# CHAPTER 3 RESULTS

## 3.0 REVIEW OF STUDY SEQUENCE

The main objective of the following studies was to examine, in patients with FGID, the relation of psychosocial factors - in particular life stress, emotional distress and personality - to the number and type of FGID, to the course of IBS over time and to GI transit, motor and sensory function in FGID. The results follow the study sequence first outlined in Table 1. Studies 1 and 2 address issues related to symptom outcomes, while Studies 3, 4 and 5 are concerned with GI transit, motor and sensory outcomes.

### 3.0.1 SYMPTOM-RELATED OUTCOMES

The focus of the first two studies was symptom-related outcomes; the diagnostic criteria for the FGID are tabled in Appendix B.

#### STUDY 1: CROSS-SECTIONAL EVALUATION OF PSYCHOLOGICAL, SOCIAL AND EXTRAINTESTINAL FEATURES OF FGID

This study identified (in a large group of patients with FGID), the psychological, social and extraintestinal (non-gut somatic symptom) predictors of:

1) the number of FGID syndromes present, and

2) each type of FGID.

It also examines the hypothesis that chronic life stress threat 'predicts' both the number and the type of concurrent FGID syndromes, extraintestinal symptoms and the severity of emotional symptoms (state anxiety or depression) in patients with FGID.

STUDY 2: LONGITUDINAL EVALUATION OF LIFE STRESS IN IBS

This study extends the cross-sectional findings in a prospective investigation of the relation of chronic life stress threat, psychological and demographic factors to subsequent symptom intensity over a 16 month period in patients with IBS.

The selection of patients with IBS, the most common of the FGID, as the study population was based in part on the findings of Study 1, in particular the causal processes suggested by the cross-sectional data, but also because when multiple FGID syndromes are present in these patients, both 'upper' and 'lower' gut syndromes are involved.

### 3.0.2 GASTROINTESTINAL MOTILITY OUTCOMES

We used new and more reliable scintigraphic, manometric and distension techniques to assess GI sensorimotor function. The outcome variables used in the following studies include delayed and normal transit (Studies 3 and 4) and, motor activity and sensitivity (perception) to balloon distension (Study 5).

STUDY 3: EVALUATION OF GASTRIC EMPTYING IN FUNCTIONAL DYSPEPSIA

This study assessed in detail the relation of psychological variables to the severity of gastric stasis in one region (the stomach) in a sample of patients with / without IBS. The outcome variables were:

a) four parameters of solid gastric emptying, and

b) two parameters of liquid gastric emptying.

STUDY 4: EVALUATION OF WHOLE GUT TRANSIT IN FGID

This study extended the previous findings by relating psychosocial and demographic variables (in FGID patients) to:

a) localised delayed transit (ie delay in transit in one of three gut regions - the stomach, the small intestine or the large intestine),

b) widespread (extensive) impaired transit (ie delay in transit in two or more gut regions), and

c) normal transit in all three regions

STUDY 5: EVALUATION OF JEJUNAL SENSORIMOTOR FUNCTION IN IBS

This study assessed the relation of psychological variables (in female outpatients with IBS with / without FD) to:

a) perception sensitivity, pain sensitivity, and postprandial and fasting motor activity; and

b) patient subgroups characterised by sensorimotor, motor (postprandial and fasting) and fasting motor abnormalities.

## 3.1 STUDY 1: CROSS-SECTIONAL EVALUATION OF PSYCHOLOGICAL, SOCIAL AND EXTRAINTESTINAL FEATURES OF FGID

The following section presents the results of the data analysis relevant to: (a) the relation of psychological, social and extraintestinal factors (non-gut somatic symptoms) to the number and type of FGID present; and relevant to (b) the relation of chronic social stressors to the severity and extent of gastrointestinal, extraintestinal and emotional symptomatologies in patients with these disorders.

### 3.1.1 PATTERNS OF ASSOCIATION BETWEEN PSYCHOSOCIAL AND EXTRAINTESTINAL FACTORS AND FGID

**Number and type of FGID syndrome(s)**

The prevalence of FGID and their subgroups are summarised in Table 6. The majority (167, 89%) of patients were classified as having one of the functional bowel disorders, and a large proportion (117, 62%) also fulfilled the criteria for one (or more) FD syndrome. The majority of patients (78%) fulfilled criteria for two or more, and one third of patients for three or more, FGID syndromes. Clusters of syndromes comprised one or more FD subgroups, with or without one of the functional bowel disorders. The functional bowel disorder most likely to coexist with FD was IBS; this contrasts with other functional bowel disorders (functional diarrhea, functional constipation) which frequently occurred alone.

**TABLE 6**

PREVALENCE OF FUNCTIONAL DYSPEPSIA SYNDROMES
AND FUNCTIONAL BOWEL DISORDERS WITHIN
THE PATIENT SAMPLE (N=188)

| **Group/subgroup** | **n** | **Sample %** |
|---|---|---|
| **Functional Dyspepsia Syndromes (62%[a])** | | |
| Ulcer-like dyspepsia | 35 | 19 |
| Dysmotility-like dyspepsia | 73 | 39 |
| Reflux-like dyspepsia | 70 | 37 |
| Unspecified dyspepsia | 31 | 17 |
| **Functional Bowel Disorders (89%[b])** | | |
| Irritable bowel syndrome | 122 | 65 |
| Functional constipation | 17 | 9 |
| Functional diarrhea | 4 | 2 |
| Unspecified functional bowel disorder | 24 | 13 |

[a] represents total number (%) with one or more functional dyspepsia syndrome (n=117)

[b] represents total number (%) with one (only) of functional bowel disorder (n=167)

The extent of overlap of FD with IBS is demonstrated in Table 7, prevalence rates showing that, for more than two thirds of the IBS patient population (n=122), one or more FD syndromes coexists with IBS.

**Gastrointestinal and emotional symptoms in FGID**

Symptom intensity

Figure 3 graphically illustrates the diversity within the patient sample in terms of the *symptom intensity* (ie the frequency and severity) of FGID symptoms that have been present for at least 3 months. Scores are not only *widely variable* (they range from 6 to 60) they are also *evenly distributed* along the intensity continuum (median value = 32; standard error = 0.9) closely resembling a normal curve distribution (skewness <0.1). Similarly, the *duration* of symptoms at this level of intensity and the *number* of FGID syndromes present also varied considerably; duration ranged from 3 to 240 months and number of syndromes from one to 6 months (see Figure 3 for median and standard error values).

Emotional distress

Depression and especially state anxiety scores were elevated for individuals within the patient sample (Figure 3). For the majority of patients (70% and 93% respectively), however, scores were more indicative of subclinical levels of emotional distress than of an emotional disorder of clinical severity. Figure 3 shows the median scores for depression and state anxiety to be well below the cut-off thresholds for a probable 'case' ie a score of 17 or more for depression (Boyd et al, 1982) and 57 for anxiety (Spielberger et al, 1970).

**TABLE 7**

PREVALENCE OF FUNCTIONAL DYSPEPSIA (FD) SUBGROUPS
IN THE IRRITABLE BOWEL SYNDROME POPULATION
(N=122)

| **IBS with and without FD syndromes** | **n** | **% of IBS** |
|---|---|---|
| IBS (no dyspepsia subgroup) | 41 | 33.6 |
| IBS + ulcerlike-dyspepsia | 8 | 6.6 |
| IBS + dysmotility-like dyspepsia | 24 | 19.7 |
| IBS + reflux-like dyspepsia | 11 | 9.0 |
| IBS + ulcer-like and dysmotility-like dyspepsia | 5 | 4.1 |
| IBS + ulcer-like and reflux-like dyspepsia | 7 | 5.7 |
| IBS + dysmotility-like and reflux-like dyspepsia | 21 | 17.2 |
| IBS + ulcer-like, dysmotility-like and reflux-like dyspepsia | 5 | 4.1 |
| TOTAL | 122 | 100% |

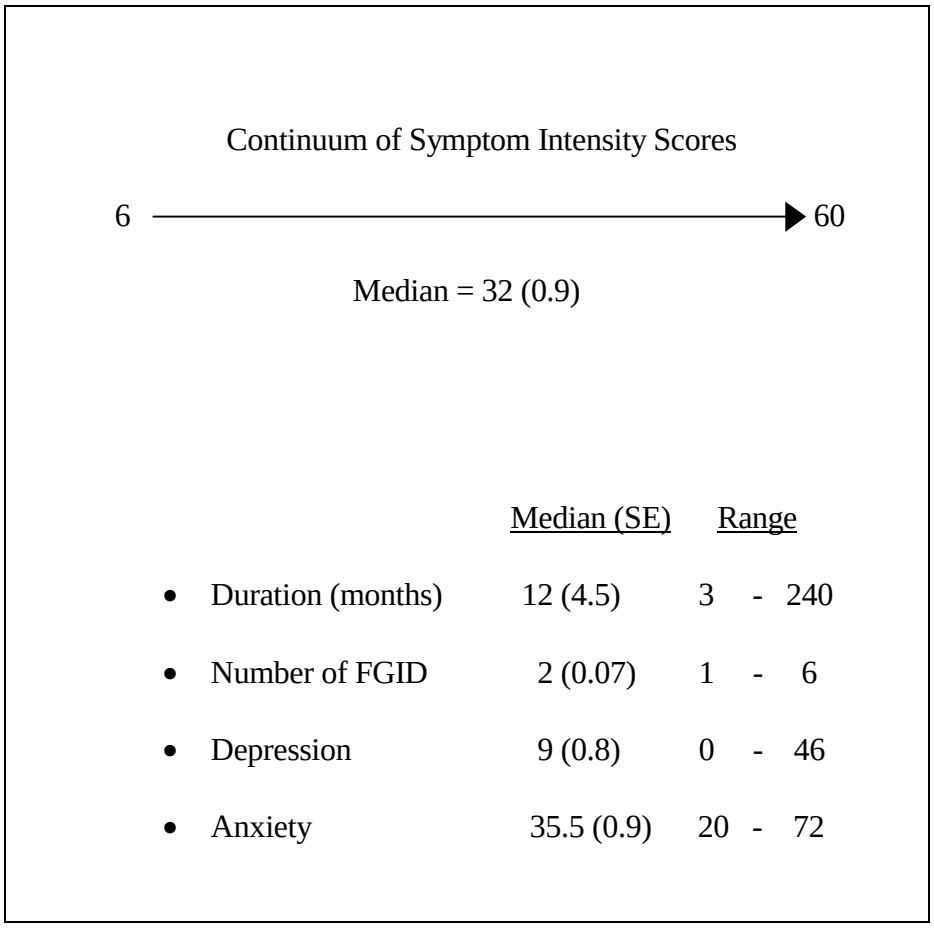



**Figure 3** WIDESPREAD DIVERSITY IN GASTROINTESTINAL AND EMOTIONAL SYMPTOMS IN FGID.

**Chronic life stress in FGID**

The vast majority of patients with FGID (98 %) had been exposed to at least one chronic social stressor (Table 8), in at least one (of seven) life stress domains (Figure 4), for more than a year. On average, patients had been exposed to $2.4 \pm 0.6$ such stressors, for an average of $3.9 \pm 4.3$ yrs; most stressors (434 / 451, 95 %) were current at interview. For 87% of all patients (FD significantly more than IBS, and IBS significantly more than non-IBS/FD), at least one chronic stressor was objectively rated as severe (highly threatening and/or highly goal-frustrating), and was independent of GI symptoms. These prevalence rates were uncommonly high. For example, in comparison with our community life stress data (Bennett et al 1991; Gilligan et al, 1987), more of our patients with functional GI disorders than healthy individuals were exposed to one or more stressor (98% vs 36%) these differences increased as the number of stressors increased (eg. 38% vs 0% for three or more stressors), and as their severity increased (87% vs 13% when at least one stressor was severe).

Table 8 summarises the prevalence among patients with FGID of chronic stressors rated as severe, moderate or low or absent severity for threat and for goal-frustration. These data show that considerably more patients were exposed to chronic stressors at the most severe level of threat (ie highly threatening chronic difficulties) than were exposed to the most severe level of goal-frustration (80% vs 39% respectively).

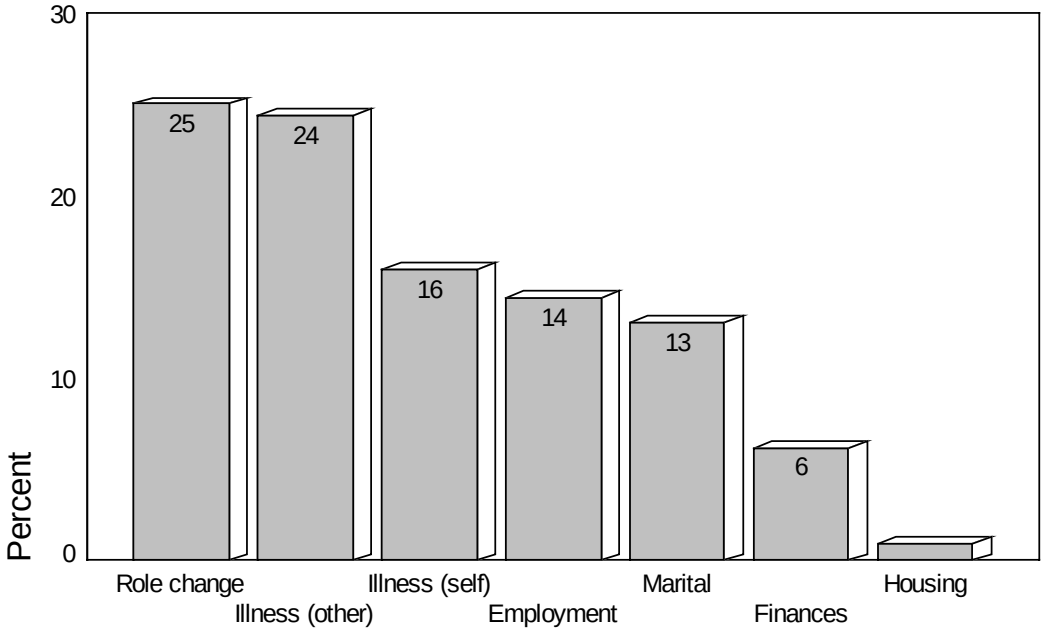
Most chronic stressor situations involved role change and/or interaction difficulties; other problems arose in the context of caring for others, or from personal

injury, accident or illness (other than FGID); the remainder involved work, marital, financial or housing difficulties (Figure 4).

**TABLE 8**

SEVERITY OF THREAT AND GOAL FRUSTRATION:
PROPORTION OF FGID PATIENTS EXPOSED TO AT LEAST ONE SUCH CHRONIC STRESSOR

| Chronic Stressor | Percent of FGID patients |
|---|---|
| **Threat** | |
| severe | 80 |
| moderate | 66 |
| low / absent | 18 |
| **Goal Frustration** | |
| severe | 39 |
| moderate | 58 |
| low / absent | 67 |
| **Proportion of patients exposed to:** | |
| One or more chronic stressor | 98 |
| One or more severe chronic stressor | 87 |




- Mean number of stressors per person = 2.4 (sd 0.06)
- Mean duration = 3.9 (SD 4.3) years

**Figure 4** Distribution of chronic stressors (n = 451) across seven life stress categories; percentages represent the relative frequency of each category of chronic stressors (as a proportion of all chronic stressors). sd = standard deviation

### 3.1.2 PREDICTORS OF NUMBER AND TYPE OF FGID

**Psychological, social and demographic features**

Multiple psychosocial variables (emphasised by bold type in Table 9) were significantly and independently associated with the *number* of FGID syndromes present. High levels on each of the following variables was associated with a larger number of syndromes - emotional distress (depression and state anxiety), personality and aspects of coping (trait anxiety, neuroticism, anger reactivity, an immature coping style and externality), emotional expression / suppression (the tendency to hold in anger) and high levels of chronic life stress threat and chronic goal-frustration.

Table 10 presents the linear regression model of best fit for these data - thus, increases on each of the following psychosocial variables together predicted an increase in the number of syndromes; personality (*trait anger reactivity*, *neuroticism*), coping style (*in this case mature attempts to cope with stress*), life stressors (featuring *severe chronic threat*), *absent or inadequate emotional support* and *increasing age*.

There was specificity, however, within these associations - each *type* of functional GI syndrome was distinguished by at least one psychosocial variable and these variables (and gender) differed between different functional GI syndromes. Table 9 shows individual associations, Table 11 the multivariate models for each FGID syndrome. In contrast, no demographic factors (eg marital, occupational and educational status) were associated with the number or type of functional GI symptomatology.

**Table 9** Pearson correlation coefficients of relations between psychological, social and demographic factors and type and number of FGID.

| Psychosocial and Demographic Variables | Type of FGID Syndrome | | | | | Number of FGID Syndromes |
|---|---|---|---|---|---|---|
| | Ulcer-like Dyspepsia | Dysmotility-like Dyspepsia | Reflux-like Dyspepsia | Irritable Bowel Syndrome | Functional Constipation | |
| **Emotional distress/mood state** | | | | | | |
| Depression | .0789 | .1377 | **.2516*** | .0675 | -.0214 | **.1962** |
| Anxiety | .0223 | .0641 | **.2687*** | .0831 | .0014 | **.1816** |
| **Personality and coping style** | | | | | | |
| Trait anxiety | .1092 | .0306 | **.2294** | .1209 | .0046 | **.2090** |
| Extraversion | -.0127 | .0942 | -.0457 | -.0175 | .1758 | -.0283 |
| Neuroticism | .0405 | .1248 | **.1773** | .1451 | -.0698 | **.2392** |
| Trait anger | .1092 | .0306 | .2294 | .1209 | .0046 | .2090 |
| Anger temperament | .0122 | .0475 | .1700 | -.0401 | .0759 | .0760 |
| Anger reactivity | .1637 | -.0435 | .1421 | -.0214 | .0679 | **.2206** |
| Other trait anger | .1556 | .0212 | -.0061 | .0135 | .0169 | .0460 |
| General hypochondriasis | .1516 | .0203 | **.1854** | **.1992** | -.0239 | .1617 |
| Defense Style | | | | | | |
| Immature | .1483 | -.0311 | **.1770** | .1386 | -.0928 | **.2038** |
| Neurotic | -.0036 | -.0401 | .0435 | .1157 | -.0548 | .0838 |
| Mature | -.0123 | .0160 | .1210 | -.0364 | -.1244 | .1551 |
| Locus of control of behaviour | .0797 | .0152 | .1308 | -.0186 | .0196 | .1067 |
| Self not in control | -.0501 | -.0328 | -.0069 | -.0721 | .1075 | -.1118 |
| External factors in control | .0983 | .0673 | .1023 | .0199 | -.0416 | **.1810** |
| Need help | .0660 | .0309 | .1536 | .0139 | -.0427 | .0922 |

Significant relations are presented in bold type. The method of Hochberg (Hochberg and Benjamini, 1990) (Appendix U) was used to adjust for multiple comparisons. * = $p<0.005$; for all others, $p<0.01$

Table 9 continued

**Table 9** Continued

| Psychosocial and Demographic Variables | Type of Syndrome | | | | | Number of FGID Syndromes |
|---|---|---|---|---|---|---|
| | Ulcer-like Dyspepsia | Dysmotility-like Dyspepsia | Reflux-like Dyspepsia | Irritable Bowel Syndrome | Functional Constipation | |
| Emotions expressed/suppressed | | | | | | |
| Anger suppressed | .0535 | -.0273 | -.0127 | .0864 | **-.1958** [a] | .0453 |
| Anxiety suppressed | .0036 | .0037 | .0633 | -.0071 | -.4137 | .1641 |
| Depression suppressed | .0233 | .0014 | -.0071 | -.0023 | -.1455 | .0386 |
| Anger held in | .0995 | -.0007 | .0795 | .0763 | **-.2235** [a] | **.2130** |
| Anger expressed | .0883 | .0046 | .0931 | .0161 | .0758 | .0447 |
| Anger controlled | -.0470 | .0699 | -.0015 | .0950 | **-.1868** [a] | .0784 |
| **Life stressors/chronic difficulties** | | | | | | |
| Total chronic threat score | .0736 | .1128 | .1524 | .0580 | -.0254 | **.2117** |
| Total chronic goal-frustration score | -.0189 | .1566 | **.2288** | .0604 | -.0551 | **.2091** |
| **Intimate emotional support** | | | | | | |
| Quality support is absent or poor (v adequate/good) | -.0008 | -.1095 | -.0258 | -.0430 | -.0501 | -.1318 |
| **Gender** | | | | | | |
| Female | | **.2081** | .1043 | .0398 | .1151 | .0289 |
| Male | **.1863** | | | | | |
| **Age** | | | | | | |
| Increasing age | .0367 | -.0763 | .1072 | -.0148 | -.0454 | .1769 |

Significant relations are presented in bold type. The method of Hochberg (Hochberg and Benjamini, 1990) (Appendix U) was used to adjust for multiple comparisons. * = $p<0.005$

**TABLE 10**

PSYCHOSOCIAL PREDICTORS OF NUMBER OF FUNCTIONAL GASTROINTESTINAL DISORDER SYNDROMES: THE REGRESSION MODEL OF BEST FIT

| | Psychosocial Predictors | Regression Coefficient (SE) |
|---|---|---|
| *Personality* | | |
| | Trait anger reactivity | 0.21 (0.023) |
| | Neuroticism (stress-proneness) | 0.19 (0.027) |
| *Coping Style #* | | |
| | Frequent use of (mature) coping strategies | 0.18 (0.006) |
| *Life Stressors* | | |
| | Chronic life stress threat | 0.16 (0.023) |
| *Emotional Support* | | |
| | Unavailable or Inadequate | 0.15 (0.131) |
| *Age* | | |
| | Increasing age | 0.16 (0.005) |

SE = standard error; $R^2 = .21$

- Psychosocial predictors are presented in order of stepwise selection into the model
- An increasing score on *each* dimension was associated with an increase in the number of functional GI syndromes
- Each predictor variable was significant at $p<0.05$ in the final model

# After adjusting for the above personality traits, some variables eg immature coping did not significantly affect the outcome

**TABLE 11**

PSYCHOSOCIAL PREDICTORS OF TYPE OF FGID SYNDROME:
LOGISTIC REGRESSION MODELS

| Functional Gastrointestinal Syndrome | Gender and Psychological Dimensions | Chronic Life Stressor |
|---|---|---|
| Ulcer-like dyspepsia | Male gender<br>Trait anger reactivity<br>Model $\chi^2$ =11;VE = 6% | |
| Dysmotility-like dyspepsia | Female gender<br>Depression<br>Model $\chi^2$ =13;VE = 5% | Chronic goal-frustration<br>Model $\chi^2$ = 5;VE= 2% |
| Reflux-like dyspepsia | State anxiety<br>Mature coping style<br>Trait anger temperament<br>Model $\chi^2$ = 24; VE = 10% | Chronic goal-frustration<br>Model $\chi^2$ = 10; VE= 4% |
| Irritable bowel syndrome | Hypochondriasis<br>Anger control<br>Model $\chi^2$ = 12; VE = 7% | |
| Functional constipation | Anger held in infrequently<br>Model $\chi^2$ = 18; VE = 16% | |

$\chi^2$ = chi-square; VE = variance explained

Each predictor variable (gender, psychological and life stressor) was significant at $p<0.05$ in the final model.

**Extraintestinal features**

After adjustments for multiple comparisons, an *unpleasant taste* was the only extraintestinal symptom to be associated directly with the overall severity and extent of functional gut disturbance (ie the number of functional GI syndromes present). In contrast to the weak relation between this variable and the number of syndromes, however, the presence of *binge eating behaviour* was strongly associated with an increased number of syndromes (Table 12) as well as its special relation with reflux-like dyspepsia (Tables 12 and 13).

Quantitative effects were found *within* the specific associations reported below; thus, extraintestinal symptoms were predictive of the combination of FD and IBS in general, and of dysmotility-like and reflux-like dyspepsia in particular (see Table 12 for specific bivariate associations, Table 13 for multivariate models).

Post hoc analysis revealed that *fatigue* was most likely to be present in patients with both dysmotility-like dyspepsia and IBS, (odds ratio = 4; 95% confidence interval = 1.8, 9.1; p=0.0006) while the probability of *unpleasant taste* was similarly greater in patients with both dysmotility-like and reflux-like dyspepsia (odds ratio = 5; 95% confidence interval = 2.2, 13.5; p=0.0003). In contrast, the relation of *binge eating behaviour* and of *dry skin* to reflux-like dyspepsia were strong and highly specific to this syndrome alone. All of the above relations remained significant after controlling for chronic life stress, current emotional distress and demographic variables (age, gender).

**Table 12** Pearson correlation coefficients of relations between extraintestinal symptoms / behaviours and type and number of FGID.

| Extraintestinal Symptoms and Binge Eating Behaviour | Type of FGID Syndrome | | | | | Number of FGID Syndromes |
|---|---|---|---|---|---|---|
| | Ulcer-like Dyspepsia | Dysmotility-like Dyspepsia | Reflux-like Dyspepsia | Irritable Bowel Syndrome | Functional Constipation | |
| **Extraintestinal symptoms** | | | | | | |
| Fatigue | -.1120 | **.2100** | .0837 | .1749 | -.0560 | .0820 |
| Tension headaches | .0671 | .0090 | -.0444 | .0531 | .0450 | .0198 |
| Migraine headaches | .0215 | -.0077 | .0636 | -.0145 | .0981 | -.0153 |
| Unpleasant taste | .0715 | **.2046** | **.2117** | -.0056 | .2019 | **.2129** |
| Nocturia | .0119 | **.1917** | .0151 | .0786 | .0683 | .0932 |
| Urinary frequency/urgency | .1020 | .0833 | .0151 | .0419 | .1287 | .1310 |
| Incomplete bladder emptying | -.0537 | .1067 | .0601 | .0288 | .0883 | .0769 |
| Dry skin | **-.1981** | -.0132 | **.2633*** | .0839 | -.0408 | .1576 |
| Insomnia | .0957 | .0183 | .0027 | -.1326 | .0840 | .0396 |
| Backache | -.1151 | .0968 | .0046 | -.0234 | .0308 | .0386 |
| **Behaviours** | | | | | | |
| Binge eating habit | .0916 | .1033 | **.2140** | -.0538 | .1205 | **.2908*** |

Significant relations are presented in bold type. The method of Hochberg (Hochberg and Benjamini, 1990) (Appendix U) was used to adjust for multiple comparisons. * = $p<0.005$

**TABLE 13**

EXTRAINTESTINAL SYMPTOM PREDICTORS OF TYPE OF FGID SYNDROME: LOGISTIC REGRESSION MODELS

| Functional GI Syndrome | Gender and Extraintestinal Symptoms | Odds ratio | (95%CI) |
|---|---|---|---|
| Ulcer-like dyspepsia | Male gender | 2.9 | (1.3, 6.2) |
| | | VE = 4% | |
| Dysmotility-like dyspepsia | Female gender | 3.0 | (1.4, 1.9) |
| | Fatigue | 2.0 | (1.1, 3.9) |
| | Unpleasant taste | 2.2 | (1.1, 4.5) |
| | | VE = 9% | |
| Reflux-like dyspepsia | Dry skin or eczema | 4.2 | (1.5,11.7) |
| | Binge eating habit | 2.1 | (1.0, 4.1) |
| | Unpleasant taste | 2.0 | (1.0, 4.1) |
| | Male gender | 3.6 | (1.5, 8.5) |
| | | VE = 11.5% | |
| Irritable bowel syndrome | Fatigue | 2.3 | (1.2, 4.3) |
| | | VE = 3% | |
| Functional constipation | Nil | | |

VE= variance explained was calculated for the model presented
CI = confidence interval

- Extraintestinal and gender predictors are presented in order of stepwise selection into the model
- Each predictor variable was significant at $p<0.05$ in the final model

**Chronic life stress threat and gastrointestinal, extraintestinal and emotional symptomatologies**

Significant linear relations were found between each of three factors - number of FGID syndromes, number of extraintestinal symptoms, and the severity of emotional distress (state anxiety). Furthermore, each of these factors correlated significantly with the total chronic life stress threat score (see Figure 5). It is noted that the correlation coefficients are modest for all relations, ranging from $r = 0.14$ (the relation between chronic life stress threat and anxiety) to $r = 0.24$ (the relation between anxiety and the number of extraintestinal symptoms present); all other coefficients were $r = 0.2$).

These global findings were, however, marked by a notable degree of specificity eg. the strength of the linear relations between the number of extraintestinal symptoms / behaviours and the number of FGID syndromes present was explained almost entirely by strong relations between specific extraintestinal feature (eg fatigue, unpleasant taste, binge eating behaviour) and certain FGID syndromes (in particular, dysmotility-like dyspepsia, reflux-like dyspepsia and IBS) (Tables 12 & 13).

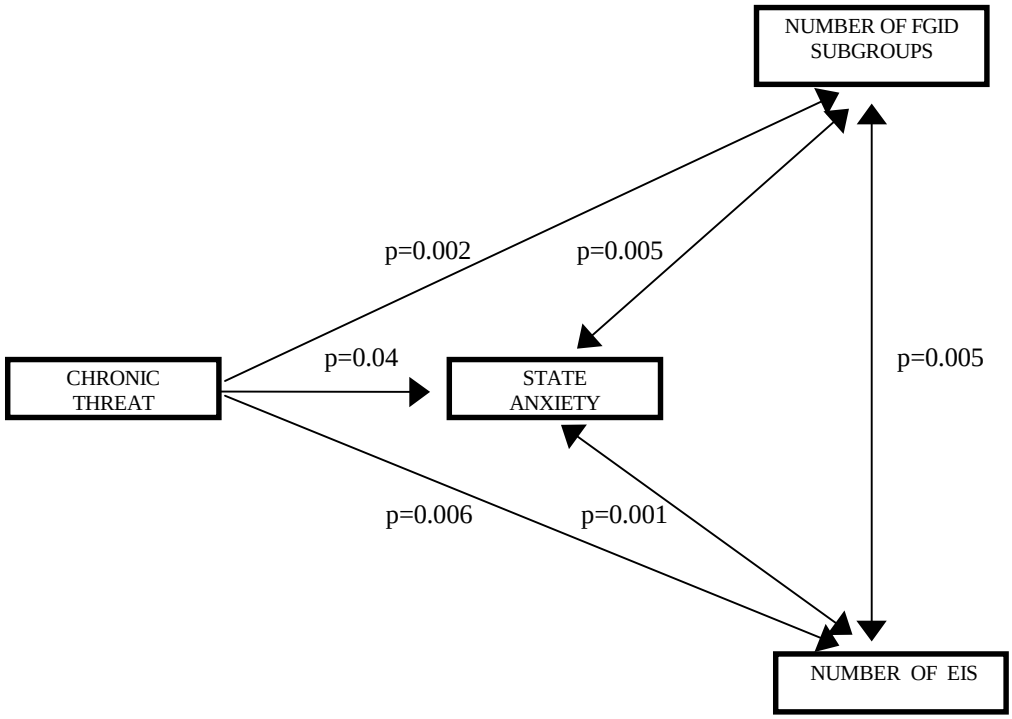



**Figure 5** Graphic representation of: a) the 3-way linear relation between emotional symptoms (state anxiety), the number of FGID syndromes present in an individual, and the number of extraintestinal symptoms (EIS); and b) the relation of chronic life stress threat to each of these dimensions. Probability values are shown for each linear relation determined from Pearson correlation analysis. See text for correlation coefficients.

**Summary of results for cross-sectional relations in FGID**

In patients with FGID:

1) increasing scores on multiple psychological, social and demographic factors predicted increases in the number of concurrent syndromes present;
2) within these global relations, the specificity of the psychosocial, extraintestinal and gender features of individual syndromes revealed marked differences between them; and
3) simple linear relations between the total severity of chronic life stress threat and gastrointestinal, extraintestinal and emotional symptomatologies suggest that the severity of *chronic life stress threat* may account, at least in part, for the coexistence of specific gut, emotional, extraintestinal and behavioural disturbances. This pattern of association was most specific for the IBS and FD group of syndromes (ie the FGID syndromes defined specifically by the presence of abdominal pain and/or discomfort), and for particular emotions and extraintestinal and behavioural factors.
4) Relations between chronic life stress threat, psychological distress and FGID symptomatology were linear throughout.

## 3.2 STUDY 2: LONGITUDINAL EVALUATION OF LIFE STRESS IN IBS

This study further examines the process suggested by the cross-sectional findings. It reports the results of the longitudinal evaluation of the strength of the relation of chronic life stress threat (relative to emotional distress and other psychological and demographic factors) to subsequent symptom intensity in patients with IBS (with and without FD).

### 3.2.1 PATTERNS OF CHANGE IN LIFE STRESS AND SYMPTOM INTENSITY OVER TIME

Mean scores reduced over the follow-up period for *life stress* (total chronic threat and total chronic goal-frustration) and for *symptom intensity* assessed at entry, at 6 months and 16 months (Figures 6 and 7 respectively). Table 14 shows that although group patterns of change for both symptom intensity and life stress scores were in the direction of a general improvement for most patients (from entry to 6 months and from entry to 16 months), symptom intensity and/or life stress either worsened or remained the same for most participants from 6 months to 16 months. That is, the direction of change became increasingly variable during the follow-up period consistent with a pattern of change that was independent of systematic extraneous influences. The same trend is demonstrated in Table 15 with respect to exposure vs non-exposure to one or more highly threatening and/or goal-frustrating stressor. These data further reveal that more than twice as many patients were exposed to highly threatening chronic stressors than were exposed to highly goal-frustrating stressors at entry, 6 months and 16 months.

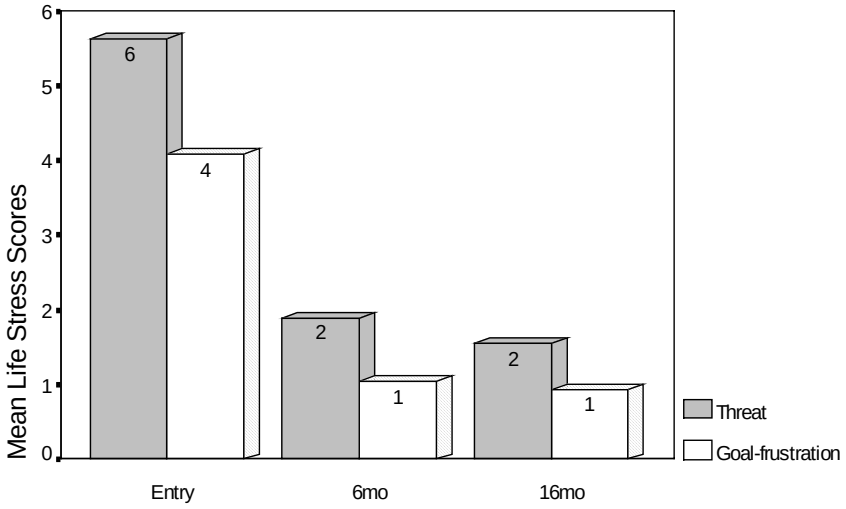



**Figure 6** Mean chronic (life stress) scores for threat and goal-frustration at entry, 6 months and 16 months

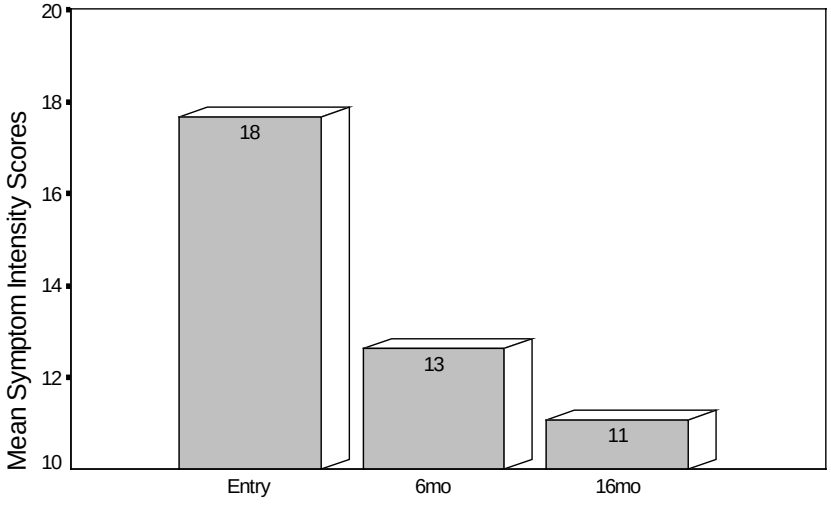



**Figure 7** Mean symptom intensity (SI) scores at entry, 6 months and 16 months

**TABLE 14**

PROPORTION OF PATIENTS WITH SAME, WORSE, IMPROVED SYMPTOM INTENSITY AND LIFE STRESSOR CHRONIC THREAT, AND/OR CHRONIC GOAL-FRUSTRATION OVER 16 MONTHS OF FOLLOW-UP.

| Parameter of change | Same (%) | Worse (%) | Improved (%) |
|---|---|---|---|
| Symptom Intensity | | | |
| Entry - 6mo | 12.8 | 9.4 | 77.8 |
| Entry - 16mo | 12.0 | 9.4 | 78.6 |
| 6mo - 16mo | 33.3 | 21.4 | 45.3 |
| Life Stressor: | | | |
| *Chronic threat* | | | |
| Entry - 6mo | 2.6 | 1.0 | 96.4 |
| Entry - 16mo | 2.6 | 0.0 | 97.4 |
| 6mo - 16mo | 50.8 | 16.4 | 32.8 |
| *Chronic goal-frustration* | | | |
| Entry - 6mo | 2.0 | 1.0 | 97.0 |
| Entry - 16mo | 3.4 | 0.0 | 96.6 |
| 6mo - 16mo | 59.0 | 18.0 | 23.0 |

mo = months

**TABLE 15**

PROPORTION OF IBS PATIENTS EXPOSED (+) AND NOT EXPOSED (-) TO ONE OR MORE CHRONIC STRESSOR THAT WAS HIGHLY THREATENING AND/OR HIGHLY GOAL-FRUSTRATING.

| Severe Chronic Stressors (one or more) | Entry (%) | 6 months (%) | 16 months (%) |
|---|---|---|---|
| Chronic highly threatening stressor(s) | + 82.1 | + 44.4 | + 35.0 |
| | - 17.9 | - 55.6 | - 65.0 |
| Chronic highly goal-frustrating stressor(s) | + 37.6 | + 17.9 | + 17.9 |
| | - 62.4 | - 82.1 | - 82.1 |

**TABLE 16**

FGID DIAGNOSIS AT 16 MONTHS

| FGID Diagnosis at 16 months | Number of subjects | Sample % |
|---|---|---|
| Irritable bowel syndrome (IBS) | 74 | 63 |
| Unspecified functional bowel disorder | 28 | 24 |
| Functional constipation | 3 | 2.5 |
| Subclinical symptoms | 9 | 8 |
| Asymptomatic > 6 months | 3 | 2.5 |
| Total: | 117 | 100% |
| IBS + one or more functional dyspepsia syndrome | 45 | 38% |

Diagnostic status at 16 months (Table 16) reveals that although the proportion of patients with a clinical diagnosis of IBS (and/or with concomitant FD syndromes) reduced over time (from 66% at entry to 38% at 16 months), only 10.5% had subclinical or no symptoms at 16 months.

**Within-subject relations**

Co-variance over three time-frames

Taking into account for each individual, *all* changes over time in symptom intensity and chronic threat, analysis revealed a high degree of covariance of life stress and symptom intensity scores. Almost all (97%) of the variance in symptom intensity over time apportioned to $Time_{ws}$ effects (Omega squared ($\Omega^2$) = 0.42) ($f_{2, 232}$ = 86, $p < 0.0001$), was accounted for by quantitative changes in one component of life stress - the severity of chronic threat. In the presence of chronic threat, chronic goal-frustration did not contribute significantly to changes in symptom intensity over time - hence, in all subsequent analyses only the chronic threat component of life stress was used.

Time-lag relations (with and without relevant covariates)

*Life stress during the first 6 months of the follow-up period* was highly predictive of symptom intensity at 16 months (see Table 17). The presence of *one or more highly threatening chronic difficulties* (from entry to 6 months) contributed significantly to this long-term prediction of symptom intensity ($f_{1,115} = 18.4$, $p < 0.0001$; variance explained = 37%). This relation remained significant even after controlling for the effects of baseline symptomatology (ie symptom intensity at entry, and duration at that level of intensity prior to entry), emotional distress (anxiety, depression), age, and gender ($f_{7,109}$ = 12, $p < 0.0001$; variance explained = 66%) (the second model in Table 17).

**TABLE 17**

THE PRESENCE OF ONE OR MORE HIGHLY THREATENING CHRONIC DIFFICULTY (0 TO 6 MONTHS), SIGNIFICANTLY PREDICTS SYMPTOM INTENSITY AT 16 MONTHS ALONE AND AFTER CONTROLLING FOR BASELINE COVARIATES.

| Outcome Variable | Predictor Models | Effect size and significance B (95% CI) |
|---|---|---|
| Symptom Intensity at 16 months | | |
| | Highly threatening CD (0- 6mo)* | 5.3 (2.8,7.7) |
| | | Model VE = 37% |
| Symptom Intensity at 16 months | | |
| | Symptom intensity at entry* | 0.63 (0.4, 0.8) |
| | Duration of SI pre-entry* | 0.04 (0.01, 0.07) |
| | State anxiety | -0.04 (-0.16, 0.07) |
| | Depression | 0.005 (-0.13, 0.14) |
| | Age | 0.03 (-0.06, 0.12) |
| | Gender | 0.09 (-2.21, 2.4) |
| | Highly threatening CD (0- 6mo)* | 4.22 (2.0, 6.23) |
| | | Model VE = 66% |

*$p < 0.05$

CD = chronic difficulty

SI = symptom intensity

B = regression coefficient; CI = confidence interval; VE = variance explained; mo = months

Post hoc analyses determined:

1) the *direction of effect* to be firmly in the direction of life stress predicting subsequent symptom intensity (explaining 97 % of the variance), and not the reverse (38% of the variance which is expected given autocorrelation effects); and
2) *proximal life stress* (during the previous 6 months or more) to significantly *exceed distal life stress* (ie more than 10 months previously) as a predictor of symptom intensity at 16 months. This is clearly demonstrated by differences in values on the effect size measure, partial $Eta^2$ which were .432 and .127 respectively.

The role of personality, coping, emotional distress, age and gender

No *personality* (trait anxiety, extroversion, neuroticism, trait anger, general hypochondriasis) or *coping style* (defense style, locus of control of behaviour, emotional expression/suppression) characteristic, *emotional state* (anxiety and depression) or *age* or *gender* variable contributed to symptom intensity at 16 months, or altered the strength of the relation of life stress to symptom intensity over time. That is, whether these variables were entered in the analysis as covariates, or included (with life stress variables) in the stepwise selection procedure, the relation of the life stress variable, *one or more highly threatening chronic difficulty* (entry to 6 months) to symptom intensity at 16 months, remained independently significant. Only in the absence of life stress variables in the model, did a psychological variable (specifically s*tate anxiety* at entry), predict symptom intensity at 6 months ($F_{3,113} = 37.0$, $p < 0.0001$) and this effect was quite modest (partial $Eta^2 = .079$).

Life stress predictors of any improvement or lack of improvement in symptom intensity over 16 months

Failure to improve symptomatically over 16 months was strongly predicted by the presence of *at least one highly threatening chronic difficulty* during the final 10 months (or to a lesser extent during the first 6 months) of the follow-up period, with a specificity of 85%, a sensitivity of 85%, and an odds ratio of 33:1 (95% confidence interval = 17, 94). Controlling for emotional distress, age, and gender did not alter this relation.

Life stress predictors of clinical improvement or no clinical improvement over 16 months

Table 18 categorises clinical (ie 50% or more) improvement in symptom intensity by presence of a significant chronic stressor. The table shows that, of the forty three patients (35% of the sample) exposed to one or more highly threatening chronic difficulty during the previous 10 months, *no patient* improved clinically in the *presence* of the stressor. Of particular relevance also, *all* who improved clinically (41% of the sample), did so in the *absence* of this stressor. That is, for these two subgroups of patients (76% of the sample), the presence / absence of the stressor significantly predicted the absence or presence of a clinical outcome. In contrast to those patients who improved in the absence of the stressor (41% of the sample), for 24% of the patients, the absence of the stressor (also personality, coping style, mood state, age and gender) failed to explain the absence of a clinical improvement.

Relative risk estimates for the cohorts - chronic stressor present and chronic stressor absent - are presented in Table 18.

**TABLE 18**

CLINICAL IMPROVEMENT AS A FUNCTION OF THE PRESENCE OR ABSENCE OF ONE OR MORE HIGHLY THREATENING CHRONIC DIFFICULTY DURING THE PREVIOUS 10 MONTHS

| Clinical Improvement [a] | One Or More Highly Threatening Chronic Difficulty (CD) | | |
|---|---|---|---|
| | Absent [b] | Present [c] | |
| Absent | 24% | 35% | n = 72 (69%) |
| Present | 41% | 0% | n = 50 (41%) |
| | n = 79 (65%) | n = 43 (35%) | n = 122 |

[a] Clinical improvement: defined as the presence or absence of a 50% or more improvement in symptom intensity at 16mo

[b] In the cohort of absent high threat chronic difficulty, the relative risk of no clinical improvement vs clinical improvement was 0.4 (95% CI = 0.3, 0.5).

[c] In the cohort of high threat chronic difficulty present, the relative risk of no clinical improvement vs clinical improvement could not be calculated as *no* patient exposed to this stressor improved by 50% or more.

### 3.2.2 RELATIONS BETWEEN LIFE STRESS, SYMPTOM INTENSITY AND DEPRESSION

**Depression and symptom intensity**

Depression and IBS frequently *coexist* - for example, at 16 months the correlation coefficient for these two variables was r =.3355, p<0.001, however, from our findings reported above, depression did not predict *subsequent* levels of symptom intensity. Furthermore, symptom intensity at entry (with and without baseline depression and life stress in the model) failed to predict depression. That is, although depression frequently coexists with IBS/FD, *no causal association* appears to exist between them.

**Life stress, depression, symptom intensity, and number of FGID**

An examination of relations between life stress, depression and various GI symptom outcomes helps to explain the coexistence of depression with GI symptoms in IBS. A comparison of outcome models shows that the presence of *one or more highly threatening chronic difficulty* during the final 10 months follow-up period (Table 19) more than during the first 6 months (Table 17), predicted depression and GI symptoms on every symptom outcome measure (symptom intensity, number of FGID syndromes present, 50% clinical improvement in symptom intensity). It is noted also that in all predictor models in Table 19, depression and GI symptoms were statistically independent of each other. Overall, these findings suggest that although depressive symptoms frequently coexist with GI symptoms in patients with IBS, the association does not appear to be strongly causal, at least within the time frame of this study. It is possible, however, that one or more highly threatening chronic difficulty may represent a common trigger (or exacerbating agent) for both depressive and functional symptoms in some patients with IBS/FD.

**TABLE 19**

SUMMARY OF FINAL PREDICTOR MODELS FOR CLINICAL AND LIFE STRESS OUTCOMES AT FOLLOW-UP (16 MONTHS)

| Clinical Outcome at 16mo | Predictor Models | Effect size and significance B (95% CI) |
|---|---|---|
| Symptom Intensity | | |
| | Highly threatening CD | 8.8 (7.2, 10.4) |
| | Symptom intensity at entry | 0.5 (0.4, 0.6) |
| | Duration of symptom intensity (pre-entry) | 0.03 (0.008, 0.05) |
| | | Model VE = 68% |
| 50% Clinical Improvement | | |
| | Highly threatening CD | (see Table 12-10) |
| Number of Syndromes | | |
| | Highly threatening CD | 0.7 (0.3, 1.0) |
| | Number of Syndromes (at entry) | 0.3 (0.1, 0.5) |
| | Female gender | 0.4 (0.2, 0.7) |
| | | Model VE = 24% |
| Depression | | |
| | Depression (at entry) | 0.6 (0.5, 0.7) |
| | Highly threatening CD | 7.4 (4.5, 10.3) |
| | | Model VE = 54% |
| Highly threatening CD [a] 6 - 16 months | Highly threatening CD (pre-entry) | 0.3 (0.03, 0.5) |
| | | Model VE = 4% |

B = regression coefficient; CI = confidence interval; VE = variance explained

Highly threatening CD (unless stated otherwise) = the presence of one or more highly threatening chronic difficulty during the period 6 to 16 months.

[a] no psychological or gender factor influenced the presence of one or more CD at 16 months

**Gender**

Female gender was the only psychological or demographic variable to influence symptomatology long-term. Compared with men, women had a larger number of coexistent IBS/FD syndromes at 16mo (Table 19), but not at entry (Study 1). Post hoc analysis revealed that the syndromes most likely to be present in women at 16mo were dysmotility-like dyspepsia (odds ratio = 4.3, 95% confidence interval = 1,13) and IBS (odds ratio = 2.7, 95% confidence interval = 1,6) with no gender difference in the likelihood of reflux-like or ulcer-like dyspepsia.

Several findings suggest that for women more than men, dysmotility-like dyspepsia is more prevalent and is more likely to develop, or not to improve, in the presence of the highly threatening stressor. Post hoc analysis revealed that the high prevalence of dysmotility-like dyspepsia at entry (Study 1) and at 16mo represents for some of the sample, no change in dysmotility-like dyspepsia over time (23% of women, 6% of men) and for others, onset of a new syndrome (12% of women, 6% of men). Moreover, the factors which together correctly classified (for 77% of the sample) the presence/absence of dysmotility-like dyspepsia at 16mo were, in order of entry into the model, *female gender*, the *chronic stressor* and the presence of *dysmotility-like dyspepsia at entry* (model not shown). Dysmotility-like dyspepsia has received particular attention in this section because the gender differences found in this study in relation to the type and the course of the disorder over time, may have relevance for gender-related differences in dysmotility found in Study 4.

**Summary of results for relations with IBS over time**

1) Overall, these longitudinal data indicate that for most patients with IBS the intensity of GI symptoms (ie severity and frequency), the number of syndromes present and the presence and extent of clinical improvement was strongly influenced by the intensity of antecedent *chronic life stress threat*.
2) These data support the process suggested by the baseline data (Figure 5) of: a) the one-way direction of effect, b) the direct (unmediated) nature of the relation over time; and c) the prominence of chronic life stress threat (and to a lesser extent, *state anxiety*) over all other psychosocial and demographic factors as a predictor of subsequent symptom intensity.
3) The relation of *personality*, *coping style* and *emotional support* to various symptom outcomes at entry (Study 1), but not at 16mo, is consistent with the notion that the effects of person factors on functional gut symptomatology is greatest during periods of increased life stress provocation. This cannot be assumed in this study, however, even though the reduced strength of these relations in the follow-up period correspond with reduced levels of life stress for the majority of patients.
4) *Depression* scores also were highly sensitive to the presence of the highly threatening stressor. Relations between life stress, depression and GI symptoms on a variety of measures indicated that, although no causal association seems to exist between the presence of depressive and GI symptoms in IBS, both types of symptoms followed exposure to severe and chronic life stress threat. These data provide at least a partial explanation for the coexistence of both depressive and gastrointestinal symptoms in some patients with IBS/FD.

5) It is noted that *female gender* adds to the effects of life stress in predicting the number of syndromes present at 16mo, but exceeds the effects of life stress in predicting the presence of dysmotility-like dyspepsia at 16 months.

## 3.3 STUDY 3: EVALUATION OF GASTRIC EMPTYING IN FUNCTIONAL DYSPEPSIA

This section presents the results of data analyses relevant to determining the relation of psychological factors to the *severity* of gastric stasis ie. the extent of delay in emptying of a standard test meal from the stomach of patients with FD.

### 3.3.1 CONTROL AND SUPPRESSION OF ANGER AND GASTRIC EMPTYING

**Solid Gastric Emptying**

Univariate analysis

Two anger suppression variables were significantly related to slower emptying of solids. *Anger-control* was strongly associated with more prolonged initial delay time before emptying commenced ($p = 0.003$). *Anger-in* was related to slower rate of emptying at both 45 minutes ($p = 0.007$) and 70 minutes ($p = 0.03$), and to an increased half emptying time ($T_{1/2)}$ ($p = 0.02$). In contrast, neuroticism correlated inversely with a slower rate of emptying at 45 minutes ($p = 0.03$). The relation of the remaining affect expression/suppression, coping style, personality, emotional distress and stress response variables to emptying was not statistically significant.

*Multiple regression*

The linear regression models for solid emptying are summarised in Table 20. After considering the individual and combined effects of all psychological variables on gastric emptying, a small number of variables reflecting *control over angry feelings* remained the most important and consistent predictors of slower emptying. Anger-control alone explained 30% of the variance in the initial delay time (solid delay), while Anger-in explained 25% of the variance in the 45 minute rate of emptying, and 18% in the 70 minute rate of emptying. After controlling for all other variables neuroticism was no longer significantly related to 45 minutes rate of emptying.

A linear combination of three variables provided the optimal prediction of an increased solid $T_{1/2}$ (half emptying time); these were Anger-in, employing a fighting spirit whilst dealing with life stressors and failure to suppress unhappiness (i.e. manifest unhappiness or depressed mood state). Together, they explained 54% of the variance on the solid $T_{1/2}$ measure. It is noteworthy that suppression of unhappiness and fighting spirit alone were not significantly correlated with solid $T_{1/2}$ ($p = 0.9$ and $p = 0.1$ respectively), but were significant predictors of solid $T_{1/2}$ in the presence of each other and Anger-In. For each of the analyses, the inclusion of gender and age did not effect the outcome.

**TABLE 20**

MODELS OF SOLID GASTRIC EMPTYING FACTORS IN TERMS OF COMBINATIONS OF PSYCHOLOGICAL FACTORS WITH INDEPENDENT STATISTICALLY SIGNIFICANT EFFECTS

| GE parameter | Predictors in the model | p-value | Variance explained |
|---|---|---|---|
| Solid $T_{1/2}$ | Anger-in | <0.0001 | |
| | Manifest unhappiness | 0.001 | |
| | Fighting spirit | 0.02 | 54% |
| Solid delay | Anger control | 0.003 | 30% |
| Rate of emptying at 45minutes | Anger-in | 0.007 | 25% |
| Rate of emptying at 70minutes | Anger-in | 0.03 | 18% |

Increasing values of the predictor lead to alterations in each gastric emptying factor that are in the direction of prolonged half-times and delay times and slower rates of emptying.

$T_{1/2}$ = half emptying time

**Liquid gastric emptying**

Univariate analysis

Two variables were significantly associated with an abnormal pattern of liquid emptying, namely suppression of anger and suppression of unhappiness. They were positively associated with a longer liquid lag ($p = 0.0003$ and $p = 0.005$ respectively) but showed weak negative relations with slower 45 minute rate of emptying ($p = 0.05$ and 0.04 respectively). Suppression of anger, and of unhappiness, were each associated with a liquid emptying pattern characterised by an initial delay followed by a rapid rate of emptying. This 'rebound' response is similar to that previously observed in FD patients (Roland et al, 1990) and also in healthy subjects during periods of mild stress (Kellow et al, 1992b).

Multiple Regression

The linear regression models determined by exhaustive search (Miller, 1990) of potential predictor variables for liquid gastric emptying (GE) are displayed in Table 21 and are consistent with the results of the bivariate correlations. The single-variable models indicate that a substantial proportion (40%) of the variance in liquid lag is explained by higher levels of suppressed anger. A lesser, though substantial, proportion (15%) of the variance in liquid 45 minutes rate of emptying is explained by lower levels of suppressed unhappiness (or manifest unhappiness). Gender and age did not influence the results.

**TABLE 21**

MODELS OF LIQUID GASTRIC EMPTYING FACTORS IN TERMS OF COMBINATIONS OF PSYCHOLOGICAL FACTORS WITH INDEPENDENT STATISTICALLY SIGNIFICANT EFFECTS

| GE parameter | Predictors in the model | p-value | Variance explained |
|---|---|---|---|
| Liquid lag | Suppressed anger | 0.0003 | 40% |
| Rate of emptying at 45minutes | Manifest unhappiness | 0.04 | 15% |

Increasing values of the predictor lead to alterations in each gastric emptying factor that are in the direction of prolonged half-time and delay times and slower rates of emptying

**Summary of results for relations with gastric emptying**

The strong positive association between the frequency of attempts to resist, control, suppress and hold in anger and the *severity* of gastric stasis was a highly consistent finding across the gastric emptying parameters. A more tenuous finding was the enhanced potency of this relation in association with an unhappy state (ie failure to suppress a depressed mood). These results did not find any relation between gender, age, personality and an anxious mood state and gastric stasis in patients with FD.

## 3.4 STUDY 4: EVALUATION OF WHOLE GUT TRANSIT IN FGID

This section presents the results of data analyses relevant to the demographic and psychological predictors of delayed GI transit (delay in one or more region), widespread delay in transit (delay in two or more regions), and normal transit in all three regions. The three regions - the stomach, the small intestine and the colon - were assessed simultaneously using a wholly scintigraphic technique.

### 3.4.1 PSYCHOSOCIAL, GENDER AND FGID FEATURES

#### Transit subgroups

The three patient subgroups comprised: a) those with delay in one region (DT1, n = 46), b) those with delay in two or more regions (DT2, n = 32), and c) those in whom all regions displayed normal transit (NT, n = 17). Of the 46 patients in the DT1 group, 35% displayed delay in the stomach, 22% in the small bowel, and 43% in the colon. The corresponding proportions for the 29 patients in the DT2 group are remarkably similar (34%, 21%, and 45% respectively).

#### Demographic factors

Group differences in age and gender were calculated for patients with normal transit (NT), delay in transit in one region (DT1), and delay in transit in two or more regions (DT2). The *age* of patients in the DT2 subgroup was significantly higher than in the DT1 or the NT subgroups; age did not differ, however, between the DT1 and the NT

subgroups (see Table 22). With respect to *gender* (Table 22), the female / male ratio was significantly greater in both subgroups with delayed transit, especially in those with delay in two or more regions. For patients with DT2 in two or more regions, the probability of being a female was almost eight to one (odds ratio = 7.6, 95% confidence interval = 1.44, p=0.02) in comparison with patients with NT. There were no differences between transit subgroups with respect to marital, educational or occupational status (data not shown).

**Psychosocial and demographic factors**

*Depression* scores were significantly higher in the subgroup of patients with widespread delay in transit (DT2) than in patients with normal transit (Table 22). In contrast, *hypochondriasis* scores were significantly lower in both delayed transit (DT1, DT2) subgroups (Table 22). Normative data (see Table 22) for depression (Boyd et al, 1982) and general hypochondriasis (Pilowsky & Spence, 1983) suggest that mean depression scores are indeed high in the widespread delayed transit (DT2) group, as are hypochondriasis scores in the normal transit group.

Logistic regression models of *widespread delayed transit* are presented in Table 23. The psychological profile of delay in transit in 2 or more regions (DT2) comprised increased depression together with low levels of hypochondriasis ($F_{2,46} = 4.8$, $p<0.05$; variance explained = 41.5%), and a post hoc analysis for those patients with three regions delayed, revealed that these same variables (depression and hypochondriasis), but also anger control very strongly predicted delayed transit in all three regions ($F_{3,16} = 12.6$, $P<0.001$; variance explained = 84%). In a separate analysis, *female gender* and

*increasing age* together predicted delayed transit in two or more regions (DT2) relative to normal transit ($F_{2,46} = 6.0$, $p<.01$; variance explained = 45%).

The psychological profile of *normal transit*, after controlling for the effects of depression, included both *male gender* and high levels of *hypochondriasis* ($F_{2,46} = 4.3$, $p<0.05$, variance explained = 40%). A post hoc evaluation of the relation of psychological, GI symptom and demographic factors to hypochondriasis revealed that scores on the hypochondriasis scale increased significantly in correspondence with increases in the number of FGID (IBS, FD, functional constipation) syndromes present, together with male gender and being young ($F_{3,105} = 7.9$, $p <0.0001$, variance explained = 43%). These models are not shown.

**FGID factors**

Table 24 summarises the prevalence of FGID syndromes for each transit subgroup. No FGID variable in the regression model (type of syndrome, combination of syndromes, or the number of syndromes present) predicted transit subgroup (NT, D1, DT2).

**TABLE 22**

SUMMARY OF DIFFERENCES IN AGE, GENDER, DEPRESSION AND HYPOCHONDRIASIS BETWEEN PATIENTS WITH NORMAL TRANSIT IN ALL THREE REGIONS (NT), DELAYED TRANSIT IN ONE REGION (DT1) AND DELAYED TRANSIT IN TWO OR MORE REGIONS (DT2)

| | NT | DT1 | DT2 |
|---|---|---|---|
| Age: mean (SD) yrs | 38 (17) | 42 (13) | 49 (14) [a] |
| Female/male ratio | 1.8:1 | 6.8:1 [b] | 9.7:1 [b] |
| Depression scores; mean (SE) $ | 13 (2.6) | 11 (1.2) | 16 (3.2) [a] |
| Hypochondriasis scores; mean (SE)* | 2.6 (0.5) | 1.4 (0.2) [b] | 1.4 (0.3) [b] |

a = $p < 0.05$ vs NT and DT1

b = $p< 0.05$ vs NT

SD = standard deviation

SE = standard error

Normative data:

$ The cut-off score to estimate 'cases' of depression is ≥17 (Boyd et al, 1983)

* The mean (SD) hypochondriasis scores is 1.44 (1.8) for general practice patients and 2.69 (2.3) for psychiatric patients (Pilowsky & Spence, 1983)

**TABLE 23**

PSYCHOLOGICAL AND DEMOGRAPHIC PREDICTORS OF *WIDESPREAD* DELAYED TRANSIT: LOGISTIC REGRESSION MODELS.

| Outcome Variable | Predictor Models | Effect size and significance B (95% CI) |
|---|---|---|
| DT2 vs NT | | |
| | Depression | 0.014 (0.002, 0.03) |
| | Hypochondriasis | - 0.107 (- 0.02, - 0.03) |
| | | Model VE = 41.5% |
| Delayed transit in 3 regions vs NT # | | |
| | Depression | 0.016 (0.007, 0.025) |
| | Hypochondriasis | - 0.01 (-0.016, 0.05) |
| | Anger control | 0.056 (0.031, 0.082) |
| | | Model VE = 84% |
| DT2 vs NT | | |
| | Female gender | 0.405 (0.08, 0.73) |
| | Increasing age | 0.01 (0.002, 0.018) |
| | | Model VE = 45% |

DT2 = delayed transit in 2 or more regions

NT = normal transit in all three regions

# = a post hoc analysis of patients with 3 regions delayed

B = regression coefficient; CI = confidence interval; VE = variance explained

$p < 0.05$ for all predictor variables

**TABLE 24**

THE PREVALENCE OF FGID SYNDROME FOR EACH GUT TRANSIT SUBGROUP - NORMAL TRANSIT (NT), DELAYED TRANSIT IN ONE REGION (DT1), AND DELAYED TRANSIT IN TWO OR MORE REGIONS (DT2).

| Transit Subgroup* | | IBS n (%) | FD [a] n (%) | UFBD [b] n (%) | UFD [b] n (%) | FC n (%) |
|---|---|---|---|---|---|---|
| NT | (n = 17) | 13 (76) | 2 (12) | 0 | 0 | 2 (12) |
| DT1 | (n = 46) | 36 (78) | 4 (9) | 1 (2) | 2 (4) | 3 (7) |
| DT2 | (n = 32) [c] | 23 (72) | 4 (12.5) | 3 (9) | 0 | 4 (13) |

* See text for further details

[a] Functional dyspepsia (FD) subgroups = dysmotility-like, ulcer-like and reflux-like dyspepsia

[b] Unspecified functional bowel disorder (UFBD) and unspecified functional dyspepsia (UFD) occurred alone

[c] Row total exceeds 32 as two patients with functional constipation (FC) also had FD

Note: no FGID subgroup, combination of subgroups, or total number of subgroups was significantly associated with gut transit status

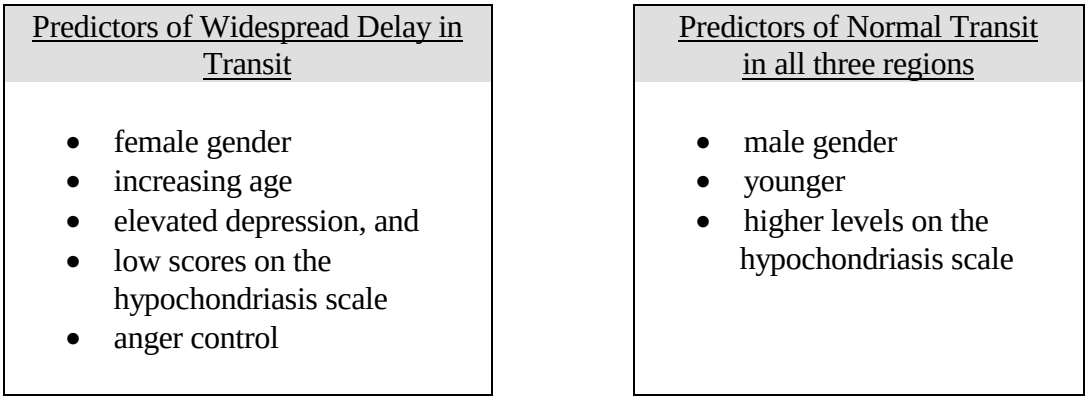



**Figure 8** Summary of demographic and psychosocial features of widespread delay in transit and normal transit in patients with functional GI disorders

**Summary of results for localised and widespread delayed transit**

The results summarised in Figure 8 strongly indicate that female gender, increasing age, depression and the control of anger are independent risk factors for the presence of widespread delay in GI transit in patients with FGID. In contrast, the likelihood of normal transit is increased if the person is male, younger and more concerned about health issues generally. With respect to other demographic (marital, educational or occupational), psychological (personality traits, coping style, an anxious mood state) and functional GI symptomatology variables, they did not differ between transit subgroups.

Two issues warrant special comment:

1. First, the presence of multiple FGID syndromes indicates the presence of upper and lower (widespread) GI symptom disturbance *only* when all patients have IBS [ie. two or more syndromes always = IBS + one or more FD]. This is not the case in a mixed

FGID patient group. Thus, in this study sample, the absence of an association between transit status (normal v delayed transit in one region vs widespread delayed transit) and the number of FGID syndromes present does not discount the possibility of an association between widespread hypomotility and the generation of FGID symptoms from both upper and lower gut regions.

2. Second, the strength of gender differences exceeded all demographic, psychological and gut symptom variables as a predictor of the presence or absence of widespread (multiple regions of) hypomotility, while the presence of elevated depression and high levels of anger control independently increased the likelihood of this extensive dysfunction in female patients with FGID.

## 3.5 STUDY 5: EVALUATION OF JEJUNAL SENSORIMOTOR FUNCTION IN IBS

The following section presents results relevant to the relation between:

a) the psychological and demographic features of GI dysfunction and
   i. hypersensitivity to distension of the small bowel (initial perception and pain thresholds), and
   ii. abnormal postprandial and fasting motor activity in the jejunum, and
b) the psychological factors that are associated with different patient groups (characterised by sensorimotor, motor (postprandial and fasting) and fasting motor abnormalities.

### 3.5.1 RELATIONS BETWEEN PSYCHOSOCIAL, SENSORY AND MOTOR DYSFUNCTION

**Independent associations**

Scores derived for each of the psychological measures according to normal and heightened *sensitivity*, and normal and abnormal *postprandial motor activity*, are summarised in Table 25. Personality and coping variables that differentiated initial perception sensitivity were generally less differentiating of pain sensitivity and postprandial motor activity. Although the sample mean scores for anxiety and depression were both high neither was discriminative, whilst a strong tendency *not* to express anger was associated with abnormal motor activity.

**Predictors of dysfunction**

The logistic regression models for initial perception sensitivity, pain sensitivity and postprandial motor activity are summarised in Table 26 and graphically illustrated in Figure 9. In each model, coping style dimensions dominated the prediction of low pain and perception thresholds and abnormal motor activity.

In relation to *perception sensitivity*, a large proportion of the variance in outcome on this parameter (84%) was explained by a model comprising three coping factors: infrequent use of mature coping strategies, self not in control and frequent attempts to suppress and control anger (see Table 26). All patients with heightened sensitivities also had abnormal postprandial and fasting abnormalities. This model is therefore strongly predictive of sensorimotor dysfunction.

In relation to *pain sensitivity*, each psychosocial variable was less differentiating of heightened versus normal sensitivity; however one variable - infrequent use of mature coping strategies - significantly predicted pain rather than normal sensitivity (see Table 26).

*Abnormal postprandial motor activity* was predicted by a combination of three psychological variables: infrequent anger expression or unexpressed anger, self not in control and external factors in control (see Table 26). Increases on these variables substantially increased the likelihood of abnormal postprandial motor activity. The remaining psychosocial (including demographic) factors and clinical features were unrelated to dysfunction.

**Table 25** Psychological characteristics according to jejunal sensitivity and postprandial motor activity: data presented as mean (standard deviation) scores

| | Perception sensitivity | | Pain sensitivity | | Postprandial motor activity | |
|---|---|---|---|---|---|---|
| | Normal | Heightened | Normal | Heightened | Normal | Heightened |
| **Emotional distress/mood state** | | | | | | |
| Depression | 17.5 (11.1) | 21.3 (16.0) | 16.9 (12.1) | 21.1 (12.9) | 19.0 (12.9) | 18.1 (12.3) |
| Anxiety | 41.2 (12.0) | 47.8 (13.5) | 40.8 (13.0) | 46.3 (11.4) | 40.4 (13.9) | 45.3 (11.0) |
| **Personality** | | | | | | |
| Trait anxiety | 41.5 (9.1) | 50.8 (14.3) | 42.0 (9.9) | 46.9 (12.9) | 41.8 (10.7) | 45.8 (11.7) |
| Extraversion | 4.5 (2.8) | 3.7 (3.0) | 4.6 (2.7) | 3.8 (3.0) | 5.4 (2.6) | 3.2 (2.7) |
| Neuroticism | 4.7 (2.8) | 6.8 (3.7) | 4.8 (3.1) | 6.0 (3.3) | 4.9 (2.8) | 5.6 (3.5) |
| Trait anger | 17.5 (4.0) | 22.5 (8.1) | 17.4 (4.1) | 21.0 (7.1) | 18.9 (4.1) | 18.7 (7.0) |
| Anger temperament | 6.5 (1.9) | 8.2 (4.3) | 6.6 (2.1) | 7.4 (3.5) | 6.7 (2.0) | 7.2 (3.3) |
| Anger reactivity | 7.5 (2.3) [a] | 10.3 (2.4) | 7.4 (2.1) [a] | 9.7 (2.9) | 8.4 (2.0) | 8.1(3.1) |
| General hypochondriasis | 1.7 (1.5) | 1.8 (2.1) | 1.8 (1.7) | 1.7 (1.7) | 1.7 (1.8) | 1.7 (1.6) |
| **Coping style** | | | | | | |
| Defense Style | | | | | | |
| Immature | 3.6 (0.7) | 4.0 (1.2) | 3.7 (0.6) | 3.8 (1.0) | 3.5 (0.5) [a] | 3.9 (1.0) |
| Neurotic | 4.7 (1.1) | 4.8 (1.2) | 4.8 (1.2) | 4.6 (1.1) | 4.9 (1.0) | 4.6 (1.2) |
| Mature [#] | 5.8 (1.0) [b] | 4.1 (1.3) | 5.8 (1.1) [b] | 4.5 (1.2) | 5.8 (0.9) [a] | 4.8 (1.4) |
| Locus of control of behaviour | 22.8 (7.7) | 26.3 (14.0) | 22.6 (8.1) | 25.4 (11.6) | 20.5 (7.7) | 26.6 (10.3) |
| Self not in control | 5.7 (2.4) [a] | 9.2 (3.9) | 5.6 (2.6) | 8.1 (3.5) | 5.3 (2.7) [a] | 7.8 (3.1) |
| External factors in control | 7.8 (5.0) | 7.2 (4.8) | 7.6 (5.2) | 7.7 (4.5) | 6.6 (5.0) | 8.6 (4.6) |
| Need help | 4.8 (3.8) | 6.5 (4.9) | 4.7 (4.1) | 6.1 (4.0) | 4.8 (4.5) | 5.7 (3.7) |

[a] $P < 0.05$, [b] $P < 0.01$; normal vs heightened or abnormal.

[#] Decreasing scores on these scales are associated with heightened or abnormal.

Table 25 continued

**Table 25** Continued

| | Perception sensitivity | | Pain sensitivity | | Postprandial motor activity | |
|---|---|---|---|---|---|---|
| | Normal | Heightened | Normal | Heightened | Normal | Heightened |
| Emotions expressed/suppressed | | | | | | |
| Anger suppressed | 16.3 (3.8) | 18.5 (2.2) | 16.4 (4.0) | 17.6 (2.8) | 16.4 (3.0) | 17.3 (4.1) |
| Anxiety suppressed | 17.7 (5.4) | 20.0 (3.1) | 18.0 (5.5) | 18.9 (4.2) | 16.8 (5.5) | 19.7 (4.2) |
| Depression suppressed | 17.4 (4.5) | 20.3 (3.1) | 17.1 (4.7) | 19.9 (3.1) | 16.4 (4.4) | 19.8 (3.6) |
| Anger held in | 15.6 (3.9) | 17.3 (4.8) | 15.9 (3.8) | 16.4 (4.8) | 16.1 (3.6) | 16.1 (4.7) |
| Anger expressed [#] | 15.0 (3.1) | 13.2 (3.5) | 14.9 (3.4) | 14.0 (3.1) | 15.9 (3.0) [a] | 13.2 (3.0) |
| Anger controlled | 20.2 (4.3) | 21.7 (4.9) | 20.3 (4.6) | 21.0 (4.3) | 20.4 (4.0) | 20.7 (4.9) |

[a] $P < 0.05$, [b] $P < 0.01$; normal vs heightened or abnormal.

[#] Decreasing scores on these scales are associated with heightened or abnormal.

**TABLE 26**

LOGISTIC REGRESSION MODELS OF JEJUNAL SENSITIVITY AND MOTOR ACTIVITY IN RELATION TO COMBINATIONS OF PSYCHOLOGICAL CHARACTERISTICS

| Jejunal sensitivity or motor activity | Psychological characteristics in the final regression model | Improvement ($\chi^2$) | p-value |
|---|---|---|---|
| Perception sensitivity [a] | Infrequent use of mature coping strategies | 8.9 | 0.003 |
| | Belief that self is not in control | 4.7 | 0.03 |
| | Frequent attempts to control anger | 8.5 | 0.004 |
| Pain sensitivity [b] | Infrequent use of mature coping strategies | 6.7 | 0.01 |
| Postprandial motor activity [c] | Infrequent anger expression | 4.4 | 0.03 |
| | Belief that self is not in control | 6.4 | 0.01 |
| | External factors in control | 9.0 | 0.003 |

Note: Increasing values of the psychological characteristics indicate increases in the likelihood that jejunal sensitivity was heightened or postprandial motor activity was abnormal (see test for details).

[a] Model $\chi^2$, 22.0, p = 0.0001, variance explained, 84%.

[b] Model $\chi^2$, 6.7, p = 0.01, variance explained, 22%.

[c] Model $\chi^2$, 20, p = 0.0002, variance explained, 62%.

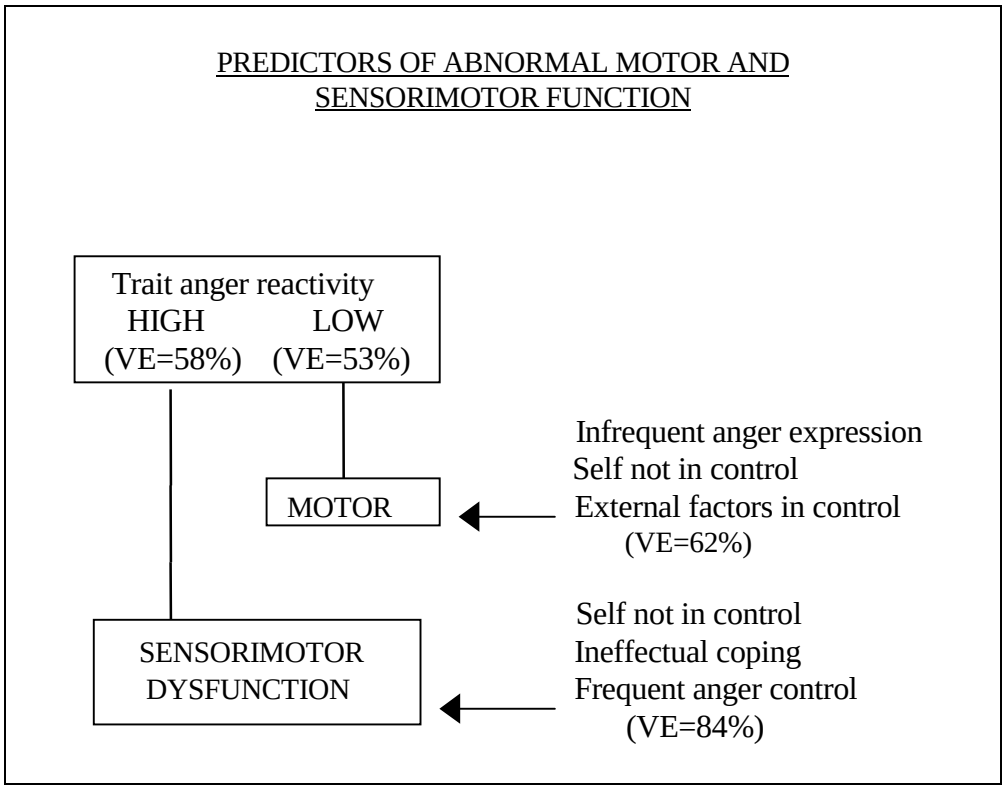



**Figure 9** Graphic summary of the psychosocial predictors of motor (ie fasting and postprandial) dysfunction and sensorimotor dysfunction.

### 3.5.2 GROUP DIFFERENTIATING CHARACTERISTICS

Three distinct subgroups labelled sensorimotor, motor and fasting motor were able to be characterised for group comparisons. The patient subgroups are defined as follows: the presence of heightened perceptual and pain sensitivity, abnormal postprandial and fasting motor activity was classified as *sensorimotor subgroup* (n=6); normal sensitivity, abnormal postprandial and fasting motor activity as *motor subgroup* (n=6) and normal sensitivity, normal postprandial motor activity and abnormal fasting

motor activity as *fasting motor subgroup* (n=11). Logistic regression methods were used to compare the sensorimotor, the motor, and the fasting motor subgroups.

*Trait anger reactivity* was the predominant differentiating factor in each case. Increasing scores on this dimension were associated with an increased likelihood of sensory (as well as motor) dysfunction (model chi-square = 9.6, p = .002, variance explained = 58%) while low trait anger reactivity and introversion together predicted abnormal postprandial motor (as well as abnormal fasting motor) activity (model chi-square = 11.8, p = .003, variance explained = 53%) (See Figure 9).

**Summary of results for sensorimotor dysfunction**

1) Three subgroups of female patients with three different and increasing levels of jejunal sensory and/or motor dysfunction were identified. Levels of severity ranged from mild (the fasting motor (only) subgroup), to moderately severe (the motor (only) subgroup), to the most severe dysfunction (the sensorimotor subgroup). It is noteworthy that the psychosocial profiles of sensory and/or motor dysfunction at each level also increased in a linear fashion.
2) A single psychological variable, *trait anger reactivity*, differentiated sensorimotor from motor dysfunction thereby suggesting a special association between frequent anger reactivity and the additional presence of heightened sensitivity of the GI viscera.