Risk factors for severe ME/CFS

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Abstract

ME/CFS (myalgic encephalomyelitis/chronic fatigue syndrome) is a serious illness affecting several hundred thousand British people. Some 25% of people with ME/CFS may be severely ill (housebound or bedbound), sometimes for decades. This observational, questionnaire-based study was designed to identify risk factors for severe disease. Exposure to potential risk factors, including familial risks, personality, and early management of the illness, was compared in 124 people with severe disease and 619 mildly ill controls. Severity was determined by self-report and the Barthel (activities of daily living) Index. Premorbid personality was assessed using the Neuroticism and Conscientiousness domains of the IPIP scale. Analysis was by tests of association and logistic regression. Early management of the illness appeared the most important determinant of severity. Having a mother with ME/CFS was also important. Smoking and personality were not risk factors, neurotic traits being more frequent among the less severely ill. Conscientiousness overall was not related to severity.

Keywords: Chronic fatigue syndrome, myalgic encephalomyelitis, epidemiology, prognosis, severity, risk factors, treatment, management.

Introduction

ME/CFS is a serious problem affecting several hundred thousand people in Britain (CMO's Working Group Report, 2002). Some 25% or more of people with ME/CFS may be severely ill (Action for ME, 2001), and may experience disabling and distressing symptoms confining them to their beds or their homes, sometimes for decades. They face social isolation, discrimination in employment and education and stigmatising, unhelpful attitudes from health, social care and other professionals. This study was designed to investigate risk factors for severe disease. An observational study, using a postal questionnaire, was undertaken to investigate risk factors for severe disease. Those investigated included personality factors, management at the outset of the illness, and a range of environmental and other factors. A pilot study (Wernham et al., 2005) was carried out initially, the results of which suggested that severe disease was associated with comorbidities, with inappropriate treatment in the early stages of the illness, and with occupational chemical exposures. This paper reports the findings of the definitive study.

It is widely asserted (though not proven) that there is an association between personality and the initial development of ME/CFS. White et al (2000) suggest that individuals who have a dominant perfectionist character trait are at risk. Hamacheck (1978) describes two sorts of perfectionism – neurotic and normal. The normal perfectionist is able to derive satisfaction from achievement, and set themselves realistic goals, the 'goalposts' of which can be adjusted to suit the situation. Neurotic perfectionists, on the other hand, often set themselves targets that are unattainable, and, upon failing to meet a desired standard, feel unworthy and lack self-esteem. Neurotic perfectionists are motivated by fear of failure and are dissatisfied the majority of the time. White et al (2000) argue that the low self esteem experienced by personalities more akin to the neurotic perfectionist could exert a pathological influence a person's immune system at a time when a CFS-causing trigger is present, thus increasing the likelihood of succumbing to ME/CFS. People with ME/CFS are often told that their illness is a psychological disorder for which counselling is offered to change attitudes and promote a positive outlook (Bass, 2001). While there is good reason to suggest

that a positive attitude will help in the prognosis of any disease including ME/CFS, there is little empirical evidence to support the assertion that attitudes, behaviour or underlying personality have a major role in determining outcomes.

There have been few studies of the impact of early treatment on disease progression, but use of sedatives and antidepressants (Schmaling et al, 2000) and post-exertional malaise (Taylor et al., 2002) have been identified as risk factors. Most patients' initial contact with the health care system is with primary care, but there has been little research on the outcomes of primary care interventions in ME/CFS. A small-scale randomised controlled trial of cognitive behavioural therapy in general practice showed no impact on the disease progression over a year (Whitehead and Campion P, 2002). There are barriers to effective care of patients with ME/CFS in the early stages of the disease, possibly related to negative attitudes held by health care professionals (Raine et al., 2004). Equally, delays and inappropriate treatment may be associated with socioeconomic factors impeding health care access (CMO's Working Group Report, 2002).

Severity is a major factor affecting prognosis, and there is more extensive literature on risk factors for poor prognosis. Severely ill patients tend to have poor prognoses, whether children (Ray et al., 1992) or adults (Pheley et al., 1999; Hill et al., 1999), associated factors including having additional unexplained symptoms, prolonged disease, lower educational attainment, and more advanced age (Clark et al., 1995). This is confirmed by a systematic review conducted by Joyce et al (Joyce et al., 1997). Little is known about the reasons for the variations in prognosis found in ME/CFS, though recent research has identified several factors associated with such variation. Social, psychological, and physical factors have all been associated with severe illness and poor prognosis (Schmaling et al, 2000; Hartz et al., 1999).

Factors associated with severe ME/CFS and poor prognosis in children include specific viral triggers, start date, and socioeconomic status (Rangel et al., 2000). In adults, co morbidities (White et al., 2000), exercise before falling ill (MacDonald et al., 1996; Van Houdenhove et al., 1995), and familial factors (Farmer et al., 1999; Bell et al., 1991) have been implicated. The systematic review by Joyce et al (1997) concluded that consistently reported risk factors for poor prognosis include older age and illness that is more chronic. Other factors that have been claimed (Clark et al.,1995) to be associated with poorer prognosis include having more than eight medically unexplained physical symptoms separate from those associated with the ME/CFS case definition, having had chronic fatigue symptoms for more than 1·5 years, having less than 16 years of formal education; and being older than 38 years. Cell-mediated immune function does not appear to affect prognosis (Wilson et al., 1995; Peakman et al., 1997). There is some evidence that cases of acute onset have a better prognosis than those with gradual onset, and that epidemic cases have a better prognosis than sporadic cases (Levine, 1997).

Methods

An observational, questionnaire-based study was undertaken in which exposure to risk factors in people with severe disease was compared to that in controls with less severe disease. The South West Multi-Centre Research Ethics Committee granted ethical approval for the study.

The participants in the study were recruited from members of voluntary organizations and patients attending NHS facilities. The ME Association, CHROME (Case History Research on ME), the 25% Group, the National ME Centre and the Wiltshire ME/CFS Service distributed 4000 questionnaires. Names and addresses of participants were unknown to the researchers. Reminders were sent by all organizations except the ME Association. Overall, 1166 questionnaires were returned, a response rate of 29%. Responses, 1104 in number, were included in the analysis if they confirmed medical diagnosis of ME/CFS and age over sixteen, and were assigned to mild, intermediate or severe groups on the basis of reported mobility status (i.e. whether housebound or bedbound or not) and Barthel score (Mahoney et al., 1965) as an objective measure of physical disability, as set out in table 1. Accuracy of ascription was assessed by comparing pain levels, mood and cognitive dysfunction between groups.

Table 1: Definition of Severity Groups.

Group	No. of cases	Criteria
Mild	619	Not housebound or bedbound, and Barthel score 70% +
Intermediate	294	Barthel score 60% +, but <70%, or Not housebound or bedbound, but Barthel <70%, or Housebound or bedbound, but Barthel score 60% +
Severe	124	Housebound or bedbound, and Barthel score <60%
Unclassifiable	67	No response re whether housebound or bedbound, &/or 2 or more omissions in Barthel response
TOTAL	1104	

Subsequent analyses focused on the comparison of the mild and severe groups, comprising 619 and 124 respondents respectively. The questionnaire sought information on exposure to possible risk factors, including familial risks, personality, pre-illness exposures including smoking, chemical exposures, occupation, exercise, immunisations, allergies, and infections in the month prior to the illness. Premorbid personality was assessed in the questionnaire using the Neuroticism and Conscientiousness domains of the International Personality Item Pool scale (Goldberg, 1999; Goldberg, 2001; IPIP, 2005). Between-group comparisons and tests were association were carried out. For chi squared tests involving 2x2 contingency tables, Yates' correction was applied. Logistic regression analysis was undertaken to determine the relative importance of various risk factors in determining outcomes. Information was also sought on the consequences of illness, in particular ability to work.

Results
The results of the study are presented as follows. Following an overall description of the participants, and in particular of those with mild or severe disease, the accuracy of assignment of cases to mild or severe categories is assessed by consideration of the prevalence and severity of symptoms of pain and discomfort, cognitive problems and mood in these two groups. Then, the impact of possible risk factors in considered on a life-course basis, beginning with familial factors,

progressing to personality, thence to pre-illness exposures (smoking, chemicals, exercise, occupation, and biomedical factors, specifically immunisations, allergies, and infections. Differences between mild and severe cases as regards the consequences of having ME/CFS, e.g. in terms of occupation, are then explored, and finally a logistic regression analysis, to identify which factors appeared most important in determining severity, is reported.

Description of the respondents
Females constituted a significantly higher proportion of the severe group than of the mild group. The average age of respondents with mild disease was 49.1 years, and for respondents with severe disease it was 43.7. The average age of onset of ME/CFS was 38.1 for mild cases and 30.6 for severe cases. Severe cases were more likely than mild cases to have juvenile onset disease, 25.0% reporting that their illnesses started at age below twenty, compared with 8.4% of mild cases (chi sq. = 47.45, p <0.001). The proportion of females rose with severity. They constituted 72.1% of mild, 81.0% of intermediate, and 88.7% of severe cases. The unclassifiable group included 68.6% females. (chi sq. = 21.45, with 2 degrees of freedom, i.e. disregarding the unclassifiable cases; p < 0.0000219).

Accuracy of assignment
Patterns of symptomatology reported by mild and severe respondents were compared, in order to confirm the accuracy of assignment of

respondents to these two groups. The findings reported are in respect of pain, cognitive dysfunction and mood.

Pain or discomfort

Participants in the severe category reported much more pain than mild cases, both immediately and over the previous four weeks. This difference was highly significant. However, few participants in either category were entirely free of pain (table 2).

Table 2: Pain Levels and Cognitive Problems.

Pain:							
		None at all	**Mild or moderate**	**Severe/very severe**	**TOTAL**	**Chi sq.**	**p**
During the past four weeks							
Mild cases	No. cases	57	415	149	621	101.20	<0.000001
	% total	9.2	66.8	24.0	100.0		
Severe cases	No. cases	2	34	85	121		
	% total	1.7	28.1	70.2	100.0		
Now							
Mild cases	No. cases	90	450	77	617	98.55	<0.000001
	% total	14.6	72.9	12.5	100.0		
Severe cases	No. cases	1	60	60	121		
	% total	0.8	49.6	49.6	100.0		
Cognitive Problems:							
		Never	**Sometimes/ infrequently**	**Frequently/ often**			
Are your thoughts muddled or slow?							
Mild cases	No. cases	25	332	262	619	25.39	0.000003
	% total	4.0	53.6	42.3	100.0		
Severe cases	No. cases	3	37	82	122		
	% total	2.5	30.3	67.2	100.0		
Do you get confused about what time of day it is, where you are or who people are?							
Mild cases	No. cases	278	268	70	616	27.99	<0.000001
	% total	43.5	43.5	11.4	100.0		
Severe cases	No. cases	52	52	35	122		
	% total	42.6	42.6	28.7	100.0		
Do you lose track of what is being said in the middle of a conversation?							
Mild cases	No. cases	73	322	226	621	121.17	<0.000001
	% total	11.8	51.9	36.4	100.0		
Severe cases	No. cases	3	39	80	122		
	% total	2.5	32.0	65.6	100.0		
Do you forget the names of people in your family or friends whom you see regularly?							
Mild cases	No. cases	229	275	114	618	8.48	0.014
	% total	37.1	44.5	18.4	100.0		
Severe cases	No. cases	35	50	36	121		
	% total	28.9	41.3	29.8	100.0		

Cognition and mood

In respect of every question bearing on cognition that respondents were asked, the proportion of severe cases reporting problems frequently or often was much greater than among mild cases. In every case, this difference was highly significant, except in response to the question 'Do you forget the names of people in your family or friends whom you see regularly?' (table 2)

In toto, eleven hypotheses re mood and cognitive function were examined, so a Bonferroni correction has been made, with a revised alpha of 0.0045. There was no difference in current anxiety levels between severe and mild cases. However, severe cases were significantly more likely to be depressed than mild cases. On this basis, the only significant difference between severe and mild cases was that a higher proportion of severe cases reported that they had not been happy any time in the previous four weeks. However, this proportion (10.7%) was still very low (table 3).

Table 3: Mood Variations by Severity.

		Not at all	Mildly or moderately	Severely/ very severely	TOTAL	Chi sq.	P
Whether anxious now							
Mild cases	No. cases	244	326	49	619	3.678	0.159
	% total	39.4	52.7	7.9	100.0		
Severe cases	No. cases	43	62	16	121		
	% total	35.5	51.2	13.2	100.0		
Whether depressed now							
Mild cases	No. cases	337	258	24	619	22.868	0.000011
	% total	54.4	41.7	3.9	100.0		
Severe cases	No. cases	58	45	17	120		
	% total	48.3	37.5	14.2	100.0		
Mood over the past four weeks: Have you:-							
		None of the time	Some/a little of the time	All/much of the time			
been very nervous?							
Mild cases	No. cases	202	340	83	625	6.72	0.035
	% total	32.3	54.4	13.3	100.0		
Severe cases	No. cases	37	57	27	121		
	% total	30.6	47.1	22.3	100.0		
felt so down in the dumps that nothing could cheer you up?							
Mild cases	No. cases	179	291	75	545	6.311	0.043
	% total	32.8	53.4	13.8	100.0		
Severe cases	No. cases	44	52	26	122		
	% total	36.1	42.6	21.3	100.0		
felt calm and peaceful?							
Mild cases	No. cases	63	329	230	622	1.885	0.39
	% total	10.1	52.9	37.0	100.0		
Severe cases	No. cases	18	63	45	126		
	% total	14.3	50.0	35.7	100.0		

	felt downhearted and low?						
Mild cases	No. cases	69	431	121	621	6.182	0.045
	% total	11.1	69.4	19.5	100.0		
Severe cases	No. cases	6	83	32	121		
	% total	5.0	68.6	26.4	100.0		
	been happy?						
Mild cases	No. cases	23	331	268	622	10.953	0.004
	% total	3.7	53.2	43.1	100.0		
Severe cases	No. cases	13	63	46	122		
	% total	10.7	51.6	37.7	100.0		

Exposure to Potential Risk Factors

Familial factors
37.9% of severe cases reported a family history of ME/CFS, compared with only 17.1% of mild cases. This was statistically highly significant (chi sq. for mild in comparison with severe cases = 6.45; p = 0.011). There was a strong association between having a mother with ME/CFS and developing severe disease, less strong associations with having a sibling or child with ME/CFS, and no association at all with having a father with the illness (table 4).

Table 4: Relatives who have had ME/CFS.

Relative		Cases				Chi sq.	p
		Mild (n = 630)		Severe (n = 120)			
		ME/CFS	No ME/CFS	ME/CFS	No ME/CFS		
Mother	No. cases	22	581	14	106	11.96	0.00023
	% total	3.5	96.5	11.7	88.3		
Father	No. cases	7	596	3	117	0.517	0.472
	% total	1.1	98.9	2.5	97.5		
Brother or sister	No. cases	24	579	14	106	10.381	0.0013
	% total	3.8	96.2	11.7	88.3		
Son or daughter	No. cases	28	575	11	109	3.175	0.075
	% total	4.4	95.6	9.2	90.8		
Any first degree relative	No. cases	69	561	26	94	9.514	0.002
	% total	10.9	89.1	21.7	78.3		
Any other relative	No. cases	13	590	24	96	62.006	<0.00001
	% total	2.1	97.9	20.0	80.0		

Personality
Two personality domains were investigated using IPIP (27, 28, 29), viz. neuroticism and severity. A logistic regression analysis indicated an inverse association between neuroticism and severity, but none between conscientiousness and severity (Table 5). The association remained significant when sex and age were excluded from the model.

Table 5: Odds Ratios for Severity – Logistic Regression Results.

	Odds Ratio (95% Confidence Interval)	
	Four variable model	**Two variable model**
Variable:		
Age now	0.74 (0.66 - 0.87)	-
Sex	0.38 (0.21 - 0.70)	-
Conscientiousness	0.99 (0.58 - 1.72)	0.77 (0.46 - 1.29)
Neuroticism	0.51 (0.35 - 0.75)	0.42 (0.26 - 0.69)
Summary Statistics		
Chi Square	40.29 (df=4)	13.05 (df=2)
P	<0.05	<0.05

Mean scores for neuroticism were consistently higher among mildly ill subjects than among the severely ill. This was true also of all sub domains of neuroticism (Figure 1, and Table 6), average scores being consistently higher among mild cases for immoderation, self-consciousness, vulnerability, depression, anger and anxiety. Logistic regression analysis showed that the sub-domains of anger, anxiety and vulnerability were more strongly associated with severity.

**Figure 1: Neuroticism Sub-domains: Mean Scores by Severity.**
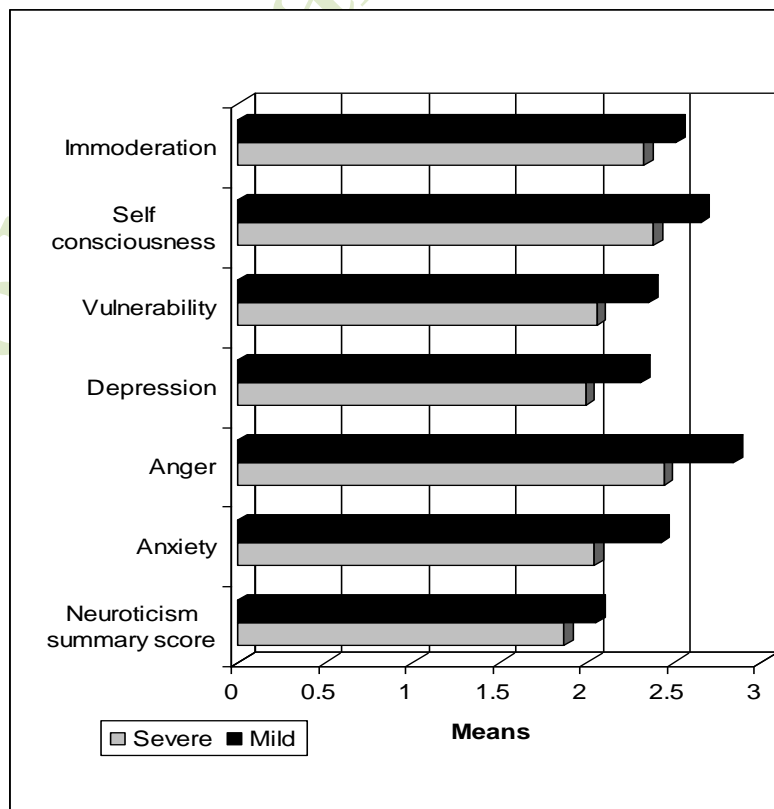
Table 6: Comparison of Mean Scores for Neuroticism in Severe and Mild Cases.

	Mean Score		Ratio of Mean
	Severe cases	**Mild cases**	**(Mild: Severe)**
Neuroticism summary score	1.87	2.05	1.10
Sub-Domain:			
Anxiety	2.04	2.42	1.19
Anger	2.44	2.84	1.16
Depression	1.99	2.30	1.16
Vulnerability	2.05	2.35	1.15
Self consciousness	2.38	2.65	1.11

An independent samples t-test indicated no significant difference between the mild and severe groups for any of the conscientiousness sub-domains (Figure 2 and Table 7). However, logistic regression indicated that, while the sub-domains of orderliness, dutifulness, perfectionism and cautiousness were not risk factors for severity, self-efficacy and self-discipline were. a high self efficacy score was associated with an increase in the risk of being severely ill of 70%, while for self discipline a high score was associated with an increase in the level of risk of 64%.

Figure 2: Conscientiousness Sub-domains and Severity.
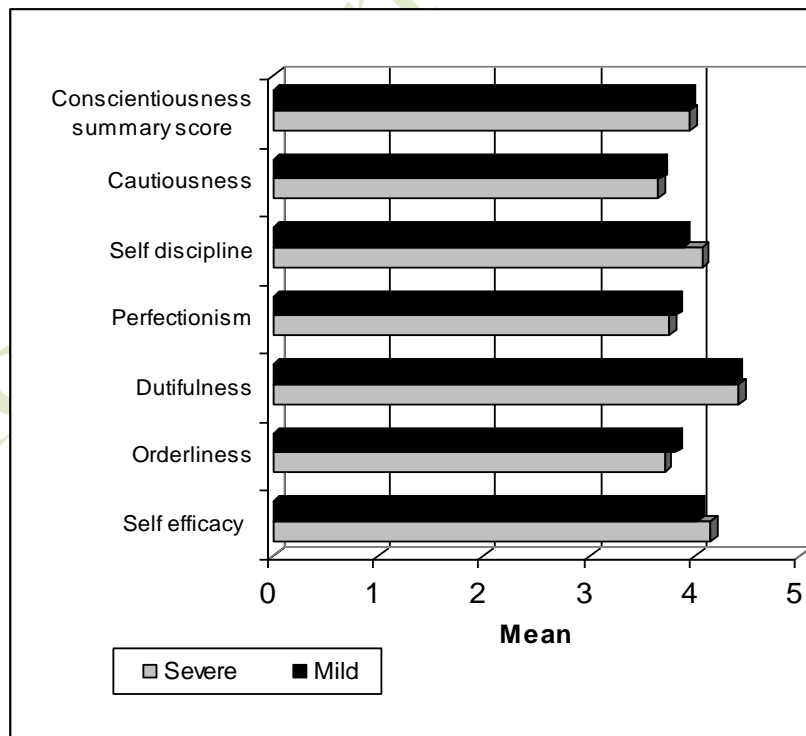
Table 7: Conscientiousness and Severity: Logistic Regression Analysis.

	Odds Ratio	**95% Confidence Interval**
High self-efficacy score	1.70	1.12 – 2.57
High self discipline	1.64	1.07 - 2.50
High conscientiousness	0.98	0.65 – 1.48
High orderliness	1.14	0.75 – 1.72
High dutifulness	0.82	0.54 – 1.24
High perfectionism	1.07	0.71 - 1.62
High cautiousness	1.70	1.12 – 2.57

Pre-Illness exposures

There was no association between smoking habits and development of severe ME/CFS (table 8) (chi sq. (Current smokers v. Non-smokers) = 2.45; p = 0.118). Severely ill subjects were more likely than mild cases to have reported exercising six or more hours per week prior to falling ill (chi sq. = 6.4; p = 0.009) (table 9). As regards last occupation before developing ME/CFS, homemakers and students were over-represented in the severe category, while teachers and academics were under-represented (table 10). Working night shifts before falling ill was not a risk factor for severity. 20.8% of severe respondents (16 out of 77) did so, and 15.6% (79 out of 597) mild ones (chi sq. = 0.97; p = 0.324).

Table 8: Smoking, and Reported Exposure to Chemicals.

	Mild		**Severe**	
	No. Cases	**% total**	**No. Cases**	**% total**
Smoking Behaviour:				
Non-Smoker	397	65.0	70	58.3
Ex-Smoker	157	25.7	33	27.5
Current smoker	57	9.3	17	14.2
Total	611	100.0	120	100.0
Reported Chemical Exposures:				
Yes, at work	111	23.8	29	27.4
Yes, at home	30	6.4	25	23.6
No	326	69.8	52	49.1
Total	467	100.0	106	100.0

Table 9: Exercise prior to falling ill.

Hours/week	Mild		Severe	
	No. cases	% total	No. cases	% total
<1	34	5.7	7	5.8
1 to 2	79	13.1	8	6.6
2 to 3	85	14.1	17	14.0
3 to 4	79	13.1	10	8.3
4 to 5	81	13.5	14	11.6
6 or more	243	40.4	65	53.7
TOTAL	601	100.0	121	100.0

Table 10: Last occupation before developing ME/CFS.

	Mild		Severe		Chi-sq.*	p
	No. cases	% total	No. Cases	% total		
Teacher/academic	134	24.3	13	11.4	8.369	0.0038167
Secretary/Office worker/administrator	131	23.7	26	22.8	0.008	0.9287300
Student	47	8.5	27	23.7	20.506	0.0000027
Healthcare professional	84	15.2	9	7.9	3.63	0.0567468
Housewife	21	3.8	14	12.3	11.985	0.0005363
Manual worker	24	4.3	6	5.3	0.033	0.8558503
Retired	13	2.4	2	1.8	0.002	0.9643294
Other	98	17.8	17	14.9	0.354	0.5518575
TOTAL	552	100.0	114	100.0		

* Category v. all others

There was a difference in reported exposure to chemicals at home, but not at work, between severe and mild cases which appears highly significant (Chi sq. (all exposures) = 15.66; p = 0.00076. For home exposures, chi sq. = 27.38, p <0.000001; for occupational exposures, chi sq. = 0.424; p = 0.52). However, this must interpreted with caution, since self-reported exposures are notoriously unreliable, and likely to be influenced by post hoc rationalisation. Information was given about the nature of the claimed exposures in a small minority of cases (table 8). Where information about the nature of chemical exposures was given, it tended to be vague, and no pattern emerged as to which specific chemical or class of chemical was being blamed for the subsequent development of illness. Responses were analysed according to whether claimed exposures were specific (i.e. specific chemical identified), unspecific (class of substance but no specific chemical identified), or vague (neither class of substance nor specific chemical identified) (table 11). Mildly ill people were more likely to have reported a specific chemical exposure than severely ill people (i.e. 21 of 62 mild cases (33.9%), compared with 4 out of 27 severe cases (14.8%), but this was not statistically significant (Chi sq. = 2.504; p = 0.114). Exposure to agricultural/horticultural chemicals was reported by 50% of those severe cases reporting exposures (24 out of 48) and 33.9% (21 out of 62) mild cases. This difference was not statistically significant (chi sq. = 2.28; p = 0.131).

Table 11: Specificity of Chemical Exposure Reports.

Category	Mention of:-			
	Agriculture/ horticulture	Construction industry	Other	TOTAL
Occupational exposures:				
Mild cases:				
Specific	2	1	9	12
Unspecific	2	2	10	14
Vague	1	1	6	8
TOTAL	5	4	25	34
Severe cases:				
Specific	0	0	2	2
Unspecific	1	0	3	4
Vague	1	1	2	4
TOTAL	2	1	7	10
ALL OCCUPATIONAL EXPOSURES	7	5	32	44
Home exposures:				
Mild cases:				
Specific	6	2	1	9
Unspecific	5	2	1	8
Vague	5	1	5	11
TOTAL	16	5	7	28
Severe cases:				
Specific	1	0	1	2
Unspecific	9	3	3	6
Vague	0	0	0	0
TOTAL	10	3	4	17
ALL HOME AND LIVING EXPOSURES	20	6	11	37
OVERALL TOTAL (all categories)	27	11	43	81

There were few variations in respect of pre-illness biomedical factors between the severe and mild categories As regards immunisation rates, severe cases were significantly less likely to have been immunised against hepatitis B and smallpox (NB. 10 related hypotheses were tested, so a revised alpha value, following the Bonferroni procedure, of 0.005 was adopted) (Table 12). For every category of potential allergen enquired about except for pollen, a higher proportion of respondents in the severe category than in the mild category reported allergies. These variations were statistically significant only in the cases of drugs and cosmetics (NB. 7 related hypotheses were tested, so a revised alpha value, following the Bonferroni procedure, of 0.007 was adopted). 86.7% severe cases, and 78.1% of mild cases, reported having had an infection in the month before they fell ill (chi sq. = 4.169; p = 0.041). This was weakly significant, as was the more frequent reporting of Epstein-Barr virus infection among severe cases (table 12).

Table 12: Immunisations, Allergies, and Infections in the month prior to illness.

	Mild cases			Severe cases			Chi sq.	p
	No. cases	% total	Total (= 100%)	No. cases	% total	Total (= 100%)		
Immunisations								
Cholera	113	20.3	556	21	18.7	115	0.14	0.707
Diphtheria	319	55.5	575	59	50.4	117	0.81	0.369
Measles	254	44.6	570	59	50.0	118	0.96	0.328
Mumps	205	36.5	562	38	32.2	118	0.60	0.438
Typhoid	177	31.9	554	25	21.9	114	4.04	0.045
Hepatitis B	163	29.1	561	16	13.9	115	10.48	0.001
Poliomyelitis	512	85.0	602	94	78.3	120	2.87	0.090
Rubella	278	48.4	574	65	55.6	117	1.70	0.193
Smallpox	283	49.4	573	37	31.4	118	12.08	0.0005
Tetanus	534	88.7	602	97	80.2	121	5.87	0.015
Allergies:								
Food	232	44.8	518	68	57.6	118	5.85	0.016
Pollen	192	36.9	520	44	37.0	119	0.009	0.992
Drugs	184	36.0	511	64	53.8	119	12.04	0.00035
Cosmetics	184	36.6	516	64	54.2	118	12.59	0.00039
Animals	139	27.4	508	32	27.4	117	0.013	0.909
House dust mite	98	19.5	502	35	29.9	117	5.48	0.019
Other	116	23.2	499	34	29.3	116	1.56	0.211
ALL ALLERGENS	451	72.4	623	110	88.7	124	13.87	0.0002
Infections in month before illness								
Coxsackie	41	8.2	499	10	9.2	109	0.019	0.890
EBV	66	13.1	504	23	21.5	107	4.352	0.037
Other viruses	306	26.1	532	55	49.1	112	2.327	0.127
Other (non-viral)	59	11.8	499	18	16.2	111	1.215	0.270

Management in the early stages of the illness
There was a significant difference between the mild and groups in the interval between falling ill and diagnosis. 336 out of 611 respondents with mild disease (55.0%) were diagnosed in less than a year. For severe cases, the proportion was 41.7% (50 out of 120 cases) (chi sq. = 6.62; p 0.01). As well as being more likely than mild cases to experience diagnostic delays, severe cases were more likely to encounter social problems in the early stages of the illness. This applied in every area investigated, in the family, education, in the home, and in the social security system. The workplace was the only exception, where mild cases were significantly more likely than severe cases to have encountered problems (Table 13).

Table 13: Social problems encountered in the early stages of the disease.

	Mild				Severe				Chi sq.	p
	Yes		No		Yes		No			
	No. cases	Col. %	No. cases	Col. %	No. cases	Col. %	No. cases	Col. %		
Work	402	71.5	160	28.5	63	52.9	56	47.1	14.82	0.0001
Social security benefits	175	33.0	356	67.0	53	44.9	65	55.1	5.55	0.019
Family	187	34.7	352	65.3	64	54.2	54	45.8	14.85	0.0001
Education	58	11.2	462	88.8	33	27.7	86	72.3	20.45	0.000006
Lack of support in the home	152	28.4	383	71.6	55	45.8	65	54.2	12.97	0.0003
Other	97	18.8	420	81.2	45	37.8	74	62.2	19.17	0.00001

Two-thirds of the respondents received treatment in the early stages of the illness (66.6% of mild cases, and 67.7% of severe cases). Among those subjects who did receive treatment in the early stages of the illness, 32.7% of mild cases (98 out of 300) found treatment in the early stages of the illness to be useful, compared with only 11.5% of severe cases (6 out of 52) (chi sq. = 8.52; p = 0.0035). By contrast, 73.1% of severe cases found it damaging, compared with only 30.0% of mild cases (chi sq. = 44.7; p <0.00001). Among those subjects who received treatment before diagnosis, people with severe disease were significantly more likely to have received analgesics, physiotherapy, or complementary therapy than people with mild disease. There were no significant differences in any other type of treatment. After diagnosis, the proportions of both mild and severe cases receiving treatment rose markedly, and severe cases were very significantly more likely than mild cases to have received physiotherapy (Table 14).

Table 14: Patterns of Treatment in the Early Stages of the Illness.

	Before Diagnosis						Immediately after Diagnosis					
	Mild		Severe		Chi^2	P	Mild		Severe		Chi^2	P
	No. cases	% total (n = 623)	No. cases	% total (n = 124)			No. cases	% total (n = 623)	No. cases	% total (n = 124)		
Pain killers	193	31.0	46	37.1	8.733	**0.003**	199	31.9	51	41.1	3.518	0.061
Tranquillisers	56	9.0	15	12.1	0.828	0.363	42	6.7	12	9.7	0.927	0.336
Antidepressants	190	30.5	36	29.0	0.047	0.828	257	41.3	69	55.6	8.135	0.004
Other drugs	97	15.6	20	16.1	0.000	1.000	88	14.1	24	19.4	1.828	0.176
Physiotherapy	35	5.6	20	16.1	15.246	**0.00009**	68	10.9	29	23.4	13.155	**0.0003**
Occupational therapy	7	1.1	4	3.2		0.070[#]	47	7.5	17	13.7	4.262	0.039
Activity management	19	3.0	4	3.2		0.217[#]	115	18.5	26	21.0	0.277	0.599
Complete bed rest	77	12.4	15	12.1	0.005	0.944	64	10.3	19	15.3	2.183	0.140
Graded exercise	23	3.7	11	8.9	5.249	0.022	100	16.1	22	17.7	0.110	0.740
Cognitive behaviour therapy	18	2.9	8	6.5	2.918	0.088	53	8.5	9	7.3	0.080	0.777
Counselling	49	7.9	16	12.9	2.700	0.100	99	15.9	25	20.2	1.071	0.301
Complementary therapies	75	12.0	28	22.6	8.802	**0.003**	152	24.4	25	20.2	0.806	0.369
Other treatment	62	10.0	21	16.9	4.424	0.035	89	14.3	19	15.3	0.026	0.872
ALL TREATMENTS	415	66.6	84	67.7	0.019	0.890	506	81.2	111	89.5	4.518	0.036

[#] Fisher's Exact Test

NB. Probability values in **BOLD** are significant at a revised α-threshold of 0.0036, following the Bonferroni procedure

For ALL TREATMENTS, the increase after diagnosis in the proportion of patients receiving treatment was statistically significant, i.e.:-
Mild cases: Chi sq. = 33.092; p <0.00001
Severe cases: Chi sq. = 16.221; p <0.00001

There were few respondents for whom there was no professional involvement in their initial treatment, and there was no significant difference between mild and severe cases in the proportions with professional involvement in their initial treatment. Most respondents, of both categories, reported that at least one helpful professional was involved in their initial care after diagnosis, though severe cases reported this less frequently than mild cases, i.e. 501 out of 623 mild cases (80.4%), compared with 76 out of 124 severe cases (61.3%). This difference was statistically significant (chi sq. = 20.50, p = 0.000006).

The GP was the professional most commonly consulted by people with ME/CFS in the early stages of their illnesses, being consulted by 79.9% of people with mild disease and 77.6% of people with severe disease. The proportion of respondents reporting a bad relationship with their GP was significantly higher among severe cases than mild ones, both before and after diagnosis, even though overall most respondents reported good relationships with their GPs (table 5). In both categories, the proportion of respondents reporting bad relationships with their GPs rose significantly after diagnosis (mild cases: chi sq. by McNemar's test = 19.04, p = 0.0001; severe cases: chi sq. = 4.15, p = 0.042).

Severe cases were more likely to have been diagnosed by hospital doctors, and less likely to have been diagnosed by GPs, than mild cases. However, this difference was not statistically significant (table 15). Psychiatrists, other hospital doctors, nurses, and social workers were significantly more likely to have been involved in the initial treatment of severe cases than of mild cases. (Table 16).

Table 15: Respondents' Relationships with Doctors.

	Mild		Severe		Chi sq.	P
	No.	%	No.	%		
Doctor making initial diagnosis						
GP	488	81.6	91	76.5	1.369	0.242
Hospital doctor	93	15.6	24	20.2	1.229	0.268
Other	17	2.8	4	3.4		0.210[#]
TOTAL	598	100.0	119	100.0		
Relationship with GP before diagnosis						
Good	401	65.8	62	50.4	9.840	**0.002**
Bad	29	4.8	19	15.4	17.364	**0.00003**
Neither good nor bad	179	29.4	42	34.1	0.883	0.347
TOTAL	609	100.0	123	100.0		
Relationship with GP immediately after diagnosis						
Good	398	65.1	51	42.5	20.750	**0.000005**
Bad	72	11.8	33	27.5	18.883	**0.00001**
Neither good nor bad	141	23.1	36	30.0	2.256	0.133
TOTAL	611	100.0	120	100.0		

[#] Fisher's Exact Test

NB. Probability values in **BOLD** are significant at α-threshold of 0.05.

Table 16: Professionals involved in Initial Treatment.

	Mild		Severe		Chi sq.	P
	No.	%	No.	%		
Professional involved	553	88.8	106	85.5	0.778	0.378
No professional involved	70	11.2	18	14.5		
TOTAL	623	100.0	124	100.0		
GP	498	79.9	95	76.6	0.509	0.476
Psychiatrist	79	12.7	35	28.2	18.141	**0.00002**
Other hospital doctor	237	38.0	65	52.4	8.289	**0.004**
Nurse	32	5.1	16	12.9	9.124	**0.003**
Occupational therapist	43	6.9	18	14.5	7.012	0.008
Physiotherapist	64	10.3	23	18.5	6.102	0.014
Clinical psychologist	43	6.9	11	8.9	0.340	0.560
Counsellor	61	9.8	20	16.1	3.666	0.566
Social worker	13	2.1	17	13.7	33.291	**<0.00001**
Complementary therapist	108	17.3	21	16.9	0.001	0.975
Other	61	9.8	14	11.3	0.118	0.731

NB. Probability values in **BOLD** are significant at a revised α-threshold of 0.0045, following the Bonferroni procedure

Table 17 summarises the extent to which respondents found the attitudes of professionals involved in their initial care after diagnosis helpful or unhelpful. It will be noted that severe cases were significantly less likely than mild cases to have found helpful the involvement or clinical psychologists, and significantly more likely to have unhelpful the involvement of social workers. As regards GPs, a significantly higher proportion of mild cases than of severe cases found their involvement helpful, while a significantly lower proportion of mild cases than of severe cases found their involvement unhelpful. There were no significant differences in respect of other professionals, but in many instances, the numbers of cases were very small. Mildly ill subjects reported that the professionals they consulted were helpful far more frequently than they reported that they were unhelpful. This was also true, though less markedly so, for severely ill subjects, except as regards clinical psychologists, who were much more frequently reported by severely ill patients to be unhelpful than to be helpful, though this was not statistically significant (chi sq. = 0.406, p = 0.52).

Table 17: Attitudes of professionals involved in initial care after diagnosis.

	Mild cases			Severe cases			Chi sq.	P
	No.	%	Total	No.	%	Total		
Respondents finding professional involvement <u>helpful</u>								
GP	377	74.8	504	47	58.0	81	9.024	0.0027
Psychiatrist	58	60.4	96	16	61.5	26	0.015	0.905
Other hospital doctor	159	61.2	260	38	58.5	65	0.065	0.799
Nurse	29	64.4	45	11	50.0	22	0.751	0.386
Occupational therapist	44	75.9	58	14	73.7	19	0.013	0.909
Physiotherapist	48	67.6	71	13	50.0	26	1.829	0.176
Clinical psychologist	42	67.7	62	4	26.7	15	6.851	0.0088
Counsellor	50	78.1	64	15	75.0	20	0.000	1.000
Social worker	14	77.8	18	9	64.3	14	4.655	0.031
Complementary therapist	108	85.0	127	19	76.0	25	0.671	0.413
Other professional	52	77.6	67	11	68.8	16	0.176	0.675
Participants finding professional involvement <u>unhelpful</u>								
GP	73	14.5	504	23	28.4	81	8.857	0.0029
Psychiatrist	33	34.4	96	9	34.6	26	0.044	0.834
Other hospital doctor	67	25.8	260	22	33.8	65	1.324	0.250
Nurse	10	22.2	45	9	40.9	22	1.703	0.192
Occupational therapist	9	15.5	58	4	21.1	19		0.224[#]
Physiotherapist	18	25.4	71	10	38.5	26	1.018	0.313
Clinical psychologist	13	21.0	62	8	53.3	15	4.851	0.028
Counsellor	8	12.5	64	4	20.0	20		0.190[#]
Social worker	3	16.7	18	5	35.7	14		0.0091[#]
Complementary therapist	13	10.2	127	5	20.0	25		0.098[#]
Other professional	11	16.4	67	4	25.0	16		0.235[#]

[#] Fisher's Exact Test

Logistic regression

A logistic regression model was constructed in order to review the relative contributions of the range of factors, which appeared to be increasing the risk of severe disease. The initial model comprised 24 independent variables. 587 mild and 116 severe cases were included in the model. This was highly significant (Initial chi sq. (-2 Log Likelihood) = 629.72; p <0.00001). The variables are listed, together with univariate chi squared results and probabilities, in Table 18.

Table 18: The Initial Overall Logistic Regression Model.

Description	Chi sq. (variable v. severity)	p
Conscientiousness summary score	2.422	0.298
Neuroticism summary score	12.596	0.0056
Gender	9.934	0.0016
Family history of ME/CFS	8.858	0.0029
History of ME/CFS in mother	5.345	0.0208
Hours of exercise per week before illness	10.642	0.1001
Hepatitis B immunisation	8.266	0.0040
Smallpox vaccination	7.212	0.0072
Occupation	38.109	<0.0001
Infection in month prior to illness	3.635	0.0566
EBV Infection in month prior to illness	2.816	0.0933
Problems at work at outset of illness	6.391	0.0115
Problems with social security at outset	24.032	<0.0001
Family difficulties at outset	4.438	0.0351
All allergens	14.455	0.0001
Interval between falling ill and diagnosis	12.991	0.0015
Value of initial treatment	19.940	<0.0001
Antidepressants after diagnosis	5.886	0.0115
Relationship with GP before and after diagnosis	28.519	<0.0001
Psychiatrist involved in initial treatment	11.224	0.0008
At least one helpful health professional	3.326	0.0681

The model was refined by successive deletion of variables. Firstly, where variables appeared covariate, those with the weaker associations with the dependent variable were deleted. Then variables were deleted in sequence, in order of weakness of association with the outcome variable. Eventually a six variable model was obtained, in which chi sq. = 633.37 (p<0.00001). Thus, successive deletions had no impact on the predictive power of the model. The independent variables in the final model were:
- Occupation
- Problems with social security
- Interval between falling ill and diagnosis
- Perceived value of initial treatment
- Relationship with GP before and after diagnosis
- Involvement of a psychiatrist in initial treatment

Consequences of severity
2.5% of those with severe ME claimed to be still working at the job they had had immediately before falling ill, compared with 21.2% of mild cases (chi sq. (still working v not working or retired) = 22.50; p = 0.000001). It is clear from comments made by respondents, though, that many of those still working were clinging on with some considerable difficulty, e.g. these comments from mildly affected respondents:- "Only just", "Up to a point", "Part time - long break", "But off sick again with ME".

4 out of 6 severe cases (66.7%) who claimed to be still working were working less than 10 hours per week, compared with 32 out of 174 (18.4%) mild cases (p by Fisher's Exact Test = 0.0014). Only 13.8% of respondents were still able to do the job they had immediately before falling ill (i.e. 29 out of 136). Of the 82.6% who were unable, to do so, 288 (30.8%) had retired on medical grounds. As might be expected, manual workers were least able to continue their previous jobs, i.e. only 2 out of 44, or 4.3%, compared with 128 out of 775 others (14.2%) (p by Fisher's Exact Test = 0.028)

Discussion
The accuracy of assignment to mild and severe categories appears to have been high, given the differences between the two groups in reported symptom frequency and severity, and also in terms of the consequences of

illness experienced by the two groups, as practically no severe cases were still working at their pre-illness job, and only a small minority of mild cases. As might be expected, manual workers were least able to continue their previous jobs. As regards last occupation before developing ME/CFS, homemakers and students were over-represented in the severe category, while teachers and academics were under-represented. Working night shifts before falling ill was not a risk factor.

Major risk factors for severe disease included being female, and having a family history of ME/CFS. Early management of ME/CFS appeared also to be a major determinant of severity. The logistic regression model was refined without loss of precision to a final model comprising just six variables, viz. occupation, problems with social security, interval between falling ill and diagnosis, perceived value of initial treatment, relationship with GP before and after diagnosis, and involvement of a psychiatrist in initial treatment, all but one of which, it will be noted, pertain to the management of the condition in its early stages.

Personality type did not appear to constitute a risk factor for severe disease. This was also the conclusion of another recent study, a controlled study of 36 patients, which determined that personality structure does not appear to play a major role in CFS (Le Bon et al., 2007) Our investigation of the possible role of personality revealed an inverse association between neuroticism and severity, but none overall between conscientiousness and severity. Mean scores for neuroticism were consistently higher among mildly ill subjects than among the severely ill. This may indicate either that severely ill people may develop a degree of stoicism that affects their responses to personality questionnaires. Indeed, a recently published case study indicates that personality profile can indeed be affected by having CFS (Van Hoof et al., 2007). Alternatively, it may indicate, as we were unable to validate diagnoses, that the mild group included people who did not actually have ME/CFS at all, but other fatiguing illnesses in which personality may play a part. In the conscientiousness domain, though there was no association overall with severity, the sub-domains of self-efficacy and self-discipline were associated with it. This may be in part a consequence of the low response rate. Completion of the questionnaire was undoubtedly a major challenge for many who were severely ill, so only the most motivated

and driven of severely ill people, i.e. those with high self-efficacy and self-discipline scores, may have persevered with it to the end.

Other less marked associations with severity included an increased likelihood among severe cases of having been immunised against hepatitis B and smallpox, of having reported allergies (except to pollen), or an infection in the month before they fell ill, and of having exercised six or more hours per week before falling ill. There were some differences in alleged chemical exposures between the mild and severe groups. However, these must be interpreted with caution, since self-reports of exposures are inherently unreliable and likely to be influenced by post hoc rationalisation. Information given was in any case vague and fragmentary. More research is clearly needed in this area before definitive conclusions can be drawn. There was no association between smoking habits and development of severe ME/CFS.

The finding that having a family history was a risk factor for ME/CFS is consistent with that of a twin study (Farmer et al., 1999) and a study of an epidemic outbreak in New York State (Bell et al., 1991). A recent study found that the prevalence of ME/CFS was much higher among members of families of people with the disease than in the general population. In genetically unrelated household contacts an intermediate level of prevalence was found, indicating a role for both genetic and environmental factors (Underhill and O'Gorman, 2006), while an increased propensity has been demonstrated among people with ME/CFS to a family history of endocrine or metabolic disorders, in comparison with normal controls (Torres-Harding et al., 2004). The strong association with having a mother with ME/CFS, but lack of association with having a father with the condition, is consistent with ME/CFS being associated with disturbed mitochondrial function (Plioplys and Plioplys, 1995). Mitochondrial DNA is of course entirely of maternal origin. This finding is consistent with the demonstration by Myhill et al of a marked correlation between degree of incapacity in people with ME/CFS and mitochondrial dysfunction (Myhill et al., 2009).

Early management is clearly a source of major problems for people with ME/CFS, and other research has demonstrated the extent of shortcomings in the primary care sector, which for most patients is where their initial contacts with the health care system take place. Raine

et al (2004) concluded, following group discussions with 46 English GPs, that they tended to stereotype ME/CFS patients as being antisocial and in conflict with their doctors. This is consistent with a survey of 121 Dutch GPs (Prins et al., 2000), which found that only half used the diagnosis CFS, mostly because of ignorance of the criteria. 68% of patients diagnosed themselves, and more than half of the GPs were relatively unsympathetic, had problems communicating with them and considered cooperation to be poor. Similarly, a survey of attitudes to and knowledge of ME/CFS of English GPs (Bowen et al., 2005) found that many lacked confidence in diagnosis (48%) or treatment (41%), though 72% accepted ME/CFS as a recognisable clinical entity.

It is clear that a good relationship with the GP from the outset of the illness is very important in achieving a good outcome and avoiding severe illness, but unhelpful attitudes and ignorance are still widespread in primary care. Levels of acceptance and knowledge of ME/CFS among doctors generally appear unsatisfactory (Ho-Yen and McNamara, 1991; Denz-Penhey and Murdoch, 1993; Steven et al., 2000). A recent survey of Irish GPs found that only 58% accepted ME/CFS as a genuine clinical entity (Fitzgibbon et al., 1997). Similarly, in a Brazilian survey less than one-third of respondents mentioned ME/CFS as a possible diagnosis when presented with a ME/CFS case scenario (Nacul et al., 1998). A primary care based randomised controlled trial (Whitehead and Campion, 2002) produced an equivocal result because recruitment was poor, and drop out high, but the authors concluded that general practitioners cannot provide a coherent management programme, or indeed any effective treatment in primary care. The importance of appropriate management in the early stages of the illness was underlined by the Chief Medical Officer's Working Group report, which stated: "Early recognition with an authoritative, positive diagnosis is key to improving outcomes" (CMO's Working Group., 2002). Given that early management is clearly implicated in the subsequent development of severe disease, the finding of the Wichita survey that most cases of CFS in the population are unrecognised by the medical community is clearly important. The recognition rate in that study was only 16%, so clearly there is still a mountain to climb (Solomon and Reeves, 2004).

Previous research has demonstrated associations between various social factors and severe illness and poor prognosis. Social factors implicated include, for example, poor education and unemployment, while having a solicitous 'significant other' (Schmaling et al., 2000) and being married (Hartz et al., 1999) have a protective effect. In adults, co morbidity can predispose to severe illness and poor prognosis (White et al., 2000). Our study has shown that personality is not a factor in the development of severe disease. While other studies have compared people with ME/CFS and normal controls (White and Schweitzer 2000; Buckley et al., 1999; Rangel et al., 2000) or people with other illnesses (Van Houdenhove et al., 1995; Henderson and Tannock, 2004; Hickie et al., 1990; Pepper et al., 1993; Christodoulou et al., 1999; Wood and Wessely, 1999), or investigated determinants of disease duration, there do not appear to have been any previous studies comparing exposure to risk factors in mild and severe cases. It is, in any case, difficult to reach conclusions from these other studies because of the diversity of instruments used and traits investigated. A recent study (Le Bon et al., 2007) suggested that personality does not play a major role in CFS. This is consistent with our findings, which are also in line with those of the Dubbo study, in which persistence of post-infective CFS was largely related to the severity of the acute illness, rather than to demographic, psychological or microbiological factors. In particular, neuroticism was unrelated to the development of prolonged illness (Hickie et al., 2006).

There is no consensus about the role of perfectionism in the development of ME/CFS from these studies. No differences in perfectionism between CFS subjects and controls were found in studies by Wood and Wessely (1999), Buckley et al (1999) and Blenkiron et al (1999). On the other hand, White and Schweitzer (2000) found higher levels on the Total Perfectionism score amongst the CFS group than among healthy controls. In a study of adolescents with CFS, conscientiousness was one of the personality features that were significantly more common (Rangel et al., 2000). Henderson & Tannock (Henderson and Tannock, 2004) found higher levels of Cluster C personality disorder (which includes perfectionism) in CFS and depressed patients than in healthy controls.

The higher neuroticism scores in the mildly ill compared with the severely ill were not consistent with other studies which have found

neuroticism (in particular, depression) to be positively associated with ME/CFS (Buckley et al., 1999; Hickie et al., 1990; Pepper et al., 1993; Blenkiron et al., 1999; Poulis,1999; Johnson et al., 1996). Abbey et al (Abbey and Garfinkel, 1990) reports that high rates of symptoms of depression and of major depressive illness are among the most consistent findings in ME/CFS patients. A review of studies published from 1982 to 1992 (Manu et al., 1992) concluded that the majority of patients with CFS have a high prevalence of current major depression and abnormal personality traits. It is likely though that studies showing a positive association between ME/CFS and depression are reporting a consequence of the way in which ME/CFS patients are treated rather than an association with pre-morbid personality or pre-existing mental illness.

The strength of this study was that it involved a large group of subjects manifesting a range of degrees of severity, and has demonstrated significant differences between mild and severe cases in exposure to a range of risk factors. The study sample was not selected to be representative of the ME/CFS population as a whole, but rather to manifest the range of severity found in the illness. There have few attempts in the past to quantify severity in reproducible ways, and most previous studies share a number of faults. Most are uncorroborated by other studies. Secondly, while they may have speculated about causation, mostly what has been demonstrated are associations. Definitions of severity have varied, and are often vague (Cox and Findley, 2000).

Weaknesses of the study were that diagnoses could not be validated, were not independently verified, and were probably of variable quality. Consequently, the study population may have included people with unexplained chronic fatigue who did not have ME/CFS. Another problem derived from the necessarily arbitrary nature of the assignment of respondents to mild and severe categories, in an illness in which there appears to be a continuous spectrum of severity, in which symptomatology is multidimensional in nature, and in which the patient may manifest different levels of severity in respects of different clinical features, e.g. fatigue, physical disability, pain, or cognitive dysfunction. This was compounded by a lack of suitable validated instruments for measuring severity in this multidimensional context, existing instruments such as the Chalder Fatigue Scale (Chalder et al., 1993) and the

Barthel Index (Mahoney and Barthel, 1965) being one-dimensional in nature. The low response rate may have introduced response bias, and, since this was a cross-sectional study, recollections may have been subject to recall bias. This could be overcome in future research by undertaking prospective cohort studies.

The use of the Barthel Index caused some respondents serious misgivings. They explained that the way the questions were framed gave misleading information about their level of disability, portraying them as mildly ill when they should have been in the severe group. For example, on the questionnaire one respondent ticked 'I can move completely independently' but wrote in the margins, "*I can move completely independently for a few metres but am basically too ill to use a standard wheelchair and am in bed 97% of the time.*" Another respondent wrote, "*The main problem is not so much with enacting something like feeding oneself, or climbing stairs. Problems arise with repetition and with delayed, post-exertional fatigue. The way you have laid out these questions cannot reflect 'how ill I am' and like the Benefits questionnaires which have caused many a ME sufferer to be denied benefit, they cannot elicit a true picture.*"

Another area of concern was with regard to personality testing. The instrument used, IPIP (Goldberg, 1999; Goldberg, 2001; IPIP, 2005), had not been validated for use by people with ME/CFS. The test was intended to reflect respondents' pre-morbid personality but did not assess this directly. Questions were in the past tense and respondents were instructed to think back to how they were in the year before they first became ill with ME/CFS. Many respondents found this difficult, especially for those who had been ill for years and decades, who had been children when they first became ill or whose illness had a gradual, non-specific onset. "*Having had ME for 6 years, it is sometimes difficult to remember what life was like as a "normal" person,*" one respondent wrote. When viewed retrospectively, the responses are undoubtedly affected by recall bias. Even with the best of intentions, the personality scores reflected respondents' current personality.

Personality tests are designed for well people and are meant to be completed rapidly. Instructions to score 135 statements in 15 minutes elicited useful feedback on the inappropriateness of these instructions for

people with ME/CFS. "*Do you seriously expect brain fogged people to do the personality questions in 15 minutes or less, to cope with things like the double negatives involved and to remember accurately what they were like pre ME*?" Multiple questions for each sub-domain were included for greater accuracy, but the cognitive dysfunction associated with ME/CFS, together with fatigue, may have contributed to inaccuracy.

The existence of a personality test in the questionnaire angered some people and may have contributed to the low response rate. Some of the comments made by respondents illustrate the strength of feeling about the role of personality in ME/CFS, e.g.: *"I hope no one answers this totally biased questionnaire. I have a physical illness!!!"* and *"I had hoped this old chestnut had been buried long since about perfectionist personality being a factor in severe ME. If any substance to it, then there would be a veritable epidemic of ME among chief executives and the driven personalities of the city."* This was no great surprise. There is widespread and deep-seated sensitivity among people with ME/CFS regarding suggestions that ME/CFS is primarily psychological in nature, to the extent that even to ask questions of this nature elicits antipathy, even though it is necessary to undertake research in this area if the hypotheses considered objectionable by people with ME/CFS are to be rejected.

Conclusion

Family history was a risk factor for severe ME/CFS. The strong association with having a mother with ME/CFS, but lack of association with having a father with the condition, is consistent with ME/CFS being associated with disturbed mitochondrial function. Being female was also a risk factor for severe disease. Early management of ME/CFS appeared also to be a major determinant of severity, with all but one of the variables in the final logistic regression model pertaining to the management of the condition in its early stages.

Personality type did not appear to constitute a risk factor for severe disease. There was an inverse association between neuroticism and severity, but none overall between conscientiousness and severity. Mean scores for neuroticism were consistently higher among mildly ill subjects than among the severely ill, which may indicate either that severely ill people may develop a degree of stoicism that affects their responses to

personality questionnaires, or that the mild category included some people whose illnesses were not ME/CFS at all, but other fatiguing conditions which may have been related to personality. There was no association overall of conscientiousness with severity, but, among the sub-domains of conscientiousness, self-efficacy and self-discipline were more marked among the severe cases, which may indicate that only the most motivated of severely ill people persevered to the end of the questionnaire.

The examination of possible associations with other pre-illness exposures and with biomedical factors was inconclusive, and more research is clearly needed in this area.

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