

Does prior psychiatric disorder predict chronic fatigue? Evidence from a national birth cohort study.

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Abstract

Objective

To test the hypothesis that individuals with self-reported chronic fatigue syndrome (CFS) or myalgic encephalomyelitis (ME) have increased rates of psychiatric disorder prior to the onset of their fatigue symptoms.

Design

Nested case control study within a longitudinal cohort study

Setting

Medical Research Council National Survey of Health and Development, a British national birth cohort

Participants and exposures

5362 participants prospectively followed over the first 53 years of their life with over 20 separate data collections. Various measures of personality, psychiatric disorder and energy levels were collected at ages 13, 15, 32, 36 and 43 years.

Main outcome measure

CFS or ME identified through self report during a semi-structured interview at age 53 years. The age at which these symptoms began was also recorded.

Results

34 (1.1%, 95% confidence interval 0.8 to 1.5%) of the 3035 participants assessed at age 53 years reported a diagnosis of CFS/ME. CFS/ME was more commonly reported by women. Those with a psychiatric disorder between the ages of 15 and 36 years reported increased rates of CFS/ME later in life with an odds ratio (adjusted for sex) of 2.62 (95% confidence interval 1.25 to 5.51, $p = 0.01$). Increased levels of psychiatric disorder were present prior to the occurrence of fatigue symptoms. There was a dose-response relationship between the severity of psychiatric symptoms and

the likelihood of later CFS/ME. Personality factors measured in childhood were not associated with a self reported diagnosis of CFS/ME.

Conclusions

Individuals who report a diagnosis of CFS/ME have increased rates of psychiatric disorder, in particular depression and anxiety, prior to the onset of their fatigue symptoms. This temporal, dose-response relationship suggests that psychiatric disorders, or shared risk factors for psychiatric disorders, are likely to have a role in the aetiology of CFS/ME.

Introduction

Fatigue is one of the most common presenting problems to primary care services in the United Kingdom and can have devastating effects on patient's quality of life.^{1 2} Chronic fatigue syndrome (CFS), or myalgic encephalomyelitis (ME), is characterised by severe persistent or relapsing fatigue, lasting six or more consecutive months, that is not relieved by rest, which can be accompanied by a number of other somatic and cognitive symptoms.³

Despite significant research interest, the aetiology of CFS/ME remains unclear.⁴ There has, however, been a consistent finding of a strong association between CFS/ME and psychiatric disorder found in numerous case control and cross sectional studies.⁵ Possible explanations for this relationship include psychiatric disorders occurring as a consequence of CFS/ME, psychiatric disorders having a causal role in the aetiology of CFS/ME or misdiagnosis and/or bias occurring within these studies.⁶ Differentiating between these possible explanations has not been possible due to the retrospective or cross-sectional nature of most previous research. Attempts have been made to investigate the temporal relationship between CFS/ME and psychiatric symptoms using prospective studies of fatigue following viral illness, however, the results in such studies have been inconclusive.⁷⁻⁹ Studies examining general practitioners' records revealed that those with CFS/ME had increased rates of GP consultation prior to their CFS/ME being diagnosed, but there did not appear to be increased rates of consultations relating to either depression or anxiety.¹⁰ However, the sampling and information bias inherent in such studies again limits the conclusions that can be drawn. Larger, population-based, prospective studies examining CFS/ME have been difficult due to the relatively low prevalence of this

outcome. Analysis of prospectively studied birth cohorts has shown that neither maternal nor childhood psychological disorders were associated with increased risk of CFS/ME as an adult.¹¹ Similar analysis of adult psychiatric disorder has not previously been possible.

In this study we have used the Medical Research Council National Survey of Health and Development, a British national birth cohort, to examine prospectively the relationship between prior psychiatric disorder and self reported CFS/ME. We aimed to test the hypothesis that individuals with CFS/ME would have increased rates of psychiatric disorder prior to the onset of their CFS/ME symptoms.

Methods

Study Design

Nested case control study within a national birth cohort study.

Sample

The Medical Research Council Survey of Health and Development was established in 1946. A random social class stratified sample of 5362 participants was selected from all single, legitimate births occurring in England, Wales and Scotland in one week of March 1946. This sample has been prospectively followed with over 20 separate data collections up to the age of 53 years. The sampling procedure and follow up has been described in detail elsewhere.¹²

Exposure

Psychiatric disorder was ascertained at several points in the adult life of the sample. At each follow up point participants were asked about any contacts with medical practitioners and about any hospital outpatient or inpatient treatments. If any hospitalisations were reported, the hospital was contacted and asked to provide details of the admission. This information was used to construct a summary of any psychiatric disorders that occurred between the ages of 15 and 32 years. Participants were assessed to either have no mental illness, trivial illness or more serious mental illness. More serious mental illness was defined as an illness with duration of more than one year; or which recurred more than four times; or that required care from a specialist mental health team.

At age 36 years, participants were visited at home and the 40-item version of the Present State Examination (PSE)¹³ was administered by a trained nurse interviewer.¹⁴ Psychiatric disorder was defined at a threshold level of ≥ 5 on the Index of Definition score,¹⁵ while the total PSE score was used as a measure of the severity of psychiatric symptoms.¹⁴

Aged 43 years, participants were again visited at home and interviewed by trained nurses using the Psychiatric Symptom Frequency scale (PSF).¹⁶ The PSF is an 18 item scale measuring psychiatric symptoms, particularly of depression and anxiety, over the last year. A cut off score of ≥ 14 was used to define psychiatric disorder.¹⁶

At ages 36 and 43 years, participants were also asked if they, or either of their parents, had ever had “nervous or emotional trouble or depression”. Participants’ mothers

were also asked about a family history of “nerves” in 1961. At age 13 years, participants completed a Pintner Personality Inventory.¹⁷ This inventory requires the child to read 114 statements and then mark themselves as “same” or “different”. It provides a measure of the child’s personality along the spectrums of neuroticism and introversion/extroversion.

Socio-demographic details including gender, father’s social class (in 1961), participant’s social class (at age 53 years) and participant’s educational level were also obtained. Social class was derived from participant’s occupation using the Registrar General’s classification,¹⁸ while highest education level achieved was coded using the Burnham classification. Participant’s body mass index was calculated using weight and height measurements taken by nursing staff during home visits.

Outcome

At age 53 years, participants were again interviewed at home by trained nurses. During this semi-structured interview they were asked if they had ever been diagnosed with chronic fatigue syndrome (CFS) or myalgic encephalomyelitis (ME). If so, they were asked at what age this problem had began. Hospital records were reviewed for all participants who reported suffering from CFS/ME. If these indicated any psychotic or serious medical disorder that would invalidate the diagnosis of chronic fatigue syndrome then they were excluded from further analysis. In line with CDC diagnostic criteria for CFS/ME those with severe obesity (body mass index greater than 45) were also excluded.³ As we aimed to investigate predisposing factors, any participants who reported CFS/ME symptoms beginning prior to the age

of 44 years were excluded from the analysis of measures collected at the age of 43 years.

In order to address the issue of early chronic fatigue syndrome being misdiagnosed as a psychiatric disorder, measures of participants' energy levels were taken at ages 15, 36 and 43 years. Reports of energy levels at age 15 were given by the participants' teachers while at age 36 and 43 years they were self reported.

Statistical Analysis

Statistical analysis was performed using STATA computer software.¹⁹ Differences between those with chronic fatigue syndrome and the remainder of the sample interviewed at age 53 were initially explored using univariate analysis. Logistic regression analysis was then used to calculate odds ratios corrected for known socio-demographic confounders, such as gender.

Results

At age 53 years, 3035 of the original participants were interviewed. After exclusion of those who had died, moved abroad or had been permanent refusers this indicated a follow up rate of 83%. Analysis reported elsewhere has shown the sample at age 53 years to remain representative of the national population.¹²

At age 53, 37 (1.2%) of the sample reported a diagnosis of CFS/ME. Hospital admission notes for these participants revealed that two had serious medical conditions and one had a psychotic disorder that required them to be excluded from further analysis. After these exclusions the lifetime prevalence estimate for CFS/ME

was 1.1 % (95% confidence interval 0.8 to 1.5%). The age that participants reported their fatigue symptoms beginning varied between 41 and 53 years. Table 1 shows the associations between socio-demographic factors and a diagnosis of CFS/ME. Women were more likely to report a diagnosis of CFS/ME, but neither social class nor educational levels were associated with the diagnosis.

The relationships between prior psychiatric disorder measures and a later diagnosis of CFS/ME are shown in table 2. At each psychiatric assessment between ages 15 and 43 years there was a trend towards increased levels of psychiatric disorder in those who later developed CFS/ME. Analysis of the PSE subscale scores, obtained at age 36 years, revealed that those who were later diagnosed with CFS/ME had significantly raised scores in the depressed mood, generalised anxiety and tension subscales. Seven of the participants who reported CFS/ME at age 53 years reported their CFS/ME symptoms beginning between the ages of 41 and 43 years, and thus were not included in the analysis involving psychiatric disorder measures at age 43 years. Their exclusion caused a reduction in the power of these analyses. Table 3 displays measures of energy and fatigue taken at different ages and the relationships between these and a later diagnosis of CFS/ME. At age 36 years there was no difference in the levels of self-reported activity, but there was a non significant trend towards lower levels of energy in those who later went on to develop CFS/ME. Despite this, only three of the patients who later reported a diagnosis of CFS/ME scored highly (above the median) on the lack of energy PSE subscale, indicating that the majority were not suffering significant fatigue at age 36 years. However, by the age of 43 years, those who were later to be diagnosed with CFS/ME were beginning to report significantly more fatigue than the rest of the sample, suggesting measures of

psychiatric disorder taken at this age may not represent true preceding psychiatric disorder. Combining the various measures of psychiatric disorder taken up to the age of 36 years produced an odds ratio (adjusted for sex) for a later diagnoses of CFS/ME in those with any prior psychiatric disorder of 2.62 (95% confidence interval 1.25 to 5.51, $p=0.01$).

In order to investigate the dose-response relationship between prior psychiatric symptoms and a later diagnosis of CFS/ME, the total PSE score at age 36 was used to construct odds ratios (adjusted for sex) for a diagnosis of CFS/ME at age 53years. This is demonstrated in figure 1.

The relationships between childhood personality measures, parental psychiatric disorder and a later diagnosis of CFS/ME are shown in table 4. Childhood personality did not have any impact on the later risk of CFS/ME, but reports of parental psychiatric disorder were associated with increased rates of later CFS/ME.

Discussion

Principal Findings

The prospective nature of this study allowed us to examine the temporal relationship between psychiatric disorder and CFS/ME. Those who report a diagnosis of CFS/ME had increased levels of psychiatric disorder, in particular depression and anxiety, prior to the onset of fatigue symptoms. Those with a psychiatric disorder in early adult life were around two and a half times more likely to report a diagnosis of CFS/ME later in life.

Possible Causal Pathways

Up to the age of 36 years those who later went on to develop CFS/ME did not have significant differences in their levels of energy or fatigue, suggesting that misdiagnosis of early fatigue symptoms as a psychiatric disorder is not a likely explanation for these results. The temporal, dose-response relationship demonstrated provides evidence for psychiatric disorders having a causal role in the aetiology of CFS/ME. Alternatively, our results may be explained by psychiatric disorders and CFS/ME sharing common vulnerability factors. A recent study using the Swedish Twin Registry demonstrated that those who reported higher levels of stress in their early adult life were at increased risk of developing a chronic fatiguing illness.²⁰ It may be that persistent stress, or the perception of persistent stress, are shared risk factors for both psychiatric disorder and CFS/ME. Personality traits are another potential shared risk factor, but our findings suggest that these are not an independent risk factor for CFS/ME. Other studies have found an association between CFS/ME and personality factors such as emotional instability²⁰ and Cluster C personality traits²¹ suggesting this is an area that requires further investigation.

Strengths and Limitations

The strengths of this study include its large size and its prospective nature. The high follow up rate and the sample's generalisability to the British population are also strengths. Both females and those with a history of psychiatric illness in early life were more likely to be followed up at age 53 years, although this did not affect the overall representativeness of the sample.¹²

While the use of self-reported CFS/ME is the main limitation of this study, it may also provide some benefits. Fatigue is a subjective experience that is difficult to define and therefore difficult to measure.²² At present there is no accepted standardised interview for diagnosing CFS/ME in the community with self reported levels of fatigue remaining at the core of the diagnostic criteria.³ Any attempt to use more structured diagnostic interviews may fail to capture the phenomena of patients who complain of fatigue in a clinical setting. In examining those who report a diagnosis of CFS/ME we have studied both those who have been given a diagnosis of CFS/ME by the medical profession and those who have self diagnosed. This method is likely to have a high degree of clinical and face validity. Clinical experience suggests that it is uncommon for a patient to complain of chronic fatigue syndrome (CFS) or myalgic encephalomyelitis (ME) and to not have sufficiently severe symptoms to warrant the diagnosis. The use of self-reported diagnosis is therefore most likely to have caused an under-ascertainment of cases and, provided this misclassification was random, will have reduced the associations we report. This assumption is supported by our prevalence estimate being lower than previous estimates of broadly defined chronic fatigue states,²³ while being higher than that reported in studies using stricter diagnostic criteria.^{24 25} The use of self-reported diagnosis is also supported by post hoc analysis showing that the association between prior psychiatric disorder and a diagnosis of CFS/ME remained when patients who had not received their diagnosis of CFS/ME from a doctor were excluded.

Another potential limitation of this study is that our findings are restricted to those who reported CFS/ME at age 53 years. However, given that community based studies

have found the prevalence of CFS/ME to peak between ages 50 and 59 years²⁵ the use of CFS/ME at age 53 years is not unreasonable.

Conclusions

Those who report a diagnosis of CFS/ME have increased rates of psychiatric disorder prior to the onset of their fatigue symptoms. When present, this psychiatric disorder typically appears to be depression or anxiety. While further studies are needed to investigate possible shared vulnerability factors including personality traits and stress, it seems likely that psychiatric disorders, or risk factors for these disorders, play a role in the multi-factorial aetiology of CFS/ME. An increased understanding regarding the roles of these factors in the aetiology of CFS/ME will hopefully provide guidance on the prevention and treatment of this debilitating and stigmatised condition.

“What this paper adds” Box

What is already known on this subject

Previous studies have demonstrated increased rates of psychiatric disorder in those diagnosed with chronic fatigue syndrome (CFS), or myalgic encephalomyelitis (ME). However, it has not been possible to determine whether increased levels of psychiatric disorder were present prior to CFS/ME developing or whether they occurred in response to the distress of fatigue symptoms.

What this study adds

This large, prospective study shows that those who report a diagnosis of CFS/ME were more likely to have a psychiatric disorder prior to their fatigue symptoms developing. There is a dose-response relationship between the severity of psychiatric symptoms in early adult life and the risk of a later diagnosis of CFS/ME.

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Competing Interest Statement

All authors declare that the answer to the questions on your competing interest form bmj.com/cgi/content/full/317/7154/291/DC1 are all No and therefore have nothing to declare

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Contributors

MH, SW, and MW conceptualised and planned this study. MW co-ordinated the data collection and retrieval. SH and MH carried out the statistical analysis. SH wrote the paper with MH, SW and MW providing detailed comments on early drafts. MH is guarantor for this paper.

Ethical Approval

Ethical approval was given by the London area multi-centre research ethics committee for the data collection at age 53 years. Cohort members gave informed consent for each assessment. Ethical approval and consent procedures at earlier ages conformed to contemporary best practice.

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Table 1: socio-demographic variables and unadjusted odds ratios (95% confidence intervals) for lifetime risk of CFS.

Age	Variable	Number of subjects	Lifetime diagnosis of CFS (%) [†]	Unadjusted odds ratio (95% CI)	p value
Birth	Gender				
	Male	1467	0.68	1.00	0.02
Female	1516	1.58	2.34 (1.12 to 4.92)		
15yrs	Father's social class				
	Manual	1582	1.01	1.00	0.33
Non-manual	1274	1.41	1.40 (0.71 to 2.76)		
53 yrs	Subject's social class				
	Manual	906	0.88	1.00	0.74
Non-manual	1869	1.02	1.15 (0.50 to 2.64)		
53 yrs	Subject's educational level				
	Below O level	1246	1.28	1.00	0.51
O Level or above	1571	1.02	0.79 (0.39 to 1.59)		

[†] expressed as a percentage of those exposed

Table 2: Prior psychiatric disorder measures and adjusted odds ratios (95% confidence intervals) for a later diagnosis of CFS

Age	Variable	Number of subjects	CFS diagnosed after this age (%) [†]	Adjusted Odds Ratio ^{††} (95% CI)	p value
32 yrs	Psychiatric disorder between ages 15 and 32 years				
	None	1678	0.95	1.00	0.07 (trend)
	Trivial	1040	1.15	1.22 (0.58 to 2.59)	
Serious	195	3.08	2.80 (1.07 to 7.32)		
36 yrs	Self reported depression, nervous or emotional troubles				
	No	2410	0.95	1.00	0.02
Yes	286	2.80	2.64 (1.16 to 6.01)		
	Psychiatric Disorder (using PSE)				
	No	2515	0.99	1.00	0.009
Yes	161	3.73	3.38 (1.35 to 8.42)		
43 yrs	Self reported depression, nervous or emotional troubles				
	No	2222	0.77	1.00	0.07
Yes	566	1.77	2.08 (0.94 to 4.60)		
	Psychiatric Disorder (using PSF)				
	No	1973	0.76	1.00	0.14
Yes	809	1.48	1.79 (0.83 to 3.86)		

† expressed as a percent of those exposed

†† adjusted for sex

Table 3: Measures of energy and fatigue and adjusted odds ratios (95% confidence intervals) for a later diagnosis of CFS

Age	Variable	Number of subjects	CFS diagnosed after this age [†]	Adjusted Odds Ratio ^{††} (95% CI)	p value
15 yrs	Teacher's report of energy levels				
	Always tired	160	2 (1.25)	1.00	0.51 (trend)
	Normal	2209	22 (1.00)	0.88 (0.20 to 3.78)	
Extreme energy	153	32 (1.96)	1.73 (0.28 to 10.54)		
36 yrs	Self reported sports or vigorous leisure activities				
	None	982	13 (1.32)	1.00	0.74 (trend)
	1-4 times a month	684	4 (0.58)	0.47 (0.15 to 1.45)	
4+ times a month	1027	14 (1.36)	1.13 (0.53 to 2.44)		
	Lack of energy syndrome score (PSE subscale)				
	Low score	2559	28 (1.09)	1.00	0.23
	High score	117	3 (2.56)	2.09 (0.62 to 7.03)	
43 yrs	Asked if there are days they tire out easily				
	Never - sometimes	2377	18 (0.76)	1.00	0.02
	Often - always	406	9 (2.22)	2.59 (1.14 to 5.89)	

[†] Number of subjects diagnosed with CFS/ME (percent of those exposed in parenthesis)

^{††} adjusted for sex

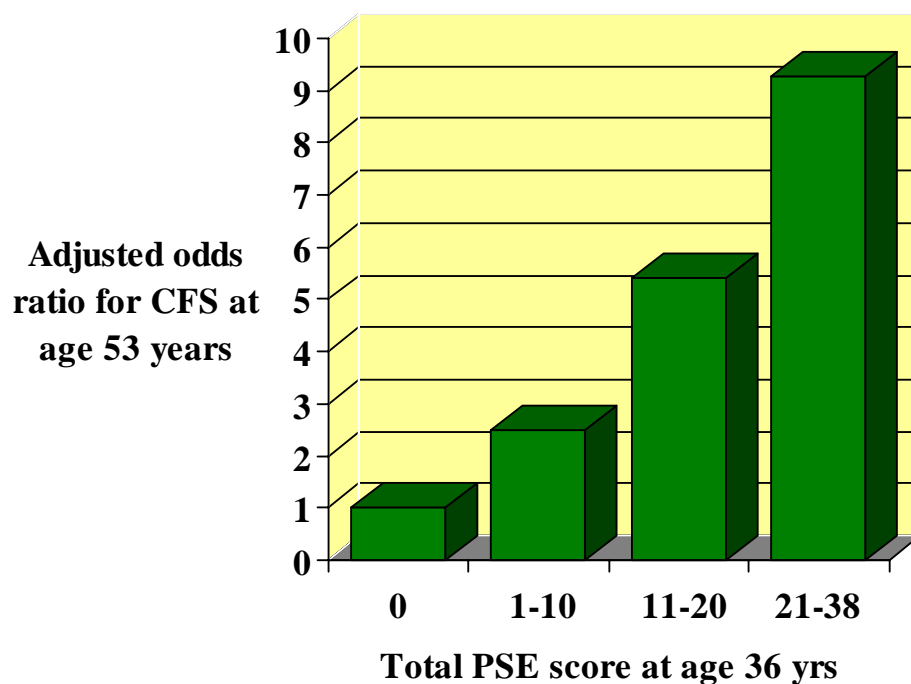
Table 4: Measures of personality and parental psychiatric disorder with adjusted odds ratios (95% confidence intervals) for a later diagnosis of CFS

Age	Variable	Number of subjects	CFS diagnosed after this age (%)[†]	Adjusted Odds Ratio^{††} (95% CI)	p value
13 yrs	Neuroticism on Pintner scale				0.59 (trend)
	Non-neurotic	874	1.14	1.00	
	Mid-neurotic	789	1.39	1.05 (0.44 to 2.51)	
13 yrs	Neurotic	479	0.93	0.75 (0.29 to 2.00)	0.67 (trend)
	Extroversion on Pintner scale				
	Introvert	727	1.38	1.00	
Up to 43 yrs	Ambivert	812	1.11	0.84 (0.33 to 2.08)	0.048
	Extravert	873	1.03	0.82 (0.33 to 2.03)	
	Either parent ever being reported as suffering from a psychiatric disorder				
	No	1740	0.80	1.00	0.048
	Yes	906	1.77	2.07 (1.01 to 4.28)	

† expressed as a percent of those exposed

†† adjusted for sex

Figure 1: Total PSE score at age 36 and odds ratios (adjusted for sex) for a later diagnosis of CFS



Age	Variable	Number of subjects	CFS diagnosed after this age [†]	Adjusted Odds Ratio ^{††}
36 yrs	Total PSE score			
	0	1273	0.55	1.00
	1-10	1269	1.50	2.50 (1.04 to 6.01)
	11-20	117	3.42	5.43 (1.55 to 19.10)
	21-38	17	5.88	9.27 (1.06 to 80.83)

[†] expressed as a percent of those exposed

^{††} adjusted for sex

p value for trend = 0.002