The associated features of multiple somatic symptom complexes

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4 Tables
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Abstract (250 words)

Objective

To assess whether two or more functional somatic symptom complexes (~~F~~SSCs) showed stronger association with psychosocial correlates than single or no ~~F~~SSC after adjustment for depression/anxiety and general medical disorders.

Methods

In a population-based sample we identified, by standardised questionnaire, participants with chronic widespread pain, chronic fatigue and irritable bowel syndrome, excluding those with a medical cause for pain/fatigue. We compared psychosocial variables in three groups: multiple (>1), single or no FSS, adjusting for depression/anxiety and general medical disorders using ordinal logistic regression. We evaluated whether multiple ~~F~~SSCs predicted health status 1 year later using ~~ANOVA~~multiple regression ~~-~~to adjust for confounders.

Results

Of 1443 participants (58.0% response) medical records were examined in 990: 4.4% (n=44) had 2 or 3 symptom complexes, 16.2% a single symptom complex. Most~~any~~ psychosocial adversities were significantly associated with number of ~~F~~SSCs in the expected direction but, for many~~some~~, statistical significance was lost after adjustment for depression/anxiety and medical illness. ~~Previously married status, neuroticism, s~~Somatic symptoms, health anxiety, ~~life events,~~ impairment and number of prior doctor visits remained significantly associated. Impaired health status 1 year later was predicted by multiple somatic symptom complexes even after adjustment for depression, anxiety, medical disorders and number of ~~somatic~~ symptoms.

Conclusions

~~Several associated features, e.g.~~ Depression, anxiety, medical illness and health anxiety ~~and recent life events~~, demonstrated an exposure-response relationship with number of ~~functional~~ somatic symptom complexes. These may be core features of all Functional Somatic Syndromes and may explain why number of somatic symptom complexes predicted subsequent health status. These features merit inclusion in prospective studies to ascertain causal relationships. ~~They may explain the independent component of multiple FSS that predicted subsequent health status.~~

Keywords: Chronic Fatigue, Epidemiology, Fibromyalgia, Functional Somatic Syndromes, Medically Unexplained Symptoms, Population based.

Introduction

Functional somatic syndromes (FSS), such as chronic fatigue syndrome (CFS), chronic widespread pain (fibromyalgia) and irritable bowel syndrome (IBS), are common reasons for presenting to medical services but their aetiology is not fully understood. The risk factors for these syndromes include: female gender, childhood adversity, prior infections, few years of education, low socio-economic status, recent threatening life events, anxiety and depressive disorders, health anxiety, neuroticism, general medical disorders and numerous somatic symptoms [1-7]. One of the most replicated risk markers, however, is the presence of another syndrome, i.e. having one FSS is strongly associated with having, or developing, another [3, 8-11]. In clinical populations between a half and a third of those with a single functional somatic syndrome have at least one more; in the general population the prevalence of "polysyndromic" functional somatic syndromes has been shown to be 2- 4%) [9, 12-15].

It is not clear why the occurrence of one functional somatic syndrome predicts the development of another, and the risk factors for multiple, as opposed to single, functional somatic syndromes have not been extensively investigated. Several studies have found that multiple syndromes are associated with a high prevalence of depression and anxiety [13,14,16]. On the other hand, studies using latent class analysis of particular groups have suggested that patients with multiple FSS form a class of their own, separate from that comprised of anxiety and depression [9,17].

Multiple functional somatic syndromes are associated with greater impairment of health status than single FSS and with a greater frequency of healthcare use [9,14,15,17]. This might reflect the high prevalence of anxiety/depressive or general medical disorders, but other associated factors, such as numerous somatic symptoms, few years of education and abuse history are known to be associated with impairment and high healthcare use [11, 18-21].

The relationship between numerous somatic symptoms and multiple somatic syndromes is not clear. To some extent these are overlapping concepts as each FSS has its own list of somatic symptoms necessary for the diagnosis so more than one FSS is bound to be associated with a greater number of somatic symptoms. This appears to be confirmed by studies using cluster or latent class analysis; increasing total somatic symptom scores are associated with multiple somatic syndromes [12-14]. However, latent class analysis of somatic symptoms indicate separate classes for multiple FSS and multiple somatic symptoms [9, 17]. One way to study these closely associated phenomena is to identify the relationship of each with outcome; there is some evidence that chronic fatigue or chronic widespread pain are independent predictors of health status, in addition to depression/anxiety and number of somatic symptoms [19, 21,22]. We are not aware of any previous prospective study that has assessed whether multiple FSS predicts outcome after adjustment for number of somatic symptoms, depression/anxiety and general medical disorders.

The current study uses data from a small, population-based study, which we have reported previously but we have not previously examined the correlates of multiple

syndromes or considered them as a predictor of health status [22, 23]. The study allowed us to examine the presence of chronic fatigue, irritable bowel and chronic widespread pain, which we refer to as "somatic symptom complexes" as the study did not formally assess the presence of these functional somatic syndromes according to standardised criteria.

This study aimed to test the following hypotheses:

1) That multiple (2 or 3) ~~functional~~ somatic symptom complexes (~~F~~SSCs) show a significantly higher number of associated features compared to single ~~F~~SSC or no ~~F~~SSC and there is an "exposure–response" relationship across the three groups (multiple, single and no ~~F~~SSC).
2) That this difference in associated features between multiple, single and no ~~F~~SSCs becomes non-significant after adjustment for depression, anxiety and general medical disorders.
3) That multiple ~~functional~~ somatic symptom complexes do not form an independent predictor of subsequent health status after adjustment for the effect of anxiety, depression, general medical illness and bothersome somatic symptoms.

Hypotheses 1 and 2 were tested in a cross-sectional design and hypothesis 3 in a prospective design.

Methods

We conducted a population-based study in which we mailed 2985 baseline questionnaires to people aged 25-65 years registered at two general practices in North West England, one in an affluent rural area and one in a more deprived inner

city area. Potential participants were selected from complete population lists (i.e. GP registers) using simple random sampling assuming that the sampled sub-group was representative of the population from which they were drawn (Figure 1). The 2490 who were eligible to participate were sent a questionnaire that assessed the presence of chronic widespread pain, chronic fatigue irritable bowel syndrome and a number of potential associated factors (see below for details). Non-responders were sent a reminder postcard after two weeks and, if necessary, a further questionnaire after two further weeks.

Written informed consent was sought to examine participant's medical records. The medical record review identified any general medical illness that could explain the presence of pain or fatigue and also allowed us to count the number of consultations for the year before and year after questionnaire completion.

Definition of functional somatic symptom complexes

Chronic widespread pain (CWP)

We used the definition of chronic widespread pain included in the American College of Rheumatology 1990 criteria for fibromyalgia (24). Participants were asked to report the presence of any musculoskeletal pain they had experienced in the past month, whether their pain had persisted for three months or more, and to shade on a four-view blank body manikin the location(s) of their pain. Using these data, participants were classified as Chronic Widespread Pain if they reported pain, present for at least three months: above and below the waist, in the right and left hand sides of the body and in the axial skeleton.

Chronic fatigue

The fatigue scale contains 11 items that inquire about symptoms of physical and mental fatigue. Individual items are scored 0 or 1, with a total score ranging from 0 to 11. Participants with fatigue scores of 4 or more on the Fatigue Scale (25) and who had reported symptoms for six months or more were classified as having chronic fatigue.

Irritable bowel syndrome (IBS)

We identified those with IBS according to the Rome II criteria [26]. To fulfil these criteria participants had to report 3 months of continuous or recurring abdominal pain or discomfort and two of the following: (1) relief with a bowel movement, (2) be coupled with a change in frequency, or (3) be related to a change in the consistency of stools.

Medical record review

For participants who had agreed, medical records were reviewed for 12 months before and after the date of baseline questionnaire by two raters (FC and CCG) to see if there was evidence of a recognised medical condition that could explain chronic fatigue, irritable bowel syndrome or chronic widespread pain. A conservative approach was used; any medical illness that could cause fatigue or widespread pain led to exclusion from the relevant functional somatic symptom complex classification; only those participants who reported the relevant symptoms but who

did not have such a medical illness evident in the GP records were classified as having chronic fatigue, chronic widespread pain or irritable bowel.

Socio- demographic details

These included age, sex, marital status, current work status (including disability status), number of years of formal education and details of any outstanding compensation claims.

Co-morbid general medical disorders: Respondents were asked if they had any common medical disorders on a checklist and to add any not listed. For analysis, participants were classified as having none, one, two or more general medical disorders.

Symptom experience: The Somatic Symptom Inventory (SSI) asks respondents to rate 13 bodily symptoms on a 5-point scale as to "how much it has bothered you over the past 6 months?" The total score ranges from 13 to 65 with high scores indicating greater bother (27).

The Whitely index is a 14-item measure of health anxiety (28). Each item is scored on a 5-point Likert scale, 1 = ''not at all'' to 5 = ''a great deal.'' The total score ranges from 14 to 70, with high values indicating greater health anxiety.

Childhood Factors

The *Childhood Physical and Sexual Abuse questionnaire* consists of 8 questions concerning abuse (29). Respondents were rated as having experienced childhood

abuse if, before the age of 16 years, they reported that an older person touched them or they were made to touch someone else in a sexual way, or intercourse was attempted or completed (sexual abuse); that they were hit, kicked or beaten often and/or their life was seriously threatened (physical abuse); they were often insulted, humiliated or made to feel guilty (psychological abuse).

The *Parental Bonding Instrument* includes 7 questions concerning perceived maternal care and 1 item concerning maternal control (30,31).

Adult attachment, personality, recent stress and mental state

The *Relationship Scales Questionnaire* measures adult attachment style by asking respondents to identify which of four sets of characteristics most closely matches the way they relate to other people (32). These are: secure (trusting in others), preoccupied (emotionally dependent, low self-esteem), fearful (low trust of others, fearful of intimacy) and dismissing (low trust in others, compulsively self-reliant).

Social Support was assessed with a question determining whether the respondent had a close confidant with whom they can discuss all concerns.

The List of threatening experiences (LTE-Q) measures the experience of 12 threatening personal situations or events in the last 6 months (33). The total score of positive responses represents recent exposure to threatening experiences; we quote the results in 3 groups (0, 1, 2 or more). We also quote separately the scores for questions regarding illness in the participant and close relatives.

The *Revised NEO Personality Inventory (NEO-PI-R)* measures the personality trait of Neuroticism (34). It has a maximum score of 48 with high scores indicating higher levels of neuroticism.

The Hospital Anxiety and Depression Scale (HADS) is a valid and reliable measure of anxiety and depression in the general population which avoids questions about physical symptoms (e.g. weight loss, pain) that might be caused by general medical illness (35) . In this study we quote the anxiety and depression scores.

Health status and healthcare use

The *Short Form 12 (SF12) Questionnaire* assesses health status (36,37). It is a validated shortened version of the 36 item version and both versions have been used in FSS. The 12 items yield summary scores for mental (SF12-MCS) and physical (SF12-PCS) components of health status, which are transformed into norm based scoring. A low score represents impairment of health status.

The Euroqol (EQ5D) asks respondents to rate, problems they experience in mobility, self care, usual activities, pain/discomfort and anxiety/depression [38]. It also asks respondents to rate, on a vertical "thermometer", their own health today on a scale from 0 (worst imaginable health state) to 100 (best imaginable). It is the latter that we used in the prospective part of this study.

Healthcare use: For participants who had agreed, medical records were reviewed, counting all consultations with the GP or practice nurse for 12 months before and after the baseline questionnaire.

The study was performed in concordance with the Declaration of Helsinki. It received ethical approval from the North Manchester Local Research Ethics Committee (REC reference number: 06/Q1406/14). All participants provided written informed consent to participate after full explanation of the study.

Statistical analysis

We divided the participants into 3 groups according to the number of somatic symptom complexes: none, one, 2 or 3 (henceforth referred to as "multiple"). These 3 groups were compared in univariable analysis in terms of the variables listed above as potential correlates; socio-demographic, childhood factors, adult attachment, recent stress and illness, and mental state measures. Odds ratios and 95% confidence intervals for ~~multiple~~number of symptom complexes ~~with 95% confidence intervals~~ are presented for categorical measures (table 1), and group means and standard deviations for continuous measures (tables 2 and 3). ~~We repeated these analyses using~~ Ordinal logistic regression was used ~~for the~~to test the association between categorical baseline variables ~~to~~ adjusting for gender, HADS anxiety and depression scores, and number of general medical disorders. Continuous baseline and 1 year follow up measures in the 3 groups were ~~adjusted~~compared using AN~~C~~OVA~~R~~. ~~The ANCOVAR~~ A multiple regression analysies was~~ere~~ ~~repeated~~ used to assess the association between number of symptom complexes and ~~for~~each continuous baseline and follow up variable, adjusting for gender, HADS anxiety and depression scores, and number of general medical disorders. ~~s measured also at 1 year follow up~~ (tables 2 and 3).

~~Subsequently, we performed a~~A multiple regression analysis was used to assess whether number of somatic symptom complexes at baseline predicted health status at 1 year follow-up. EQ5D "health thermometer" at follow-up was ~~used as~~ the dependent variable (table 4). The following were entered as independent variables: age, gender, number of general medical disorders, somatic symptom score (SSI) , total HADS score (anxiety and depression combined) , baseline EQ5D thermometer score and number of somatic symptom complexes. ~~In addition, we used ANOVA to quantify the difference in EQ5D at follow-up for the 3 somatic symptom groups after adjusting for age, gender, HADS anxiety/depression scores, number of general medical disorders, Somatic Symptom Inventory and baseline EQ5D score.~~

In the adjusted analyses, inverse probability sampling weights were also used to adjust for the non-completion of questionnaires and non-availability of medical records and/or 1 year follow up data. For non-completion of baseline questionnaires (961 returned out of 1657 eligible), the probability of completion was calculated using logistic regression with independent variables, centre, age group and gender. For non-availability of medical records and 1 year follow data, the probability of obtaining data was calculated using logistic regression with all the baseline variables as independent variables. These probabilities were multiplied together, and their reciprocal was used as the sampling weight. All analyses were carried out using Stata version 14.

Results

Participation rates

Of the 2490 questionnaires mailed, 1999 (80.3%) were returned, of which 556 (22.3%) were blank or did not contain usable information (see figure 1). A total of 1443 (58.0%) participants returned a completed questionnaire and participated in the study. Non-responders were significantly more likely to be male (53.1% versus 42.3%), and younger (mean=43.9 versus 47.0 years) than the remaining eligible participants. The participation rates at the two practices were similar (56.3% and 59.3%).

We examined 990 medical records of the 992 participants who gave permission for this. Those who refused permission were younger (45.8 v 47.5 years, p = 0.013) and more likely to be female (63.2% v 55.5%, p = 0.008) but did not differ in terms of marital status, years of education, unemployment, prevalence of somatic symptom complex (assessed by questionnaire alone), anxiety, depression or somatic symptoms scores. Completed *follow up* questionnaires were received from 741 (75% of the 989 who agreed), of whom 638 (86.1%) also had their medical notes examined (figure 1). The 990 participants on whom we had complete baseline data were used in the first, cross-sectional part of this study. Data from the 638 participants who were followed up were used in the prospective part of the study.

Prevalence of syndromes

Of the 990 participants, 20 with chronic widespread pain, 9 with IBS and 28 with chronic fatigue had pain or fatigue that could be attributed to a co-existing general medical illness so these participants were excluded from the relevant somatic symptom complexes. After these exclusions 9.4 % (n=93) had Chronic Widespread

Pain, 3.5 % (n=35) had Irritable Bowel Syndrome and 12.6 % (n=125) had Chronic Fatigue. Approximately half of those who reported fatigue, widespread pain or abdominal pain had consulted their GP with the relevant symptom and, of these, one third had undergone investigations which showed no indication of underlying medical illness. Overall, 161 participants (16.3 %) had one syndrome, 40 (4 %) had two syndromes and four (0.4 %) reported all three. Figure 2 shows the overlap of syndromes.

Comparison of somatic symptom complexes ~~groups~~

Many of the features associated with FSS were most frequently recorded in those with multiple syndromes and they were distributed in an exposure-response relationship across the groups of multiple, single and no somatic symptom groups (table 1). After adjustment for gender, anxiety, depression and general medical disorders, many of the features were no longer associated with number of symptom complexes but ~~previously married status, neuroticism,~~ number of somatic symptoms (Somatic Symptom Inventory), health anxiety (Whitely index)~~, life events (Threatening Experiences score)~~ and number of doctor visits in the previous year remained significantly associated. All 3 measures of health status (SF-12 PCS, MCS and EQ5D) showed greatest impairment in the multiple FSS group (table 2).

At 1 year follow-up, after adjustment for gender, HADS anxiety and depression and number of general medical disorders, the number of somatic symptoms and all 3 measures of health status showed worst outcome for those with multiple somatic symptoms complexes at baseline. The same was true for number of consultations

during the follow-up year, though this became non-significant after adjustment for gender, anxiety, depression, and general medical illness (table 3).

Prediction of health status at 1 year follow-up

Multiple regression analysis which adjusted for the potential confounders of age, gender, number of current medical disorders, Somatic Symptom Inventory (number of bothersome somatic symptoms), HADS (anxiety and depression) score and baseline EQ5D score demonstrated that number of somatic symptom complexes was an independent predictor of health status at follow-up (table 4). ~~ANOVA which adjusted for these confounders yielded follow-up EuroQol scores of 80.6 (95%CI: 79.4-81.7), 78.8 (95%CI: 76.3-81.4) and 70.1 (S95%CI: 64.8-75.4)~~ The significant downward trend ~~-~~for none, 1 and multiple somatic symptom complexes at baseline ~~respectively~~ (a low score represents impaired health status ~~-)~~table 2) is maintained at follow up (table 3).The mean reductions from baseline to follow up have been added to table 3. The positive significant regression coefficient for increase (improvement) in EQ5D from baseline to follow up suggest that the improvements are greater for participants with more syndromes. The data for SSI is similar, with negative regression coefficient for the change because for SSI a reduced score represents improvement.

All the analyses combining these with the participants who had 2 symptom complexes have been repeated with these 4 participants in a separate higher group. The results are very similar to those presented and do not alter any conclusions. Therefore we conclude that this extra category has only a negligible influence on the

results. For example in table 4, the regression coefficient for symptom complexes in 4 groups (0 vs 1 vs 2 vs 3 on an ordinal scale) is -3.58, 95% CI -6.79 to -0.37, p=0.029.

Discussion

Our first hypothesis was upheld, the presence of multiple somatic symptom complexes was associated with a wide range of the usually accepted risk factors for these disorders and there was an "exposure–response" relationship across the three groups: none, one and multiple functional somatic symptom complexes. Many of these associations became non-significant when we adjusted for depression, anxiety and general medical illness, confirming, in part, our second hypothesis, but ~~previously married status and~~ the scores for ~~neuroticism,~~ bothersome somatic symptoms, health anxiety, ~~life events,~~ impairment of health status and number of prior doctor visits remained significantly ~~higher in the multiple~~ associated with more symptom complexes ~~ndromes group~~. Our third hypothesis was not upheld; multiple somatic symptom complexes formed an independent risk factor for poor outcome after adjustment for the effect of anxiety, depression general medical illness and bothersome somatic symptoms.

Before discussing these results further it is important to note a number of limitations of this study. This was a questionnaire-based study which meant we were not able to establish the diagnosis of the 3 functional somatic syndromes according to standardised criteria. We used the questionnaire-based syndrome definitions of irritable bowel syndrome and chronic widespread pain which have been used widely in population-based studies, but we measured chronic fatigue, rather than chronic fatigue syndrome. We did, however, examine participants' medical notes and

excluded from our functional somatic symptom groups those who had a medical illness that might explain the fatigue, pain or disturbed bowel function. This is a strength of this study compared to many other population-based ones. Another major strength of the study was the statistical analysis which, unlike many others, adjusted for the well-recognised associated features of anxiety, depression and general medical disorders, revealing, for the first time, further independent associated features.

Another major limitation is the cross-sectional design of the associated features part of the study. This needs to be replicated in a prospective design to establish whether the associated features we have identified predict subsequent syndrome development rather than being a consequence of the syndrome. The small number of respondents and the relatively low response rate are also limitations though we were able to show a) how the responders and non-responders differed and b) that, among those who did and did not agree to a medical record review, there were no major differences on many of the key variables. We also adjusted for possible bias between our sample and the population of eligible participants using inverse probability weighting in our analyses.

The prevalence of the 3 somatic symptom complexes in this study is comparable with other studies using similar criteria (13, 39,40). The threshold for inclusion in the somatic symptom complex groups might be considered to be rather low (e.g. we measured chronic fatigue not chronic fatigue syndrome) but these criteria did yield satisfactory numbers for statistical analysis and the prevalence of 2 or more somatic

symptoms complexes (4.4%) is not far outside the range of previous studies (9,12-15). The group with multiple somatic symptom complexes had greater impairment of health status than those with a single or no functional somatic syndromes and this difference remained at one year follow-up (table 3). The magnitude of the differences on EQ5D thermometer at baseline and at follow-up were quite marked in line with other studies (9,14,15,17). In addition, the multiple somatic symptom group attended primary care more frequently both before and during the year after our first assessment. These findings suggest validity of the somatic symptom complex groups we identified. Furthermore, we found that most of the purported risk factors for the functional somatic syndromes were associated with one or more somatic symptom complexes in our cross-sectional analysis. The main exception is the lack of a predominance of females; the reason for this is not clear.

The associated features of the somatic symptom complexes in this study show differences in the expected direction, ~~i.e. the difference from the no syndrome group was greatest for those~~ with a higher incidence of risk factors being associated with more ~~with multiple~~ symptom complexes. The unadjusted odds ratios ~~comparing them with the remainder~~ were quite marked (column ~~5~~4 in table 1). Although we have confirmed that anxiety, depression and comorbid physical conditions are associated with multiple somatic symptom complexes, there are others, namely: ~~previously married status, neuroticism,~~ somatic symptoms and~~,~~ health anxiety ~~and threatening life events~~. This confirms the notion that those people who have more than one somatic symptom complex have a greater load of “risk factors” than those with one or no such complex, at least in a cross-sectional analysis.

Much previous research concerning multiple functional somatic syndromes has used latent class analysis to define groups of participants. Three studies, both population-based and clinical, found separate groups for multiple functional somatic syndromes and for anxiety/depression; one study also found an additional group with numerous somatic symptoms (9,14, 17). This, together with our analysis showing the predictors of health status, suggests that the dimensions of a) multiple somatic syndromes, b) numerous somatic symptoms and c) anxiety/depression need to be considered as separated dimensions in future research. It has been previously assumed that numerous somatic symptoms is synonymous with anxiety and depression, and we have shown this is not the case.

There has been less work concerning the associated features of multiple functional somatic syndromes. A *preponderance of females* in this group was reported by one other study but contradicted by another (9,15). *General medical disorders*, a feature neglected in some studies, is another feature (5,6,9,11, 41) as are *health anxiety* and *frequent consultation* (14). *Numerous other somatic symptoms* or *syndromes, mood disorder, health anxiety, neuroticism, adverse life events, impaired quality of life and increased health care seeking* emerged from a study of patients with irritable bowel syndrome and another somatic syndrome (42). This list is similar to our findings. It is also similar to the features reported to be common to several individual functional somatic syndromes; *female gender, high health anxiety, other somatic symptoms, childhood psychological abuse* and *recent adverse life events* (10, 23). Thus there seems to be a growing consensus of the risk factors which may be regarded as the

"core features" or predisposing factors that are encapsulated in the "lumpers" argument that all functional somatic syndromes are manifestations of the same underlying disorder (43). They are common to all FSS and a greater number of these features is associated with multiple FSS.

The main implication of this study involves further research. Firstly, we need to know whether these correlates are true risk factors associated with the development of new syndromes and, secondly, we need to understand whether a high "risk load" predicts the development of multiple syndromes. Alternatively, or, in addition, they may predict persistence of somatic symptoms which could contribute to the development of multiple syndromes. Answering these questions would need large prospective studies. Further research is needed to assess whether our findings hold in functional somatic syndromes other than Irritable Bowel Syndrome, Chronic Fatigue syndrome and Chronic widespread pain.

From the clinical perspective, patients with multiple functional somatic syndromes should be assessed for all of these associated features, as this may help guide the clinician in management decisions as well as being helpful in predicting outcome (44).

Declaration of Competing Interests The authors have no competing interests to report.

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