Mortality of people with chronic fatigue syndrome: a retrospective cohort study in England and Wales from the South London and Maudsley NHS Foundation Trust Biomedical Research Centre (SLaM BRC) Clinical Record Interactive Search (CRIS) Register

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Summary

Background Mortality associated with chronic fatigue syndrome is uncertain. We investigated mortality in individuals diagnosed with chronic fatigue syndrome in secondary and tertiary care using data from the South London and Maudsley NHS Foundation Trust Biomedical Research Centre (SLaM BRC) Clinical Record Interactive Search (CRIS) register.

Methods We calculated standardised mortality ratios (SMRs) for all-cause, suicide-specific, and cancer-specific mortality for a 7-year observation period using the number of deaths observed in SLaM records compared with age-specific and sex-specific mortality statistics for England and Wales. Study participants were included if they had had contact with the chronic fatigue service (referral, discharge, or case note entry) and received a diagnosis of chronic fatigue syndrome.

Findings We identified 2147 cases of chronic fatigue syndrome from CRIS and 17 deaths from Jan 1, 2007, to Dec 31, 2013. 1533 patients were women of whom 11 died, and 614 were men of whom six died. There was no significant difference in age-standardised and sex-standardised mortality ratios (SMRs) for all-cause mortality (SMR 1·14, 95% CI 0·65–1·85; p=0·67) or cancer-specific mortality (1·39, 0·60–2·73; p=0·45) in patients with chronic fatigue syndrome when compared with the general population in England and Wales. This remained the case when deaths from suicide were removed from the analysis. There was a significant increase in suicide-specific mortality (SMR 6·85, 95% CI 2·22–15·98; p=0·002).

Interpretation We did not note increased all-cause mortality in people with chronic fatigue syndrome, but our findings show a substantial increase in mortality from suicide. This highlights the need for clinicians to be aware of the increased risk of completed suicide and to assess suicidality adequately in patients with chronic fatigue syndrome.

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Introduction

Chronic fatigue syndrome is an illness characterised by persistent or relapsing fatigue of a debilitating nature, which is present for at least 6 months, in addition to at least four symptoms from a range including memory loss, poor concentration, joint pain, and tender glands.[1,2] Patients with chronic fatigue syndrome usually have extensive investigations to ensure any potential treatable medical causes of fatigue are addressed. By definition, at diagnosis, individuals with chronic fatigue syndrome are free of prespecified major medical and psychiatric disorders leading to prolonged fatigue, and therefore might be expected to have a mortality risk similar to, or indeed lower than, the general population.[1–3]

Although claims have been made on the basis of small, uncontrolled, clinical case series of higher overall death risks for heart failure, cancer, and suicide in people with chronic fatigue syndrome,[4,5] a review of descriptive studies that reported follow-up or outcome data from patients with a primary diagnosis of chronic fatigue syndrome showed no convincing evidence of increased all-cause mortality or suicide-specific mortality.[6] Specifically, only one study has compared the mortality within a cohort of individuals with chronic fatigue syndrome (n=641) with that of the general population,[7] and reported no significant increase in all-cause mortality adjusted for sex, race, age, and calendar time (standardised mortality ratio [SMR] 0·7, 95% CI 0·4–1·2; 14 deaths). Although the relative risk of suicide was raised in this cohort (SMR 3·6, 95% CI 0·4–12·9; two deaths), limited statistical power made it difficult to draw conclusions about excess suicide risk in people

Research in context

Evidence before this study

We searched Embase, MEDLINE, and PsycINFO for all studies published from database inception to April 1, 2015, using the following search terms: ["mortalit*" and ("chronic fatigue syndrome" or "chronic-fatigue syndrome" or "CFS" or "post-viral fatigue syndrome" or "post viral fatigue syndrome" or "CFS/ME" or "ME/CFS" or "myalgic encephalomyelitis" or "myalgic encephalomyelopathy")]. We initially assessed the titles and abstracts identified by the search and excluded articles that were deemed not relevant. We reviewed the full text of the remaining articles for inclusion, and all relevant references were checked for additional citations. We included studies that compared mortality in individuals with chronic fatigue syndrome with that of controls without the disorder.

The search process identified 121 unique records. We assessed three full text articles for eligibility and included one study comparing the mortality of individuals with chronic fatigue syndrome with that of a general population control. The results suggested no increased all-cause or suicide-specific mortality in 641 individuals with chronic fatigue syndrome (standardised mortality ratios [SMRs] 0·7, 95% CI 0·4–1·2 and 3·6, 0·4–12·9, respectively); however, the study was limited by its small sample size, with both all-cause and suicide-specific mortality outcomes receiving a GRADE rating of very low quality evidence. As such whether chronic fatigue syndrome is associated with a differing mortality compared with the general population remains unknown.

Added value of this study

We report the largest study of mortality in patients with chronic fatigue syndrome available so far, with 2147 individuals diagnosed with chronic fatigue syndrome. Our findings showed that although the overall and cancer-specific mortality of patients with chronic fatigue syndrome was not significantly different to that of the general population, we noted an increased risk of completed suicide in patients with chronic fatigue syndrome when compared with a population control. Individuals with a diagnosis of chronic fatigue syndrome and a lifetime diagnosis of depression might be at increased risk of completed suicide.

Implications of all the available evidence

The evidence highlights the need for clinicians to be aware of the increased risk of completed suicide and to assess suicidality adequately in patients with chronic fatigue syndrome. Future studies should focus on identification of protective measures that can reduce suicide-related mortality in patients with chronic fatigue syndrome.

with chronic fatigue syndrome. By contrast, anecdotal accounts in various internet and patient forums repeatedly report increased all-cause mortality.[8,9]

Mortality associated with chronic fatigue syndrome remains uncertain, and larger studies are needed to further address the issue of chronic fatigue syndrome as a risk factor for all-cause and specific causes of mortality. Therefore, we investigated a retrospective cohort consisting of people diagnosed with chronic fatigue syndrome, using data from the national research and treatment service for chronic fatigue at the South London and Maudsley NHS Foundation Trust (SLaM) and King's College London Hospital (KCH).

Method

Setting and study population

The cohort of patients assessed in this study was assimilated from the Clinical Record Interactive Search (CRIS),[10] a case register system that provides de-identified information from electronic clinical records relating to secondary and tertiary mental health care services across SLaM. SLaM is a National Health Service (NHS) mental health trust that provides secondary mental health care to a population of roughly 1·3 million residents of four London boroughs (Lambeth, Southwark, Lewisham, and Croydon), and additionally in collaboration with King's College Hospital (KCH), provides a single secondary and tertiary care national referral service for individuals with suspected chronic fatigue syndrome, accepting referrals from general practitioners, general and specialist physicians, occupational physicians, consultant psychiatrists, and community mental health teams. As is the system in the NHS in England and Wales, all referrals need to be approved by the local clinical commissioning groups before they can be seen at the service.

Electronic clinical records have been used comprehensively across all SLaM services since 2006. CRIS was established in 2008 to allow searching and retrieval of full but de-identified clinical information for research purposes with a permission of secondary data analysis, approved by the Oxfordshire Research Ethics Committee C (reference 08/H0606/71+5).[10]

The chronic fatigue syndrome service follows a routine assessment procedure, in which all patients undergo medical screening to exclude detectable organic illness, including a minimum of physical examination, urinalysis, full blood count, urea and electrolytes, thyroid function tests, liver function tests, tissue transglutaminase, and erythrocyte sedimentation rate. Patients were interviewed with a semi-structured diagnostic interview to establish whether they had fatigue and whether they met the 1994 case definition or Oxford criteria for chronic fatigue syndrome.[1,11,12] Additionally, we had information about whether patients fulfilled chronic fatigue syndrome criteria as defined by the National Institute of Health and Care Excellence (NICE).[13] Patients with the 1994 case

definition-specified exclusionary psychiatric disorders and also somatisation disorder (DSM-IV) were excluded from this study. For this study we adopted the most inclusive criteria, and thus included all patients with a clinical diagnosis of chronic fatigue syndrome. A subsample of 755 patients had full diagnostic criteria applied prospectively of which 65% met Oxford criteria, 58% the 1994 case definition criteria, and 88% NICE criteria. All patients in this sample met at least one criterion. All were clinic attendees referred within the UK NHS and have been shown to be a representative sample of patients with chronic fatigue syndrome in secondary and tertiary care, similar to those in Australia, the USA, Scotland, England, and Northern Ireland.[14–16]

Study participants were included if they had had contact with the chronic fatigue service (referral, discharge, or case note entry) and received a diagnosis of chronic fatigue syndrome from Jan 1, 2007, to Dec 31, 2013.

Anyone who was active as a patient with chronic fatigue syndrome or newly diagnosed as a patient with chronic fatigue syndrome at any point of this period was followed up until their death or the end of the observation period. The diagnosis was ascertained from having received the prespecified clinic code for a chronic fatigue syndrome diagnosis, which was the ICD-10 code for neurasthenia (F48.0) in structured fields within CRIS, and was supplemented by a bespoke natural language processing application developed at SLaM using General Architecture for Text Engineering (GATE) software, which extracts and returns diagnostic statements from open-text fields of the source electronic health records.[17] We emphasise that we do not use the category or criteria for neurasthenia in either our clinical or research practice—it is just a computer code imposed by our data or financial management systems that run across the trust and which are based on the ICD-10.

Mortality identification

The analysis outcome is mortality over a 7-year observation window (2007–13, the at-risk period). In each NHS trust, a list of deceased people is obtained on a monthly basis from the "Service User Death Report" of "the Spine", maintained by NHS Care Records Service.[18] Therefore, the date of death of each deceased patient ever served by SLaM is recorded. Further routine checking occurs for details, including the cause of death, which were retrieved from the diagnosis (1a) in death certificate via linkage with nationwide data from the UK Office of National Statistics, and classified by code of the 10th edition of the WHO International Classification of Diseases (ICD-10). ICD-10 codes for cause of death were searched and ascribed to malignant neoplasm (ICD-10 codes: C00-97), suicide (ICD-10 codes: X60-84), or other causes.

Covariates in analysis

Date of birth, sex, and ethnic origin were routinely recorded in NHS medical records. For the classification of age bands, the index date was set as July 1, 2010 (ie, the mid-point of the at-risk period), or at death, whichever came first, to define age. Ethnic group was divided into four categories: white, black, Asian, and mixed, unknown, or other. Presence of a lifetime diagnosis of depression was defined as having had a recorded depressive episode (ICD-10 code: F32.x) or recurrent depressive disorder (F33.x). Multiple deprivation score (or the indices of multiple deprivation), a measure of socioeconomic status developed by the UK Office of National Statistics, which combines various indicators to include a range of economic, social, and housing dimensions into one deprivation score for each small area in the UK, was also available for analysis.[19]

Statistical analysis

SMRs were calculated for the cohort of patients with chronic fatigue syndrome during the 7-year observation period, using number of deaths observed in SLaM records as the numerator. The denominator was the expected number of deaths, estimated by 5-year age bands, and sex-specific mortality rates for the England and Wales population in 2011 multiplied by the weighting of average person-years in the at-risk period experienced by chronic fatigue syndrome patients in each age and sex category.[20] We also did stratified analyses of SMRs by splitting the target population into groups for ethnic category, presence or absence of a lifetime diagnosis of depression, and tertiles of multiple deprivation scores. Focusing on suicide-related mortality of particular interest, we adapted competing risk regression, a modified Cox modelling method developed by Fine and Gray[21] for univariate and multivariate analysis, with suicide-specific deaths as the target events and other causes of death as competing outcomes. Subhazard ratios and their 95% CIs were thus generated with the existence of lifetime diagnosis of depression as the major exposure of interest. This time-to-event analysis method accounts for the fact that cohort members are subject to various potential competing causes of death, which might occur ahead of the specific cause of interest. The main purpose of the modification of the Cox model was to discriminate censoring between deaths from other causes and end of follow-up or loss to follow-up to have a better estimation of relative risk on the specific event of interest (suicide-specific mortality) within the chronic fatigue syndrome cohort. We regarded age and sex as potential confounders in the multivariate analysis. Tertile of multiple deprivation score and ethnic origin were too extreme (because no one died in some smaller categories) to be imputed as potential confounders in multivariate analysis. All analyses were done by STATA SE (version 12) and the significance level was set as 0·05.

	All-cause mortality				Suicide-related mortality				Cancer-related mortality			
	Observed deaths	SMR	95% CI	p value	Observed deaths	SMR	95% CI	p value	Observed deaths	SMR	95% CI	p value
All (n=2147)	17	1·14	0·65–1·85	0·67	5	6·85	2·22–15·98	0·002*	8	1·39	0·60–2·73	0·45
Men	6	1·14	0·42–2·48	0·86	2	4·83	0·58–17·44	0·13	2	1·15	0·14–4·16	1·00
Women	11	1·14	0·55–2·10	0·75	3	9·49	1·96–27·75	0·009*	6	1·49	0·55–3·24	0·44
White†	16	1·44	0·82–2·34	0·20	5	9·12	2·96–21·27	<0·0001*	7	1·09	0·36–2·55	0·96
With lifetime depression diagnosis	4	2·44	0·66–6·24	0·17	2	3·06	0·37–11·07	0·28	1	0·22	0·01–1·22	0·11
Without lifetime depression diagnosis	13	1·05	0·56–1·79	0·94	3	4·57	0·94–13·36	0·06	7	1·37	0·55–2·82	0·51
Lower MDS tertile‡	6	1·34	0·49–2·92	0·58	2	8·96	1·08–32·35	0·04*	2	1·08	0·13–3·90	1·00
Middle MDS tertile‡	8	1·78	0·77–3·51	0·17	2	8·75	1·06–31·61	0·045*	5	2·67	0·87–6·23	0·08
Upper MDS tertile‡	2	0·44	0·05–1·60	0·34	0	..	..	..	1	0·55	0·01–3·08	1·00

SMR=standardised mortality ratio. MDS=multiple deprivation score. *p<0·05. †All the patients who died were white. ‡Tertile of MDS (or the indices of multiple deprivation) a measure of socioeconomic status developed by the UK Office of National Statistics that combines various indicators to include a range of economic, social, and housing dimensions into one deprivation score. 64 patients had missing MDS values of whom one died from suicide and was excluded from the analysis.

Table 1: **Age-standardised and sex-standardised mortality ratios of all-cause, suicide-related, and cancer-related mortality in patients with chronic fatigue syndrome, compared with the general population in England and Wales in 2011**

Role of the funding source

The funders had no role in study design; in the collection, analysis, or interpretation of data; in the writing of the report; or in the decision to submit the paper for publication. ER and C-KC had full access to all the data in the study and all authors had final responsibility for the decision to submit for publication.

Results

We identified 2147 cases of chronic fatigue syndrome in CRIS with 17 deaths. Of them, 1533 patients were women of whom 11 died, and 614 were men of whom six died. Eight deaths were from malignant neoplasm, five from suicide, and four from other causes.

There was no significant difference in age-standardised and sex-standardised mortality ratios for all-cause mortality (SMR 1·14; 95% CI 0·5–1·85; p=0·67) or cancer-related mortality (1·39; 0·60–2·73; p=0·45). This remained the case when stratified by sex, and when those deaths from external causes were removed from the analysis. However, there was a significant increase in suicide mortality with an SMR of 6·85 (95% CI 2·22–15·98; p=0·002; table 1). Although the suicide-specific SMR was significantly increased compared with the general population, if there had been two fewer deaths by suicide, this result would have been non-significant, although the effect size (SMR>4) would still be indicative of a strong effect. Table 1 shows detailed SMRs for the study cohort.

1583 patients were white, 93 black, 48 Asian, and 423 other, mixed or unknown ethnic origin (table 2). One patient who died from cancer had a missing ethnicity value and was excluded from the analysis. All other patients who died were white. When restricted to only include white patients, there remained no significant difference in age-standardised SMR for all-cause mortality (SMR 1·44, 95% CI 0·82–2·34; p=0·20) or cancer-specific mortality (1·09, 0·36–2·55; p=0·96; table 1). Suicide-specific mortality remained significantly elevated (9·12, 2·96–21·27; p<0·0001).

	All patients with chronic fatigue syndrome (n=2147)	Patients with chronic fatigue syndrome who died (n=17)
Mean age (years)	39·1	48·3
Women	1533	11
Men	614	6
White	1583	16
Black	93	0
Asian	48	0
Mixed, other, or unknown	423	1
Documented lifetime diagnosis of depression	216	4

Table 2: **Baseline characteristics**

When stratified by lifetime diagnosis of depression, 216 patients had a recorded lifetime diagnosis of F32.x or F33.x. Four (26%) of 17 patients who died had a lifetime diagnosis of depression, for two of whom the cause of death was suicide. No significance was identified for all-cause (SMR 2·44, 95% CI 0·66–6·24; p=0·17), suicide-specific (3·06, 0·37–11·07; p=0·28), or cancer-specific mortality (0·22, 0·01–1·22; p=0·11) by the presence of lifetime diagnosis of depression.

The mean multiple deprivation score (MDS) was 22·4% (SD 12·4), suggesting that the average patient in our cohort lived in less deprived areas than 78% of the UK population. 64 (3%) of 2147 patients had missing MDS values of whom one died from suicide and was excluded from the analysis. There was no significant difference in age-standardised

	Univariate analysis			Multivariate analysis*		
	Subhazard ratio	95% CI	p value	Subhazard ratio	95% CI	p value
Age	1·01	0·97–1·06	0·67	1·01	0·96–1·05	0·83
Sex	2·57	0·37–17·89	0·34	2·63	0·37–18·71	0·33
Lifetime diagnosis of depression	9·57	1·34–68·13	0·02	9·61	1·44–64·21	0·02

*Age and sex were controlled as confounders in multivariate analysis.

Table 3: **Univariate and multivariate analysis outcomes for risk factors of suicide mortality by competing risk regressions in patients with chronic fatigue syndrome (n=2174)**

and sex-standardised SMRs for all-cause or cancer-related mortality in any tertile of the MDS. Suicide-specific mortality remained significantly increased in the lower (SMR 8·96, 95% CI 1·08–32·35; p=0·04) and middle (8·75, 1·06–31·61; p=0·045) MDS tertile. There were no deaths from suicide in the upper MDS tertile (table 1).

With regards to the outcomes of competing risk regression using the significantly increased suicide-related mortality as the specific event of interest, univariate analyses showed that women with chronic fatigue syndrome had a highly raised but not significant relative risk of death from suicide-specific causes (subhazard ratio 2·57; 95% CI 0·37–17·89; p=0·34). Patients with a lifetime diagnosis of depression had a high risk of dying from suicide (subhazard ratio 9·57; 95% CI 1·34–68·13; p=0·02). The result remained significant when age and sex were controlled as confounders (9·61, 1·44–64·21; p=0·02; table 3).

Discussion

Although the all-cause and cancer-specific mortality of patients with chronic fatigue syndrome in specialist care was not significantly different to that of the general population, the risk of suicide was higher. This is the first study to show a specific increased risk of suicide in a population of patients with chronic fatigue syndrome compared with the general population; however, if there had been two fewer deaths by suicide, this risk would not be significantly increased.[22]

There are limitations to our data including that, despite being the largest study of mortality in chronic fatigue syndrome available so far, the sample size is still modest. The all-cause mortality gave an estimation of SMR close to 1, and the study had insufficient statistical power to identify such a small effect size with a wide confidence interval. The SMR for suicide is greatly increased and although the estimate is imprecise, it is highly unlikely that the result is due to chance. The modest sample size limited our ability to explore other cause-specific mortality, or the effect of chronic fatigue syndrome on mortality in subgroups of patients. In view of the observational nature of the study design, and the limited number of confounders measured and controlled, it is possible that the findings are a result of confounding. For example, because we relied on population mortality rates, we were unable to control for smoking, BMI, and a range of chronic diseases that might affect mortality risk. Although the joint chronic fatigue syndrome service offered by SLaM and KCH is a national referral service, more than 80% of patients in the cohort were resident in the south of England, and as such national mortality statistics may not be representative of this region. However, previous work to establish sensitivity between mortality in "England and Wales" and London concluded there was no significant difference between the mortality estimates.[18] We also accept that the cohort is quite young and it might, at least theoretically, be possible that differential mortality rates could have emerged after the 7-year observation window.

Patients concerned by ongoing fatigue symptoms might not wish to be referred to mental health services or be assessed by a psychiatrist. Reasons for this are multifactorial but include the perceived stigma of psychological and rehabilitation treatment, and some patients' views that the cause of their symptoms is biological precludes any form of psychological treatment. Because the referral pathway for this centre includes a full assessment including a psychiatric evaluation, an argument could be made that cases referred to the joint SLaM and KCH service may not be representative of chronic fatigue syndrome cases seen in secondary and tertiary care, and may include a referral bias, favouring patients with more severe chronic fatigue syndrome, psychiatric comorbidity, and higher socioeconomic status. However, the study sample has previously been shown to be typical of secondary and tertiary care cases in the UK and internationally.[15] We recognise the sample might not be generalisable to primary-care or community-based samples of patients with chronic fatigue syndrome,[14,23] or generalisable to health-care settings in which services are not free to consumers. However, due to the no-cost setting, we are more likely to capture a broad coverage of source population when compared with insurance-based national services, and only moderate to severe cases not seen by the service would be those that can afford private medical care in the UK. Because this study is restricted to patients aged over 15 years the results cannot be extrapolated to children with chronic fatigue syndrome. Finally, our results might be affected by prevalence bias whereby cases known to a service within a given time are dominated by those with prolonged clinical courses; therefore, they cannot be taken to generalise to incident cases.

Much research has been done to investigate the association between chronic fatigue syndrome and psychiatric disorder comorbidity. A significant cross-sectional and prospective association exists between chronic fatigue syndrome and non-exclusionary psychiatric disorder comorbidity,[24–26] with depression and anxiety disorders being strongly associated with chronic fatigue syndrome. The incidence of detected comorbidity of psychiatric disorder are similar to those seen elsewhere.[27]

The lack of increase in all-cause mortality within the chronic fatigue syndrome cohort compared with the general population contrasts with that observed in most psychiatric disorders, which show increased mortality especially due to accidents, cancer, and cardiovascular disease.[18] The reasons for the normal all-cause mortality may be that these patients might have good health behaviours, an inherently smaller effect size, or that all-cause mortality is confounded by the higher socioeconomic status of the patient cohort.

Although the suicide-specific SMR is raised compared with the general population, it is lower than for psychiatric disorders including affective disorders, personality disorders, and alcohol dependence reported in other population-based studies.[28]

This study highlights the importance of adequate assessment of mood and other psychiatric symptoms in patients with chronic fatigue syndrome, because lifetime diagnosis of depression is an independent risk factor for increased risk of completed suicide in this population. Although completed suicide was a rare event, the findings strengthen the case for robust psychiatric assessment by mental health professionals when managing individuals with chronic fatigue syndrome.

Contributors

ER contributed to the literature search, study question and design, data collection, analysis, and interpretation, prepared the first draft of the report, and contributed to subsequent versions; SW and TC contributed to data interpretation and drafting of the final report; C-KC and MH contributed to study design, data synthesis and analysis, and drafting of the final report. All authors approved the final version.

Declaration of interests

ER, SW, C-KC, and MH declare no competing interests. TC received funding from the Biomedical Research Centre during the conduct of the study and receives royalties in relation to three self-help books.

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