**74.0**	**38.4**	**26.2**	**58.1**	**39.0**
	69	*231*	*345*	*108*	*38*	*97*	*223*	*57*
Fatigue for no reason	**61.5**	**62.2**	**95.3**	**95.9**	**27.1**	**19.7**	**64.8**	**78.1**
	59	*230*	*366*	*140*	*26*	*73*	*249*	*114*
Easily feel too hot/sweating	**61.0**	**51.1**	**79.7**	**75.3**	**28.0**	**20.5**	**45.6**	**36.3**
	61	*189*	*306*	*110*	*28*	*76*	*175*	*53*
Feeling out of breath for no reason	**58.6**	**26.5**	**52.1**	**62.3**	**27.3**	**6.8**	**20.8**	**20.5**
	58	*98*	*200*	*91*	*27*	*25*	*80*	*30*
Difficulty getting to sleep	**58.0**	**49.2**	**79.9**	**72.6**	**28.0**	**14.9**	**45.8**	**36.3**
	58	*182*	*307*	*106*	*28*	*55*	*176*	*53*
Hands tremble or shake	**57.0**	**18.1**	**48.4**	**46.6**	**25.0**	**4.6**	**11.2**	**10.3**
	57	*67*	*186*	*68*	*25*	*17*	*43*	*15*
Irritable	**55.6**	**55.4**	**71.4**	**63.0**	**15.2**	**13.8**	**21.1**	**14.4**
	55	*205*	*274*	*92*	*15*	*51*	*81*	*21*
Difficulty concentrating	**53.1**	**51.9**	**90.4**	**93.8**	**14.3**	**14.6**	**49.2**	**54.1**
	52	*192*	*347*	*137*	*14*	*54*	*189*	*79*
Itchy skin	**51.5**	**41.6**	**66.7**	**41.8**	**21.2**	**14.9**	**23.7**	**8.9**
	51	*154*	*256*	*61*	*21*	*55*	*91*	*13*
Fatigue increasing the day after you are active	**50.0**	**40.5**	**93.0**	**97.9**	**28.3**	**12.7**	**54.4**	**61.6**
	46	*150*	*357*	*143*	*26*	*47*	*209*	*90*
Itchy eyes	**49.0**	**36.2**	**57.8**	**45.2**	**13.0**	**8.6**	**20.8**	**8.2**

	49	*134*	*222*	*66*	*13*	*32*	*80*	*12*
Very cold hands or feet	**48.5**	**59.7**	**79.4**	**72.6**	**25.3**	**30.3**	**46.9**	**47.3**
	48	*221*	*305*	*106*	*25*	*112*	*180*	*69*
Memory problems	**48.0**	**48.6**	**90.4**	**91.1**	**20.0**	**14.3**	**52.3**	**58.2**
	48	*180*	*347*	*133*	*20*	*53*	*201*	*85*
Back pain	**47.9**	**45.9**	**87.5**	**58.2**	**24.5**	**15.1**	**58.6**	**28.8**
	45	*170*	*336*	*85*	*23*	*56*	*225*	*42*
Urinating two or more times per night	**47.0**	**32.2**	**46.1**	**39.7**	**27.0**	**14.1**	**25.3**	**17.1**
	47	*119*	*177*	*58*	*27*	*52*	*97*	*25*
Thirsty all the time	**47.0**	**40.0**	**68.8**	**52.7**	**18.0**	**11.4**	**33.6**	**28.8**
	47	*148*	*264*	*77*	*18*	*42*	*129*	*42*
Easily feel too cold	**47.0**	**61.4**	**84.1**	**76.0**	**20.0**	**31.1**	**55.7**	**47.3**
	47	*227*	*323*	*111*	*20*	*115*	*214*	*69*
Mental fog	**46.9**	**50.5**	**90.9**	**93.2**	**15.3**	**14.3**	**49.0**	**56.2**
	46	*187*	*349*	*136*	*15*	*53*	*188*	*82*
Cramps in leg, foot or bottom	**46.0**	**26.2**	**59.9**	**39.0**	**15.0**	**1.9**	**19.3**	**4.8**
	46	*97*	*230*	*57*	*15*	*7*	*74*	*7*
Feeling anxious for no reason	**45.5**	**53.0**	**64.1**	**50.0**	**14.1**	**20.3**	**22.1**	**15.1**
	45	*196*	*246*	*73*	*14*	*75*	*85*	*22*
Bloating of the stomach	**45.4**	**81.1**	**66.9**	**53.4**	**5.2**	**30.8**	**17.4**	**12.3**
	44	*300*	*257*	*78*	*5*	*114*	*67*	*18*
Sensitive or tender skin	**44.9**	**34.6**	**84.6**	**51.4**	**25.5**	**14.6**	**52.6**	**13.7**
	44	*128*	*325*	*75*	*25*	*54*	*202*	*20*
Pain in legs and arms (which is not due to hard exercise)	**44.3**	**29.5**	**94.8**	**71.9**	**20.6**	**10.5**	**71.4**	**37.0**
	43	*109*	*364*	*105*	*20*	*39*	*274*	*54*
Numbness/ tingling/ pins and needles	**44.0**	**31.6**	**75.3**	**55.5**	**11.0**	**7.0**	**39.8**	**17.1**
	44	*117*	*289*	*81*	*11*	*26*	*153*	*25*
Jittery. easily startled, often worried	**44**	**52.7**	**68.8**	**51.4**	**18**	**19.2**	**25.8**	**17.8**
	44	*195*	*264*	*75*	*18*	*71*	*99*	*26*

Pain increasing the day after you are active	**43.8**	**32.2**	**94.0**	**85.6**	**20.8**	**8.6**	**59.6**	**39.0**
	42	*119*	*361*	*125*	*20*	*32*	*229*	*57*
Racing heart	**43**	**34.3**	**53.6**	**56.8**	**17**	**3.8**	**11.2**	**18.5**
	43	*127*	*206*	*83*	*17*	*14*	*43*	*27*
Restless legs	**41.4**				**14.1**			
	41				*14*			
Blocked nose	**40.8**	**29.5**	**47.7**	**41.1**	**18.4**	**6.8**	**15.6**	**13.0**
	40	*109*	*183*	*60*	*18*	*25*	*60*	*19*
Very vivid dreams	**40.4**	**41.6**	**51.0**	**53.4**	**11.1**	**7.6**	**13.8**	**13.7**
	40	*154*	*196*	*78*	*11*	*28*	*53*	*20*
Headaches	**40**	**38.9**	**65.9**	**63.7**	**11**	**5.4**	**16.1**	**17.8**
	40	*144*	*253*	*93*	*11*	*20*	*62*	*26*
More clumsy than others	**39.8**	**32.7**	**69.0**	**69.9**	**17.3**	**9.5**	**26.8**	**28.8**
	39	*121*	*265*	*102*	*17*	*35*	*103*	*42*
Swollen painful joints	**39.4**	**22.7**	**66.1**	**39.7**	**18.2**	**8.9**	**38.0**	**10.3**
	39	*84*	*254*	*58*	*18*	*33*	*146*	*15*
Swollen painful joints	**39.4**	**0.0**	**0.0**	**0.0**	**18.2**	**0.0**	**0.0**	**0.0**
	39	*0*	*0*	*0*	*18*	*0*	*0*	*0*
Chest pain	**36.7**	**19.5**	**42.7**	**30.1**	**9.2**	**2.7**	**8.9**	**5.5**
	36	*72*	*164*	*44*	*9*	*10*	*34*	*8*
Depression	**36.4**	**34.3**	**53.9**	**38.4**	**17.2**	**13.8**	**26.8**	**11.0**
	36	*127*	*207*	*56*	*17*	*51*	*103*	*16*
Running nose	**36.4**	**33.2**	**41.9**	**32.9**	**9.1**	**9.5**	**11.5**	**9.6**
	36	*123*	*161*	*48*	*9*	*35*	*44*	*14*
Face flushes	**35.7**	**27.8**	**53.9**	**36.3**	**15.3**	**7.6**	**15.6**	**8.2**
	35	*103*	*207*	*53*	*15*	*28*	*60*	*12*
Pain moving from one place of body to another on different days	**35.4**	**24.1**	**89.1**	**62.3**	**16.7**	**7.3**	**58.6**	**25.3**

Table 3. Pattern similarity indexes between groups of people

	Asthma	IBS	FMS	Asthma -low	Asthma -high
Asthma				0.90	0.96
IBS	0.57			0.60	0.49
FMS	0.75	0.57		0.55	0.81
CFS	0.66	0.56	0.88	0.49	0.72
Asthma -low					0.75

Figure Legends

Figure 1. Graphical representation of the relationship between four symptom pattern indices. The line created by the severe asthma group is a monotonic decreasing line because the symptoms along the x axis are ordered my magnitude of the symptom mean. The symptom with the greatest mean value is to the left of the x axis. The mean symptoms of the IBS group are most similar in magnitude to the severe asthma symptoms. However, the symptom pattern index of the severe asthma group is most similar to the FMS group because the line created by the FMS group is most parallel to the montonic decrease of the severe asthma group.

Figure 2. Graphical relationship of the relationship between three symptom pattern indices. The symptoms along the x axis are in the same order as for figure 1 so that the two asthma groups would average to the monotonic line shown in figure 1.