

Alimentary tract and pancreas

Major life event stress and dyspepsia of unknown cause: a case control study

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SUMMARY Stress is purported to be a major cause of non-ulcer dyspepsia, defined here as dyspepsia where peptic ulcer, oesophagitis, and cancer are excluded by endoscopy. There is a subgroup of non-ulcer dyspepsia patients who have no definite cause for their dyspepsia, provisionally termed essential dyspepsia. The aim of the present study was to determine if stress, as measured by major life events, was associated with essential dyspepsia. The frequency of life events during the year before the diagnosis of essential dyspepsia in 68 consecutive patients was compared with the frequency of these events over the same time period in 68 randomly selected age and sex-matched community controls. The mean number of events and the associated life change and distress scores were similar for both groups. Concerning individual events, patients reported more minor personal illness ($p=0.008$). When events were broadly categorised, only one difference was found – more controls reported bereavements ($p=0.008$). Age, sex, social class, and the duration of dyspepsia did not influence the number and nature of events. Although the study suggests that stress, as measured by major life events, is not associated with dyspepsia of unknown cause, it does not exclude the fact that other forms of stress, especially that associated with chronic difficulties, may be relevant.

Non-ulcer dyspepsia, also called radiographically negative dyspepsia or nervous dyspepsia,¹⁻³ is one of the commonest conditions seen by gastroenterologists and general practitioners. It is a commonly held belief that this disorder occurs when the patient is exposed to psychological stress²⁻⁶ but there has been no formal study of stress and non-ulcer dyspepsia. Stress may be defined as a response to a situation or stimulus – for example, death of a spouse, birth of a child – and, in the context of this study, the stimuli are major life events. Holmes and Rahe,⁷ Paykel and associates⁸ and Tennant and Andrews⁹ have defined a number of such stressful events, and the distress and change in life patterns that each event may cause have been quantified.

The aim of the present study was to determine whether a subgroup of non-ulcer dyspepsia patients who have no definable cause for their dyspepsia, provisionally termed essential dyspepsia, experience an excess of life events during the one year preceding diagnosis, when compared with a community control population.

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Methods

DEFINITION OF TERMS

Dyspepsia is defined as abdominal pain, discomfort or nausea, referable only to the upper alimentary tract, which may be intermittent or continuous, has been present for one month or more and is not precipitated by exertion and relieved within five minutes by rest.¹⁻¹⁰ Patients with jaundice, only lower abdominal pain, or only belching, full feelings or other symptoms were excluded. As the majority of peptic ulcer patients do not have pain related to meals¹¹ we did not include any relationship to eating in the definition.

Non-ulcer dyspepsia is defined as dyspepsia where clinical evaluation fails to reveal an obvious organic cause for the symptoms and where panendoscopy has excluded peptic ulceration, oesophagitis, and malignancy.⁴⁻¹⁰ It is a heterogeneous syndrome⁴⁻⁵⁻¹⁰⁻¹² and can be further divided into two subgroups: (a) those patients who on detailed clinical and radiological review have gall stones, gastro-oesophageal reflux without oesophagitis, irritable bowel syndrome, or rarely other diseases. (b) Those with no definite cause for their dyspepsia.

For want of a better term, we have provisionally named this group essential dyspepsia.

PATIENT SELECTION

The study group was chosen from 292 consecutive outpatients who presented at the endoscopy clinic, Royal North Shore Hospital, with dyspepsia during 1983; all underwent panendoscopy for dyspepsia which revealed no evidence of peptic ulceration, oesophagitis or malignancy. Patients were initially contacted by letter, and within one week interviewed by telephone (a well validated method of data collection),^{13 14} when a structured history questionnaire was completed.

Patients were subsequently excluded if they had: (a) clinical evidence of the irritable bowel syndrome (51 patients), defined as dyspepsia associated with a chronic abnormal bowel habit¹⁵ and/or by more than three of the six criteria of Manning *et al.*¹⁶ (b) Clinical evidence of gastro-oesophageal reflux (49 patients), defined as typical heartburn and/or acid regurgitation.¹⁷ In addition, 37 patients who had irritable bowel syndrome plus gastro-oesophageal reflux were excluded. (c) Overwhelming mental or physical disease (28 patients). (d) A history of previous gastric surgery (six patients), proven peptic ulceration in the preceding six months (eight patients) or less than one month of dyspepsia (10 patients). (e) An inability to speak English (nine patients), lived outside the metropolitan area of Sydney (seven patients) or did not possess a telephone (nine patients). (f) Radiological evidence of gall stones (10 patients) – all patients who did not have irritable bowel syndrome, gastro-oesophageal reflux and were not excluded for other reasons underwent ultrasonography or oral cholecystography.

The remaining 68 patients (26 men, 42 women) with no definite cause for their dyspepsia have been provisionally labelled as having essential dyspepsia. Their mean age was 48 years (range 19–81 years). Included were 16 patients (24%) with gastroduodenitis macroscopically, and 19 patients (28%) with no evidence of irritable bowel syndrome, gastro-oesophageal reflux or other disease but who did have significant abdominal pain as well as distension and belching with or without rectal flatus and borborygmi; we considered these latter patients to have aerophagy.¹⁸ As there does appear to be a significant overlap between aerophagy and essential dyspepsia patients, and as the aerophagy group may not have excess intestinal gas,¹⁸ we included this group in the study.

All patients were personally interviewed by one author (NJT) to confirm the history obtained by telephone and then completed a self report inven-

tory of major life events.⁹ The majority of patients (68%) were interviewed within one month of diagnosis; the remaining patients completing the interview within a mean of 3.6 (SD±1.6) months after diagnosis. Of those studied, 46% had developed their non-ulcer dyspepsia in the 12 months before diagnosis, while 43% had been free of symptoms before experiencing an acute exacerbation before diagnosis. Only 11% of patients had a history of continuous dyspepsia for longer than one year which had become disabling enough for them to seek medical advice.

Patients were otherwise unselected and of those eligible 95% agreed to participate.

CONTROL SELECTION

Controls were persons randomly selected from the electoral rolls (in Australia, all Australian citizens 18 years and over have to register to vote), and each control was matched with a patient for age (within five years), sex and social class (based on Congalton's prestige ratings of suburbs).¹⁹ All potential controls were sent an introductory letter and then within one week were contacted by telephone. Up to 96% of persons in this region have a telephone, and over 95% of eligible persons contacted agreed to participate in the study. Those with a history of dyspepsia or peptic ulceration were excluded (17%). All those who lived outside the metropolitan area, who were non-English speaking or who had overwhelming mental or physical disease were also excluded. At a personal interview, the same inventory of major life events was completed in the presence of one of us (NJT).

ASSESSMENT OF LIFE EVENT STRESS

Sixty two life events were measured using a modified self report inventory resembling that used by Tennant and Andrews.⁹ Each event has been scaled for the distress and life change they cause, according to the responses of an Australian urban population. Each of the scalings was consistent across the sociodemographic groups in the population. The two scales allow the significance of life events to be scored recognising two conceptual issues; Holme's emphasis on life change, defined as the amount of change likely to be produced in one's way of life by an event whether desirable or undesirable,⁷ and Paykel's emphasis on distress, defined as the amount of suffering or upset likely to be caused by each event.⁸

Only the events experienced during the 12 months before diagnosis in the patient group, or before the interview date in the controls were noted. Each event was counted only once. The one year period was chosen to minimise memory recall bias.

STATISTICAL ANALYSIS

To assess the associations between each of the study variables and essential dyspepsia, the paired *t*-test, χ^2 test of independence, McNemar's test of significance, Fisher's exact probability test and the exact probability test for a binomial distribution were used as applicable.^{20 21} All data were skewed to the right because they were counts of rare events, and therefore square or cube root transformations were carried out before the assessment of sample means by paired *t*-tests. When these transformations were undertaken, the distribution of differences were approximately normal in all cases. Because of the multiple test comparisons, the selected alpha level of probability was set at 0.01, and only the differences present at this level were considered significant. Stepwise regression analysis was undertaken to determine the extent to which major life event differences between patients and controls were related to age, sex, social class, aerophagy symptoms, the duration of dyspepsia and macroscopic gastroduodenitis.

The project had been ethically approved by the Ethics Committee of the Royal North Shore Hospital, and informed consent was obtained from the patients.

Results

To make the results comparable with similar studies on duodenal ulcer and gastric ulcer patients,^{22 23} this study was analysed in a similar way. As there were no significant differences in any of the comparisons between patients interviewed within one month or a mean of 3.6 months after diagnosis, using stepwise regression analysis, these two groups were combined and the results presented apply to all patients.

NUMBER OF EVENTS AND DISTRESS AND LIFE CHANGE SCORES

Essential dyspepsia patients reported a total of 166 events while the controls reported 157 events over the one year study period. Using paired *t*-tests, the mean number of events were similar for patients and controls ($p > 0.70$), as were also the mean distress and life change scores ($p > 0.60$ and $p > 0.90$ respectively).

AGE, SEX, SOCIAL CLASS, DURATION OF DYSPEPSIA AND GASTRODUODENITIS

Stepwise regression analyses were undertaken to determine the extent to which differences in the number of events, distress and change scores between patients and controls were related to age, sex, social class, the presence of aerophagy symptoms, the duration of dyspeptic symptoms and macroscopic

gastroduodenitis. In only one comparison did one of these covariables make a statistically significant additional contribution; the life change scores were higher in patients with gastroduodenitis macroscopically than matched controls ($p < 0.002$, $r^2 = 0.14$).

DISTRIBUTION OF NUMBER OF EVENTS PER PERSON AND DISTRESS AND LIFE CHANGE SCORES (Table 1 and Figure)

There was no significant difference between patients and controls concerning the distribution of the number of events per person using a χ^2 test of independence ($p = 0.81$) (Table 1).

While the raw change and distress scores were not distributed normally (Figure), the form of the distribution was similar for both change and distress for patients and controls. With increasing scores, the number of subjects in each score range tended to decrease. Only three patients and one control scored above 125 for change, and only two patients and no controls scored above 125 for distress (the highest possible score for change or distress was 1120).

INDIVIDUAL EVENTS (Table 2)

Table 2 presents a matched pairs analysis of the nine most common events, which were those reported by at least 10 patients and/or 10 controls before discarding tied pairs for analysis.

Four of the events were reported more frequently by patients and four more frequently by controls. McNemar's test for matched pairs²¹ showed that the only significant differences were patients had more minor personal illness ($p = 0.008$) and controls reported the death of a close relative or friend in the year before interview more often ($p = 0.01$).

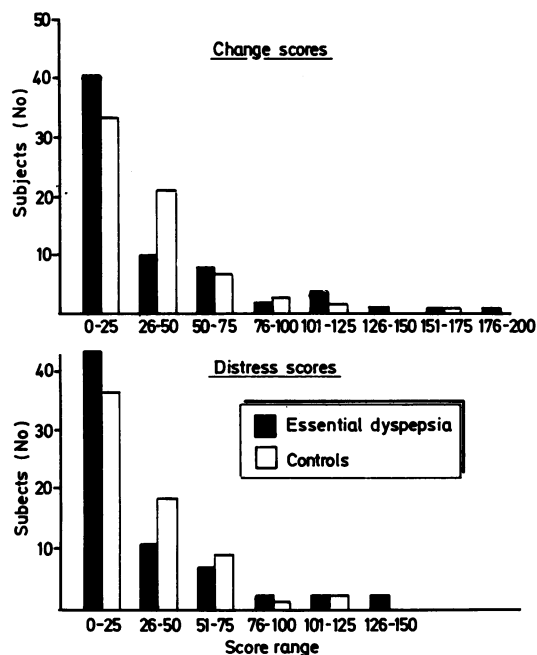
CATEGORISATION OF EVENTS (Tables 3a, b)

Assessments were made by either the χ^2 test, Fisher's exact probability test or the exact probability test for a binomial distribution.

Table 1 *Distribution of number of events: dyspepsia patients and controls*

	Patients (no)	Controls (no)
Nil	10	11
1-3	43	44
4-6	8	9
≥ 7	7	4
Total	68	68

$\chi^2(3df) = 0.95$. $p = 0.81$



Figure

AREAS OF ACTIVITY (Table 3a)

In only one of the seven areas did dyspepsia patients differ from controls – more controls reported bereavements ($p=0.008$).

DESIRABLE AND UNDESIRABLE EVENTS, SEPARATION AND CHRONIC DIFFICULTIES (Table 3b)

When events were classified as desirable (13

events), undesirable (35 events) or ambiguous (14 events), no significant differences were found between patients and controls. As well, separation events (from familiar people – 23 events) and chronic difficulties (situations persisting over time – 12 events) were equally distributed in patients and controls.

Discussion

Stressful life events are suspected of being able to cause disease because they originate from the environment and affect individuals through higher neural interconnections.²⁴ As stress has been shown to precipitate changes in function²⁵ and as non-ulcer dyspepsia is suspected to be a disorder of function,^{4,5,26} the role of stress is justifiably postulated to be important.²⁻⁶

The evidence that non-ulcer dyspepsia is stress related, however, is largely anecdotal as there have been very few pertinent studies.²⁷⁻²⁹ It has been reported that there is a high prevalence of recent or unresolved bereavement among patients with unexplained abdominal pain.^{27,28} A longitudinal investigation of air traffic controllers,²⁹ an occupation associated with stress, showed that 13 subjects developed dyspepsia over a three year period, but only three (23%) had peptic ulceration. Firm conclusions cannot be drawn from these studies because they were all uncontrolled. The data of the present study suggest the hypothesis that there is a relationship between major life events and essential dyspepsia is unlikely to be correct.

The problems in studying stress and disease include non-quantitative methods to assess stress and misclassification of disease status. In the present study, diagnosis has been based on careful clinical evaluation and endoscopy, and stress has been

Table 2 Matched pairs analysis of nine most frequent individual events (68 patients and 68 controls)

Event	Unit scaling for distress		Patient only	Control only	Patient and matched control	Neither patient nor matched control	RR	p value
	distress	change						
1 (minor personal illness – self)	2	2	24	8	14	22	3.0	0.008*
2 (serious personal illness – self)	16	16	11	4	0	53	2.8	0.12
3 (serious illness – close relative)	16	9	9	8	2	49	1.1	1.0
13 (death – close relative, friend)	30	12	2	13	3	50	0.2	0.01*
24 (child married – with approval)	2	10	4	4	1	59	1.0	1.0
32 (improvement relationship relatives at home)	1	10	3	7	1	57	0.4	0.34
34 (increasing problems relatives at home)	16	16	5	8	2	53	0.6	0.58
36 (started a course)	3	16	7	4	0	57	1.8	0.55
54 (moderate financial difficulties)	9	10	3	5	1	59	0.6	0.72

* Significant.

Table 3a *Categorised events analysis*

Events Category	Subjects experiencing		
	One event	Two events	≥ Three events
Health (9 events)			
Patients (47)	33	12	2
Controls (34)	30	4	0
Distribution of one and two events – Fisher's exact p=0.10			
Bereavement (4 events)			
Patients (8)	8	0	0
Controls (21)	21	0	0
Binomial distribution p=0.008*			
Family and social (22 events)			
Patients (25)	14	7	4
Controls (30)	20	8	2
Distribution of one and ≥ two events χ^2 (1df) 0.66 p=0.42			
Education (6 events)			
Patients (9)	5	4	0
Controls (8)	5	2	1
Distribution of one and two events – Fisher's exact p=1			
Work (9 events)			
Patients (14)	8	3	3
Controls (17)	13	4	0
Distribution of one and two events – Fisher's exact p=0.44			
Moving (3 events)			
Patients (5)	5	0	0
Controls (3)	3	0	0
Binomial distribution p=0.22			
Financial and legal (9 events)			
Patients (11)	9	1	1
Controls (15)	12	3	0
Distribution of one and two events – Fisher's exact p=1			

* Significant.

Table 3b *Categorised events analysis*

Events Category	Subjects experiencing				
	One event	Two events	Three events	Four events	≥ Five events
Desirable (13 events)					
Patients	17	2	1	0	0
Controls	14	6	1	0	0
Distribution of one and two events – Fisher's exact p=0.32					
Undesirable (35 events)					
Patients	26	13	8	2	5
Controls	20	18	6	4	1
Distribution of one, two, three and ≥ four events χ^2 (3df) 1.97 p=0.58					
Ambiguous (14 events)					
Patients	14	6	0	1	2
Controls	18	5	1	1	0
Distribution of one and two events – Fisher's exact p=0.60					
Separation (23 events)					
Patients	21	8	4	1	1
Controls	33	6	3	1	0
Distribution of one, two and ≥ three events χ^2 (2df) 2.56 p=0.28					
Chronic difficulties					
Patients	12	2	4	0	0
Controls	9	4	4	0	0
Distribution of one and two events – Fisher's exact p=0.62					

quantified in terms of the number of events experienced and their associated change and distress scores. Community controls were chosen because the patient population was an outpatient group fulfilling their normal role in society, and controls chosen otherwise – for example, hospital controls – may be biased towards atypical social stresses perhaps because of other illness (Berkson's bias).³⁰ It is conceivable that major life event stress could cause dyspepsia and/or exacerbate the symptoms. In this study, a time period of one year before diagnosis was chosen to minimise recall bias, and therefore included patients with the recent onset of non-ulcer dyspepsia (46%) and patients with recent exacerbations of symptoms (43%). It was found, however, that regardless of the relationship of the onset of dyspepsia to the study period, major life event stress was no more common in patients than controls.

It is important to note that there remain several problems with interpretation in this and other controlled studies relating life events to illness. Lipowski defines psychological stress as internal or external stimuli that are important to the individual and so activate emotions and induced physiological alterations which threaten health.³¹ This response

may depend on many variables including intelligence, verbal skills, personality, social support, past experience, age, level of education and occupation.^{32 33} It is possible that essential dyspepsia patients may react abnormally to some or all life events and this may in turn be related to an underlying personality characteristic, such as anxiety, and maladaptive coping mechanisms of the individual. It is noted that using the same instrument, results similar to this study have been found in both duodenal²² and gastric ulcer patients.²³

In conclusion, this study suggests that life stress events are no more frequent or significantly different in type in a population with dyspepsia of unknown cause than in a community control population. The measures applied cannot assess a particular individual's reaction to events and do not assess chronic stress, and for these reasons emotional stress may still play some role in the aetiology of the disorder.

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Addendum

List of life events with scale to measure their degree of stress*

Event	Distress	Change
Health		
1 You had a minor illness or injury like one needing a visit to a doctor or a couple of days off work	2	2
2 You had a serious illness, injury or operation needing hospitalisation or a month or more off work	16	16
3 A close relative had a serious illness (from which they did not die)	16	9
Women only:		
4 You found out that you were pregnant (with a wanted pregnancy)	2	26
5 You found out that you were pregnant (with an unwanted pregnancy)	33	29
6 You had a stillbirth	40	22
7 You had an abortion or miscarriage	26	13
8 You had a baby	5	47
9 Your change of life (menopause) began	14	18
Bereavement		
10 Your wife/husband died	83	79
11 A child of yours died	80	57
12 A close family member died – for example, parent, brother, fiance, etc.	57	27
13 A close family friend or relative died – for example, aunt, uncle, grandmother, cousin, etc.	30	12
Family and social		
(If you are or were married)		
14 You married	5	59
15 You adopted a child (women only)	4	47
16 Your wife had a child or you adopted a child (men only)	4	41
17 There have been increasing serious arguments with your wife/husband	26	25
18 There has been a marked improvement in the way you and your wife/husband are getting on	2	18
19 You have been separated from your husband/wife for more than a month because of marital difficulties	31	29
20 You have been separated from wife/husband for more than a month for reasons other than marital difficulties – for example, hospitalisation, business etc.	12	15
21 You have gotten back together again after a separation, due to marital difficulties	5	25
22 You have been divorced	54	62

Event	Distress	Change
<i>(If you have or had children)</i>		
23 A child of yours became engaged	2	6
24 A child of yours married with your approval	2	10
25 A child of yours married without your approval	22	16
26 A child of yours left home for reasons other than marriage	11	14
<i>(If you are single)</i>		
27 You became engaged or began a 'steady' relationship	2	17
28 You broke off your engagement	25	21
29 You broke off a 'steady' relationship	18	18
30 You had increasing arguments or difficulties with your fiance or steady friend	15	13
<i>Friends or relatives</i>		
31 A new person came to live in your household (apart from a new baby)	8	20
32 There has been a marked improvement in the way you get on with someone close to you (excluding husband or wife)	1	10
33 You have been separated from someone important to you (other than a close family member)	13	13
34 There has been serious increase in arguments or problems with someone who lives at home (excluding husband or wife)	16	16
35 There have been serious problems with a close friend, neighbour, or relative not living at home	10	8
<i>Education</i>		
36 You started a course – that is, university, technical college, apprenticeship or other occupational training course	3	16
37 You changed to a different course	5	11
38 You completed your training programme	2	27
39 You dropped out of your training programme	14	22
40 You studied for, or did, important exams	10	13
41 You failed an important exam	20	18
<i>Work</i>		
42 You have been unemployed and seeking work for a month or more	20	22
43 Your own business failed	38	44
44 You were sacked	32	34
45 You retired	15	53
46 You were downgraded or demoted at work	20	18
47 You were promoted	2	18
48 You began to have trouble or disagreements with your boss, supervisor or fellow workers	10	9
49 You had a big change in the hours you worked	5	16
50 You started in a completely different type of job	8	24
<i>Moving house</i>		
51 You moved to Sydney from overseas	19	48
52 You moved to Sydney from elsewhere in Australia	8	26
53 You moved house in Sydney	4	11
<i>Financial and legal</i>		
54 You had moderate financial difficulties	9	10
55 You had a major financial crisis	34	37
56 You are much better off financially	1	23
57 You were involved in a traffic accident that carried serious risk to health or life of yourself or others	31	22
58 You had minor difficulties with the police or the authorities (which have not required a court appearance)	4	2
59 You had more important problems with the police or the authorities (which have not required a court appearance)	21	15
60 You had a jail sentence or were in prison	59	72
61 You were involved in a civil law suit – for example, divorce, debt, custody, etc.	25	21
62 Something you valued or cared for greatly was stolen or lost	9	5

* Based on: Tennant C, Andrews G. A scale to measure the stress of life events. *Aust NZ J Psychiatry* 1976; **10**: 27–32.

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