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Childhood stressors in the development of fatigue syndromes: a review of the past 20 years of research

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Background. Chronic fatigue syndrome (CFS) and fibromyalgia (FM) are both highly prevalent conditions associated with extreme disability and with the development of co-morbid psychiatric disorders, such as depression and anxiety. Childhood stressors have been shown to induce persistent changes in the function of biological systems potentially relevant to the pathogenesis of both CFS and FM, such as the inflammatory system and the hypothalamic–pituitary–adrenal (HPA) axis. In this review, we examined whether multiple forms of childhood stressors are contributing factors to the development of these disorders, and of the associated psychiatric symptoms.

Method. Using PubMed, we identified 31 papers relevant to this narrative review. We included cohort studies and case-control studies, without any exclusion in terms of age and gender. No study characteristics or publication date restrictions were imposed.

Results. Most studies across the literature consistently show that there is a strong association between experiences of childhood stressors and the presence of CFS and FM, with rates of CFS/FM being two- to three-fold higher in exposed than in unexposed subjects. We also found evidence for an increased risk for the development of additional symptoms, such as depression, anxiety and pain, in individuals with CFS and FM with a previous history of childhood stressors, compared with individuals with CFS/FM and no such history.

Conclusions. Our review confirms that exposure to childhood stressors is associated with the subsequent development of fatigue syndromes such as CFS and FM, and related symptoms. Further studies are needed to identify the mechanisms underlying these associations.

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Key words: Anxiety, childhood abuse, childhood maltreatment, chronic fatigue syndrome, chronic pain, depression, fibromyalgia, stress.

Introduction

Chronic fatigue syndrome (CFS) is a debilitating and complex disorder, relatively common in adults and associated with a myriad of symptoms (Kawatani *et al.* 2011). This condition, also known as myalgic encephalomyelitis (ME), is characterized by persistent severe fatigue, unrelated to exertion and not relieved by rest, that lasts at least 6 months and is associated with muscle/joint pain, significant impairment of short-term memory, poor concentration and disturbed sleep (Reeves *et al.* 2003; Sanders & Korf, 2008; CDC, 2012a). Overall, evidence suggests a population prevalence of at least 0.2–0.4% (NICE, 2007). Individuals with a diagnosis of CFS generally experience physical

impairments and difficulties in cognitive and psychological functioning (Brooks *et al.* 2011), which contribute to considerable personal suffering and a decreased quality of life (Solomon *et al.* 2003). Fibromyalgia (FM) is also a common condition that, like CFS, is concomitant with a myriad of symptoms, including chronic widespread pain, muscular stiffness, debilitating fatigue, cognitive and mood dysfunction, and sleep disturbance (CDC, 2012b; Low & Schweinhardt, 2012; Sommer *et al.* 2012). Despite the high incidence of these conditions, a vast proportion of patients presenting with chronic fatigue, pain and cognitive dysfunctions do not show specific organic abnormalities (Kroenke & Mangelsdorff, 1989; Cho *et al.* 2006; Henningsen *et al.* 2007). Studies have assessed the involvement of psychological, social and biological factors (Wessely, 1998; Lyall *et al.* 2003; Caseras *et al.* 2006, 2008).

Both CFS and FM are known to be associated with other co-morbid psychiatric disorders (Wolfe, 1997; Van Houdenhove *et al.* 2005). Indeed, the prevalence

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of both depression and anxiety is high in CFS and FM patients (Wessely & Powell, 1989; McBeth & Silman, 2001; Chou, 2013), and a recent study in a sample of 640 CFS patients found that 14% of patients had an anxiety disorder, 14% had a depressive disorder and 18% had both depression and anxiety disorders (Cella *et al.* 2013). A previous study in FM found that 57% of patients reported concurrent depression (Okifuji *et al.* 2000) and another study reported that a quarter had a current depressive episode and two-thirds a prior depressive episode (Epstein *et al.* 1999).

One risk factor suggested as being relevant to the onset of these disorders is the occurrence of childhood stressors. Childhood stressors, especially maltreatment and abuse, are highly prevalent in the general population: for example, a 2009 meta-analysis, examining 65 studies from 22 countries, reported the global prevalence of childhood sexual abuse (CSA) as 19.7% for females and 7.9% for males (Pereda *et al.* 2009). In addition, a UK survey of 2869 young adults found that maltreatment (both intra- and extra-familial) was experienced by 16% of the sample, with 11% of respondents reporting experiences of more severe forms of sexual abuse (May-Chahal & Cawson, 2005). Several review studies have shown that individuals who suffer childhood abuse are more likely to be depressed, to experience other types of psychiatric disorders, and to have more physical symptoms (Arnow, 2004; Maniglio, 2009). In fact there is now a wealth of evidence confirming childhood abuse as a vulnerability factor for adulthood depression (Chen *et al.* 2010; Danese & McEwen, 2012) and anxiety (Sareen *et al.* 2013), and also for somatoform disorders (Lampe *et al.* 2003). With specific relevance to patients with fatigue syndromes, CFS patients have a high prevalence of stressful life events (Johnson *et al.* 1999), and a history of childhood abuse in FM patients has been associated with more severe physical symptoms and greater functional disability (Walen *et al.* 2001). Indeed, there is some evidence to suggest that a history of childhood abuse may play an important role in the development and severity of both CFS (Johnson *et al.* 2010) and FM (Van Houdenhove *et al.* 2005). A review by Häuser *et al.* (2011), assessing emotional, physical and sexual abuse during childhood in FM patients, found a significant correlation between all three types of abuse and FM. This association is particularly relevant from a mechanistic point of view because childhood abuse has been shown to induce changes in the function of biological systems, such as the inflammatory system and the hypothalamic–pituitary–adrenal (HPA) axis (Danese & McEwen, 2012), which have been found to be abnormal in patients with CFS (Fuite *et al.* 2008).

The aim of this review was to summarize the existing literature about the association between multiple forms of childhood abuse and CFS or FM. As mentioned, there is one existing review on the association between emotional, physical and sexual abuse during childhood in FM patients (Häuser *et al.* 2011). However, in this review we have also included two other types of childhood abuse (emotional and physical neglect), and have reviewed studies in both CFS and FM patients. Moreover, we looked at the clinical symptoms associated with the occurrence of childhood abuse in these patients, including depression, anxiety and pain.

Method

We performed a search of the literature using PubMed and considering cohort studies and case-control studies without any exclusion in terms of age and gender. Keywords included: ‘childhood abuse’ or ‘childhood trauma’; ‘chronic fatigue syndrome’ or ‘fibromyalgia’ or ‘myalgic encephalomyelitis’ or ‘chronic pain’. No study characteristics or publication date restrictions were imposed. Papers concerning animal models were excluded. The search was limited to English-language studies. We identified a total of 31 papers, three of which were identified from references.

Results

We identified seven papers regarding CFS, 21 papers regarding FM, and three papers that considered both CFS and FM.

Childhood stressors and CFS

Childhood sexual and physical abuse

Ten studies examined the association between childhood sexual and/or physical abuse, and CFS (Table 1). Among these, four were case-control studies. The first two studies, conducted by Taylor & Jason (2001) and Heim *et al.* (2006), reported a higher incidence of childhood sexual (range 16–28% *v.* 2–10%) and physical abuse (range 28–29% *v.* 5–9%) in CFS patients than in controls. More recently, these results were replicated in studies by Heim *et al.* (2009) and Heins *et al.* (2011), where CFS patients were again found to be more likely to report a previous history of childhood sexual (range 10–33% *v.* 4–11%) and physical abuse (range 6–33% *v.* 1–10%) when compared with control subjects.

Some studies investigated CFS-only populations or used non-healthy comparison samples with medical conditions, and reported similarly high rates of childhood sexual and physical abuse. Tietjen *et al.* (2010)

Table 1. Studies examining the association between childhood stressors and chronic fatigue syndrome

Author	Type of study	Sample	Clinical measurements	Sexual and/or physical abuse	Emotional abuse	Emotional and/or physical neglect
Clark <i>et al.</i> (2011)	Longitudinal cohort	127 CFS, 241 CFS-like illness	Self-reported diagnoses of CFS, GHQ-12, Malaise Inventory, Self-reported childhood sexual and physical abuse	↑		
Heim <i>et al.</i> (2006)	Case-control	43 CFS, 60 controls	SF-36, MFI, CDC Symptom Inventory, CTQ	↑	↑	↑
Heim <i>et al.</i> (2009)	Case-control	113 CFS, 124 controls	SF-36, MFI, CDC Symptom Inventory, CTQ	↑	↑	↑
Heins <i>et al.</i> (2011)	Case-control	216 CFS, 227 controls	CTQ-SF, CIS, SIP, SF-36	↑	↑	↑
Johnson <i>et al.</i> (2010)	Longitudinal cohort	93 CFS	Wessely and Powell's attribution scale, CTQ-SF (Wessely & Powell, 1989)	↑	↑	↑
Kempke <i>et al.</i> (2013)	Cross-sectional	90 CFS	CDC Symptom Inventory, CTQ	↑	↑	↑
Post <i>et al.</i> (2013)	Longitudinal cohort	968 patients with bipolar disorder	tCAS	↑		
Taylor & Jason (2001)	Case-control	32 CFS, 47 controls	The CFS Screening Questionnaire, SPAQ	↑		
Tietjen <i>et al.</i> (2010)	Cross-sectional	1348 migraine patients	Self-reported physician-diagnosed history of CFS, CDC Symptom Inventory, CTQ	↑	↑	↑
Van Houdenhove <i>et al.</i> (2001)	Cross-sectional	95 CFS/FM, 52 RA/MS, 95 controls	CDC Symptom Inventory, ACR criteria, Questionnaire on Burdening Experience	↓	↓	↓

CFS, Chronic fatigue syndrome; GHQ-12, 12-item General Health Questionnaire; SF-36, Medical Outcomes Study Short Form 36-item Health Survey; MFI, Multidimensional Fatigue Inventory; CDC, Centers for Disease Control and Prevention; CTQ, Childhood Trauma Questionnaire; CTQ-SF, Childhood Trauma Questionnaire Short Form; CIS, Checklist Individual Strength; SIP, Sickness Impact Profile; tCAS, total childhood adversity score; SPAQ, Sexual and Physical Abuse Questionnaire; ACR, American College of Rheumatology; FM, fibromyalgia; RA, rheumatoid arthritis; MS, multiple sclerosis; ↑, high prevalence of childhood abuse; ↓, low prevalence of childhood abuse.

showed that a large percentage of patients with CSF reported a history of childhood sexual or physical abuse (35% and 26.5% respectively). These results are supported by a study investigating the prevalence of childhood sexual and physical abuse in CFS patients compared with patients with CFS-like illness; Clark *et al.* (2011) demonstrated that childhood sexual and physical abuse were both associated with the development of CFS. Other studies have also found a high prevalence of a previous history of childhood sexual (17.8%) (Kempke *et al.* 2013) and physical abuse (range 15–25%) in CFS patients (Johnson *et al.* 2010; Kempke *et al.* 2013). Finally, a study investigating a sample of 58 CFS patients found a significant association between a previous history of childhood physical abuse and diagnosis of CFS (Post *et al.* 2013).

To our knowledge only one study has reported conflicting evidence. In a sample of 95 patients suffering from CFS or FM, 52 with rheumatoid arthritis (RA) or multiple sclerosis (MS), and 95 healthy controls, Van Houdenhove *et al.* (2001) demonstrated that CFS or FM patients had a lower prevalence of childhood victimization, including childhood sexual, physical and emotional abuse, and physical and emotional neglect, when compared with RA/MS patients and healthy controls; however, the results were not significant (14% *v.* 17% *v.* 20%).

Childhood emotional abuse

Among the above-mentioned papers, six assessed the association between childhood emotional abuse and CFS (Table 1). Two case-control studies reported that subjects with CFS had a higher prevalence of childhood emotional abuse when compared with healthy controls (range 13–42% *v.* 4–20%) (Heim *et al.* 2006, 2009; Heins *et al.* 2011).

Some studies have investigated CFS-only populations, without including a control group. Tietjen *et al.* (2010) showed that 53% of CFS patients experienced childhood emotional abuse. Similarly, two descriptive studies demonstrated a high prevalence of previous episodes of childhood emotional abuse in patients with a diagnosis of CFS (range 24–38%) (Johnson *et al.* 2010; Kempke *et al.* 2013).

Childhood emotional and physical neglect

Six of the above-mentioned papers assessed the association between childhood emotional and/or physical neglect, and CFS (Table 1). Three case-control studies showed that subjects with CFS have significantly higher rates of both childhood emotional (range 24–60% *v.* 8–28%) and physical neglect (range

13–25% *v.* 3–7%) when compared with healthy controls (Heim *et al.* 2006, 2009; Heins *et al.* 2011).

Other studies have also investigated this association. Tietjen *et al.* (2010) demonstrated that a large proportion of patients with CSF reported a history of childhood emotional (45.6%) and physical neglect (32%). Two more studies reported a high prevalence of childhood emotional (range 31–37%) (Johnson *et al.* 2010; Kempke *et al.* 2013) and physical neglect (14%) in patients with a diagnosis of CFS (Johnson *et al.* 2010).

Childhood stressors and FM

Childhood sexual and physical abuse

Twenty-four studies have examined the association between childhood sexual and/or physical abuse, and FM (Table 2). Among these, six were case-control studies. Three studies reported a higher incidence of childhood sexual (range 7–37% *v.* 6–22%) and physical abuse (range 8–34% *v.* 4–12%) in FM patients than in controls (Boisset-Piolo *et al.* 1995; Ruiz-Perez *et al.* 2009; Smith *et al.* 2010). Anderberg *et al.* (2000) also demonstrated that FM patients had a higher prevalence of childhood sexual (7.5% *v.* 5%) and physical or psychological abuse (27.5% *v.* 13%) than patients without a history of abuse. In two other case-control studies, FM patients were more likely to report a previous history of childhood sexual (10.5% *v.* 0) (Imbierowicz & Egle, 2003) and physical abuse (42% *v.* 34%) (Ciccone *et al.* 2005) when compared with controls.

Ten studies have investigated FM-only populations, without including a control group, and reported similarly high rates of childhood sexual and physical abuse. Malleson *et al.* (1992) showed that, in a sample of 81 children with diffuse idiopathic pain, 35 patients fulfilled criteria for FM diagnosis and 7% of patients also had a previous history of CSA. However, the authors did not specify whether patients reporting CSA were also diagnosed with FM. In addition, Goldberg *et al.* (1999) reported that 65% of FM patients had a previous history of CSA and 47% experienced childhood physical abuse. Four more studies reported a high prevalence of childhood sexual (range 11–33%) and physical abuse (range 11–55%) in FM patients (Bell *et al.* 2004; Weissbecker *et al.* 2006; Pae *et al.* 2009; Kosseva *et al.* 2010). Similarly, in a sample of 88 FM patients, 8% were reported to have a previous history of sexual abuse and 16% experienced severe physical abuse, in childhood or adulthood (Häuser, 2005). Accordingly, in a sample of 26 FM patients, five patients experienced episodes of childhood sexual or physical abuse (McLean *et al.* 2006). However, the authors did not report the specific percentage for

each type of abuse separately. Tietjen *et al.* (2010) demonstrated that a large percentage of patients with FM had a history of childhood sexual (39%) and physical abuse (27%). More recently, Loevinger *et al.* (2012) found that 19 out of 107 FM patients had a high total mean score (of 77.2) on the childhood trauma questionnaire (CTQ; Bernstein & Fink, 1998), but the specific results for the childhood sexual and physical abuse subscale were not reported.

These results are supported by three studies investigating the prevalence of CSA in FM patients compared with patients with RA or osteoarthritis (OA). In the first study, Walker *et al.* (1997) found a higher mean score on the childhood sexual (15.0 *v.* 10.4) and physical abuse (15.3 *v.* 10.9) subscale of the CTQ in FM patients when compared with RA patients (Walker *et al.* 1997). Moreover, FM patients were more likely to report a history of sexual (51% *v.* 32%) and physical abuse (39% *v.* 16%) during childhood or adulthood, and also increased duration of sexual abuse when compared to RA patients (Carpenter *et al.* 1998). More recently, Nicolson *et al.* (2010) demonstrated that FM patients had a higher mean score on the CSA subscale of the CTQ when compared with OA patients (8.9 *v.* 6.7). However, when considering any experience of childhood physical abuse, Nicolson *et al.* (2010) found was no difference between the two groups (3.9 *v.* 3.9).

Several studies have investigated female-only populations and found similar results. Finestone *et al.* (2000) showed that women who had experienced CSA had a greater risk of FM diagnoses than non-abused control patients (23% *v.* 8%). In a sample of 62 adolescent female in-patients from a psychiatric unit, CSA was assessed in patients who also met criteria for juvenile primary fibromyalgia syndrome (JPFS; Lommel *et al.* 2009). The authors found a higher prevalence of CSA in JPFS patients than in patients without JPFS (416% *v.* 286%). Sigurdardottir & Halldorsdottir (2013) investigated a sample of seven women who had experienced CSA and reported that five out of seven women also had FM. Finally, a study investigating a sample of 29 FM patients did not find any association between a previous history of childhood physical or sexual abuse and diagnosis of FM (Post *et al.* 2013). However, the study did report a significant relationship between the total childhood adversity score (tCAS), including childhood sexual and physical abuse, and the overall number of co-morbidities, including irritable bowel syndrome and diabetes.

To our knowledge only one study has reported conflicting evidence. The case-control study of Ciccone *et al.* (2005) provided no evidence for a significant increase in CSA in the FM group when compared with controls (26.9% *v.* 30.2%).

Childhood emotional abuse

Among the papers discussed, eight assessed the relationship between childhood emotional abuse and FM (Table 2). Three studies assessed a previous history of emotional abuse using the CTQ. Specifically, Walker *et al.* (1997) report a higher mean CTQ score on the childhood emotional abuse subscale in FM patients when compared with RA patients (15.3 *v.* 11) (Walker *et al.* 1997). A later study by Nicolson *et al.* (2010) demonstrated that FM patients had a higher mean score when compared with OA patients (11.4 *v.* 9.0). More recently, the descriptive study by Loevinger *et al.* (2012) found that 19 out of 107 FM patients had a considerably high total mean score on the CTQ (77.2); however, the authors did not report the specific result for the childhood emotional abuse subscale.

In line with previous reports, other studies have investigated this association and found similar outcomes. Smith *et al.* (2010) showed that FM patients had a higher prevalence of childhood emotional abuse (58.5% *v.* 18%) when compared with controls, and Kosseva *et al.* (2010) found that 16% of FM patients reported experiencing severe childhood emotional abuse. Lastly, Tietjen *et al.* (2010) demonstrated that a large percentage of patients with FM had a history of childhood emotional abuse (54%).

By contrast, the descriptive study by Weissbecker *et al.* (2006) found a low mean CTQ score for FM patients (10.6) when considering childhood emotional abuse. However, their results were still higher than scores reported for a female normative Health Maintenance Organization (HMO) sample (Bernstein & Fink, 1998). Lastly, Ruiz-Perez *et al.* (2009) report a similar prevalence of childhood emotional abuse in FM patients when compared with controls without a diagnosis of FM (15.5% *v.* 17%).

Childhood emotional and physical neglect

Eight papers also assessed the association between childhood emotional and/or physical neglect, and FM (Table 2). Three papers used the CTQ to assess these specific forms of abuse. Walker *et al.* (1997) found a higher mean score on the childhood emotional (49.2 *v.* 34.3) and physical (5.0 *v.* 3.7) neglect subscales in FM patients than in RA patients. In addition, Nicolson *et al.* (2010) found that FM patients had a higher mean CTQ score on the childhood emotional neglect subscale when compared with OA patients (10.7 *v.* 9.5). However, when looking at the childhood physical neglect subscale, the authors did not find any difference between the two groups (7.1 *v.* 7.1) (Nicolson *et al.* 2010). Lastly, as mentioned, Loevinger *et al.* (2012) found that 19 out of 107 FM patients had

Table 2. Studies examining the association between childhood stressors and fibromyalgia

Author	Type of study	Sample	Clinical measurements	Sexual and/or physical abuse	Emotional abuse	Emotional and/or physical neglect
Anderberg <i>et al.</i> (2000)	Case-control	40 FM, 38 controls	All FM patients fulfilled ACR criteria, Self-made questionnaire on childhood abuse	↑		↑
Bell <i>et al.</i> (2004)	Longitudinal cohort	53 FM	Physician diagnosis of FM, CECA.Q	↑		↑
Boisset-Pioro <i>et al.</i> (1995)	Case-control	83 FM, 161 controls	Questionnaire (short version of interviews on abuse of the NPSC)	↑		
Carpenter <i>et al.</i> (1998)	Cross-sectional	205 FM, 84 RA	Self-made questionnaire on childhood abuse	↑		
Ciccone <i>et al.</i> (2005)	Case-control	52 FM, 53 controls	Sexual and Physical Abuse Interview	↓		
Finestone <i>et al.</i> (2000)	Cross-sectional	26 women with history of CSA, 54 controls	MPI, CSA questionnaire	↑		
Goldberg <i>et al.</i> (1999)	Cohort	91 patients with chronic pain	CHQ, Childhood Traumatic Events Scale, McGill Melzack Pain Questionnaire, PDI	↑		
Häuser <i>et al.</i> (2005)	Cohort	88 FM	All FM patients fulfilled ACR criteria, CTQ	↑		
Imbierowicz & Egle (2003)	Case-control	38 FM, 71 somatoform pain disorders, 44 controls	SBI-P, ACE, VAS	↑		
Kosseva <i>et al.</i> (2010)	Cohort	293 FM	CTQ	↑	↑	↑
Loevinger <i>et al.</i> (2012)	Cross-sectional	107 FM	All FM patients fulfilled ACR criteria, CTQ	↑	↑	↑
Lommel <i>et al.</i> (2009)	Cohort	62 adolescent females assessed for JPFS	CSI, FIQ-C, YSR, PSQ	↑		
Malleson <i>et al.</i> (1992)	Longitudinal cohort	81 RA	Yunus and Masi criteria for JPFS	↑		
McLean <i>et al.</i> (2006)	Cross-sectional	26 FM	All FM patients fulfilled ACR criteria, CIDI	↑		
Nicolson <i>et al.</i> (2010)	Longitudinal	35 FM, 35 OA	CTQ-SF	↑ (sexual abuse) =(physical abuse)	↑	↑ (sexual neglect) =(physical neglect)
Pae <i>et al.</i> (2009)	Longitudinal cohort	112 FM	Sexual and Physical Abuse Questionnaire, FIQ	↑		
Post <i>et al.</i> (2013)	Longitudinal cohort	968 patients with bipolar disorder	tCAS	↑		
Ruiz-Perez <i>et al.</i> (2009)	Case-control	287 FM, 287 controls	All FM patients fulfilled ACR criteria Self-made questionnaire (based on WHO Multi-Country Study on Women's Health and Life Events)	↑	↓	

Sigurdardottir & Halldorsdottir (2013)	Longitudinal cohort	Seven women with CSA history	Sexual Abuse Interview	↑
Smith <i>et al.</i> (2010)	Case-control	41 FM, 44 controls	Rheumatologist confirmation of diagnoses history of FM, Questionnaire (standardized self-report measures of civilian trauma)	↑
Tietjen <i>et al.</i> (2010)	Cross-sectional	1348 patients with migraine	Self-reported physician-diagnosed history of FM, CDC Symptom Inventory, CTQ	↑
Walker <i>et al.</i> (1997)	Cohort	36 FM, 33 RA	CTQ, CMI	↑
Weissbecker <i>et al.</i> (2006)	Cohort	85 FM	CTQ	↑ ↓

FM, Fibromyalgia; ACR, American College of Rheumatology; CECA-Q, Childhood Experience of Care and Abuse Questionnaire; NPSC, National Population Survey of Canada; RA, rheumatoid arthritis; MPI, McGill Pain Questionnaire; CHQ, Childhood History Questionnaire; PDI, Pain Disability Index; CTQ, Childhood Trauma Questionnaire; SBI-P, Structural Biographical Interview for Pain Disorders; ACE, Adverse Childhood Experiences Questionnaire; VAS, Visual Analogue Scale; JPFS, juvenile primary fibromyalgia syndrome; CSI, Children's Somatization Inventory; FIQ-C, Fibromyalgia Impact Questionnaire for Children; YSR, Achenbach Youth Self Report; PSQ, Pain Symptom Questionnaire; CIDI, Composite International Diagnostic Interview; OA, osteoarthritis; CTQ-SF, Childhood Trauma Questionnaire Short Form; FIQ, Fibromyalgia Impact Questionnaire; iCAS, total childhood adversity score; WHO, World Health Organization; CSA, childhood sexual abuse; CDC, Centers for Disease Control and Prevention; CMI, Child Maltreatment Interview; ↑, high prevalence of childhood abuse; ↓, low prevalence of childhood abuse; =, no difference in prevalence of childhood abuse.

a considerably high total mean CTQ score but they did not report the specific score on the childhood emotional and physical neglect subscales.

Four other studies were able to replicate these results. Anderberg *et al.* (2000) demonstrated that FM patients had a higher prevalence of childhood neglect when compared with controls (17.5% *v.* 8%), but the authors did not specifically assessed physical and emotional neglect. Tietjen *et al.* (2010) found that a large percentage of patients with FM had a history of childhood emotional (47%) and physical neglect (32%). Similarly, Bell *et al.* (2004) and Kosseva *et al.* (2010) found a high prevalence of childhood emotional (range 25–46%) and physical neglect (range 8–13%) among FM patients.

By contrast, the descriptive study conducted by Weissbecker *et al.* (2006) found unclear evidence, as mentioned earlier, reporting a low mean CTQ score for FM patients when considering childhood emotional (12.6) and physical neglect (10) subscales. However, as for the emotional abuse, those results were still higher than scores reported for a female normative HMO sample (Bernstein & Fink, 1998).

Effects of childhood stressors on symptom profiles

Depressive symptoms

To our knowledge, only one study has examined the association between childhood abuse and depression in CFS patients (Table 3). Heins *et al.* (2011) demonstrated that CFS patients with a history of childhood stressors, including sexual, physical and emotional abuse, and physical and emotional neglect, were more likely to report a lifetime history of depression when compared to patients without a history of abuse (44% *v.* 25%). Sigurdardottir & Halldorsdottir (2013) examined this association in FM patients, and reported that, in a sample of seven women with CSA, five had FM and all had depression.

Anxiety symptoms

The study mentioned above in patients with CFS also examined the interaction between childhood abuse and anxiety (Table 3). Heins *et al.* (2011) reported that CFS patients who had experienced childhood abuse, including sexual, physical and emotional abuse, and physical and emotional neglect were more likely to develop anxiety disorder when compared to controls (21% *v.* 15%).

Pain symptoms

To our knowledge, no studies have investigated the association between childhood abuse and pain in CFS patients. However, two studies have examined

Table 3. Studies examining the association between childhood stressors and symptom profiles

Author	Type of study	Clinical symptoms	Sample	Clinical measurements	Findings
Heins <i>et al.</i> (2011)	Case-control	Depression	216 CFS, 227 controls	BDI-PC	CFS patients with a history of childhood abuse had a higher prevalence of depression compared with non-abused patients (44% <i>v.</i> 25%)
Sigurdardottir & Halldorsdottir (2013)	Longitudinal cohort	Depression	Seven women with CSA	Not reported	Five out of seven women had FM and all had depression
Heins <i>et al.</i> (2011)	Case-control	Anxiety	216 CFS, 227 controls	SCL	CFS patients with a history of childhood abuse reported higher levels of anxiety compared with controls (21% <i>v.</i> 15%)
Sigurdardottir & Halldorsdottir (2013)	Longitudinal cohort	Pain	Seven women with CSA	Not reported	Five out of seven women had FM and all reported chronic and widespread pain
Walker <i>et al.</i> (1997)	Cohort	Pain	36 FM, 33 RA	SF-36	Childhood abuse was significantly associated with pain symptoms in FM patients when compared to RA patients

CFS, Chronic fatigue syndrome; BDI-PC, Beck Depression Inventory for Primary Care; FM, fibromyalgia; CSA, childhood sexual abuse; SCL, Symptom Checklist Questionnaire; RA, rheumatoid arthritis; SF-36, Medical Outcomes Study Short Form 36-Item Health Survey.

the interaction between childhood abuse and pain in patients with FM (Table 3). In the study by Walker *et al.* (1997), a significant association was found between childhood abuse, including sexual, physical and emotional abuse, and physical and emotional neglect, and pain symptoms, in FM patients when compared to RA patients. In a sample of seven women with a history of CSA, five were diagnosed with FM and all seven suffered chronic and widespread pain (Sigurdardottir & Halldorsdottir, 2013).

Discussion

This review presents the current literature on the relationship between multiple forms of childhood stressors and the fatigue syndromes, CFS and FM. Our results highlight a strong relationship between experiences of childhood abuse and the occurrence of CFS and FM. However, when looking at a specific type of abuse, such as CSA, and the presence of CFS/FM, only two studies have reported conflicting evidence. The first study by Van Houdenhove *et al.* (2001) demonstrated that CFS or FM patients had a lower prevalence of childhood victimization, including CSA, when compared with RA/MS patients and healthy controls. This inconsistent result may be attributed mainly to the administration of a specific questionnaire when assessing experiences of CSA, the Questionnaire on Burdening Experiences, which has not been validated according to international standards. Similarly, the second study, by Ciccone *et al.* (2005), provided no evidence for a significant increase in CSA in the FM group when compared with controls. In this case, one of the major causes of this contrasting finding may be due to the inclusion in both groups (FM patients and controls) of subjects with co-morbid depression, which might partly explain the increased rate of childhood trauma in the controls. Aside from those two studies, overall our findings confirm and extend evidence linking early life experience and CFS/FM, also providing evidence for an association between childhood abuse and other co-morbid symptoms, such as depression, anxiety and pain, in individuals with CFS and FM.

There may be several underlying mechanisms driving the association between childhood abuse and a higher prevalence of CFS and FM. We focus on two, not mutually exclusive, possible biological mechanisms linking a history of childhood stressors and the increased risk of CFS/FM: increased inflammation and abnormal HPA axis activity (Fig. 1); however, it is important to stress that the biological substrates of CFS and FM are still unclear. Moreover, we cannot exclude the possibility that psychological changes associated with a history of childhood stressors play

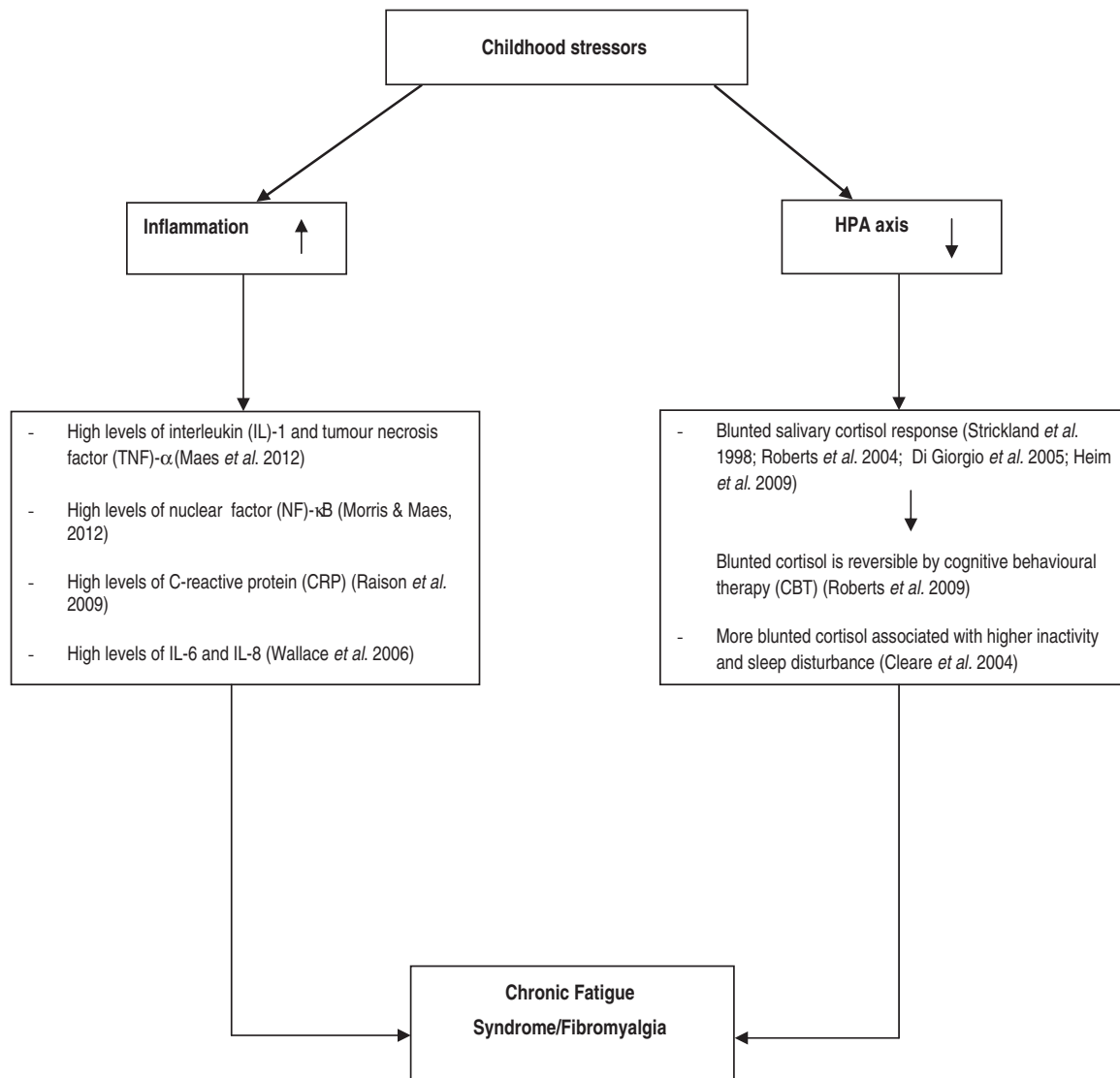


Fig. 1. Biological mechanisms involved in the interaction between childhood stressors and the development of fatigue syndromes. HPA, hypothalamic–pituitary–adrenal.

a role in this increased risk of CFS/FM, including low self-esteem, greater social introversion, lower general activity levels and unhelpful perceptions and coping skills (Masuda *et al.* 1994; Chartier *et al.* 2009).

The first such mechanism is inflammation, whereby childhood stressors lead to increased inflammation and the subsequent development of CFS (Maes & Twisk, 2010). There is an increasing body of evidence supporting the activation of the immune system and of abnormal inflammatory processes in individuals with a history of childhood stressors. Specifically, we have demonstrated that adults with a history of childhood abuse and social isolation have elevated inflammation levels in adulthood, as shown by the levels of the inflammatory marker, C-reactive protein (CRP) (Danese *et al.* 2007, 2009; Hepgul *et al.* 2012).

Carpenter *et al.* (2010) examined plasma interleukin (IL)-6 concentrations in healthy subjects without depression or post-traumatic stress disorder (PTSD), during a standard stress challenge, the Trier Social Stress Test (TSST). Their results still showed a significant relationship between a previous history of childhood maltreatment and an increased level of plasma IL-6 concentration, when compared with individuals without such history. More recently, a study by Heath *et al.* (2013) reported that individuals exposed to a history of sexual or physical abuse are more likely to be diagnosed with PTSD and exhibit high CRP levels than patients without PTSD, suggesting a possible role of PTSD in explaining the association between childhood stressors and immune system activation. The inflammatory response in patients with a previous

history of childhood stressors has also been shown to be exaggerated in the presence of stressful conditions during adulthood (Pace *et al.* 2006). This evidence is consistent with the notion that inflammatory markers may also play a role in the pathophysiology of CFS and FM (Pariante, 2009). Levels of pro-inflammatory cytokines, such as IL-1, tumour necrosis factor (TNF)- α (Maes *et al.* 2012) and nuclear factor (NF)- κ B (Morris & Maes, 2012), have been shown to be higher in CFS patients than in healthy controls. In addition, Raison *et al.* (2009) demonstrated that CRP levels are significantly higher in subjects with CFS and insufficient fatigue (ISF, a milder form of chronic fatigue) when compared with healthy control subjects. Furthermore, a dysregulation of cytokines, including IL-1, IL-6 and IL-8, has been shown to be present in FM patients and to be associated with more pain and fatigue symptoms (Wallace, 2006). Therefore, it is plausible that increased inflammation in individuals with a history of CSA may in turn cause fatigue and somatic symptoms such as those seen in CFS patients (Maes & Twisk, 2010). Indeed, this increase in inflammatory markers as a result of childhood maltreatment has also been associated with the later development of other adult psychiatric conditions, such as depression (Danese *et al.* 2008). For example, individuals with a history of adversities during childhood are at greater risk of both inflammatory abnormalities and mood disorders later in life, especially in the context of additional adult stressors (Heim *et al.* 2001). Clearly, the association between childhood abuse, inflammation and adult fatigue may not need to be 'causal': fatigue and inflammation may both be only associated with the third, common factor, childhood trauma (Pariante, 2009). To the best of our knowledge, no studies have investigated inflammatory markers in individuals with childhood abuse and a diagnosis of CFS or FM. Hence, future research would need to clarify whether indeed inflammation may, at least in part, mediate the relationship between childhood stressors and the development of these chronic conditions.

The HPA axis may also be involved in the association between childhood abuse and CFS/FM. Of note, most studies have found a reduced basal cortisol output in CFS, whereas FM and depression tend to be associated with an increased cortisol output. For example, patients with CFS have lower activity of the HPA axis (Strickland *et al.* 1998; Di Giorgio *et al.* 2005), including a blunted salivary cortisol response to awakening (Roberts *et al.* 2004), that is associated with poorer response to cognitive behavioural therapy (CBT) (Roberts *et al.* 2009). There are many other factors that may affect HPA axis hypoactivity in CFS patients, such as inactivity, sleep disturbance and medication (Cleare, 2004), but there is no evidence

for a unique or uniform dysfunction of the HPA axis in these conditions. By contrast, studies in FM patients have shown higher cortisol levels (Catley *et al.* 2000; Crofford *et al.* 2004) and exaggerated HPA axis response to stimulation (Griep *et al.* 1993; Crofford *et al.* 1994). Of interest, HPA axis hyperactivity is one of the most consistent findings in depression; indeed, it is conceptualized not only as a consequence of depression but also as a biological marker of vulnerability, often brought about by childhood stressors, and predisposing to the development of depression (Pariante & Lightman, 2008). Moreover, childhood abuse *per se* is associated with abnormal HPA axis activity, although both hyper- and hypoactivity have been described. For example, some clinical studies have shown that individuals who have been sexually or physically abused during childhood exhibit hyperactivation of the HPA axis when exposed to a standardized psychosocial stress, the TSST (Heim & Nemeroff, 2002; Heim *et al.* 2008a). By contrast, other studies have shown that adults reporting a previous experience of childhood abuse have a hypoactivation of the HPA axis and a consequent lower production of cortisol (Bremner *et al.* 2003, 2007; Carpenter *et al.* 2007). It is possible that early and severe stress may lead to an initial heightened stress response, which reduces over time (Gunnar & Vazquez, 2001; Susman, 2006; Heim *et al.* 2008b). Of note, the relationship between childhood abuse and HPA axis activity was assessed in two of the papers we reviewed and they showed contrasting evidence, with one study reporting an increased (Weissbecker *et al.* 2006) and one a blunted cortisol awakening response (Heim *et al.* 2009). Of note, Heim *et al.* (2009) reported that only those individuals with CFS and exposure to childhood trauma exhibit decreased mean cortisol levels after awakening whereas individuals with CFS without childhood trauma experience do not differ from controls. Therefore, further studies are needed to obtain a clearer understanding of the involvement of the HPA axis.

One of the main limitations of our review is that the quality of the findings varied across the studies reviewed. Indeed, many of the studies, being case-control, were empirically weakened by the inability to examine cause and effect in the relationship between childhood abuse and CFS or FM. There was also no uniformity in the diagnostic criteria used for the assessment of childhood abuse and other clinical symptoms. Furthermore, sample sizes were often small and several studies did not include a control or a comparison group.

In conclusion, to our knowledge this is the first review to summarize the existing literature on the relationship between different forms of childhood

abuse, and CFS and FM. Despite the limitations of the available literature, we show evidence for the involvement of childhood abuse in the aetiology of both these conditions. In addition, we highlight the link between childhood abuse and the development of other symptoms such as depression, anxiety and pain, in both CFS and FM patients. Demonstrating a causal relationship between childhood abuse and an increased risk for the development of CFS and FM could have significant implications in terms of raising awareness, targeting more vulnerable individuals and identifying biological mechanisms underlying this putative causal relationship. Finally, it is important to note that these biological mechanisms, such as low cortisol, are potentially reversible as has been shown in a previous study of CBT (Roberts *et al.* 2009).

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Declaration of Interest

None.

References

- Anderberg UM, Marteinsdottir I, Theorell T, von Knorring L (2000). The impact of life events in female patients with fibromyalgia and in female healthy controls. *European Psychiatry* 15, 295–301.
- Arnold BA (2004). Relationships between childhood maltreatment, adult health and psychiatric outcomes, and medical utilization. *Journal of Clinical Psychiatry* 65, 10–15.
- Bell IR, Lewis DA 2nd, Brooks AJ, Schwartz GE, Lewis SE, Caspi O, Cunningham V, Baldwin CM (2004). Individual differences in response to randomly assigned active individualized homeopathic and placebo treatment in fibromyalgia: implications of a double-blinded optional crossover design. *Journal of Alternative and Complementary Medicine* 10, 269–283.
- Bernstein DP, Fink L (1998). *Childhood Trauma Questionnaire: A Retrospective Self-Report Manual*. The Psychological Corporation: San Antonio, TX.
- Boisset-Piolo MH, Esdaile JM, Fitzcharles MA (1995). Sexual and physical abuse in women with fibromyalgia syndrome. *Arthritis and Rheumatology* 38, 235–241.
- Bremner D, Vermetten E, Kelley ME (2007). Cortisol, dehydroepiandrosterone, and estradiol measured over 24 hours in women with childhood sexual abuse-related posttraumatic stress disorder. *Journal of Nervous and Mental Disease* 195, 919–927.
- Bremner JD, Vythilingam M, Anderson G, Vermetten E, McGlashan T, Heninger G, Rasmusson A, Southwick SM, Charney DS (2003). Assessment of the hypothalamic-pituitary-adrenal axis over a 24-hour diurnal period and in response to neuroendocrine challenges in women with and without childhood sexual abuse and posttraumatic stress disorder. *Biological Psychiatry* 54, 710–718.
- Brooks SK, Rimes KA, Chalder T (2011). The role of acceptance in chronic fatigue syndrome. *Journal of Psychosomatic Research* 71, 411–415.
- Carpenter LL, Carvalho JP, Tyrka AR, Wier LM, Mello AF, Mello MF, Anderson GM, Wilkinson CW, Price LH (2007). Decreased adrenocorticotropic hormone and cortisol responses to stress in healthy adults reporting significant childhood maltreatment. *Biological Psychiatry* 62, 1080–1087.
- Carpenter LL, Gawuga CE, Tyrka AR, Lee JK, Anderson GM, Price LH (2010). Association between plasma IL-6 response to acute stress and early-life adversity in healthy adults. *Neuropsychopharmacology* 35, 2617–2623.
- Carpenter MT, Hugler R, Enzenauer RJ, Des Rosier KF, Kirk JM, Brehm WT (1998). Physical and sexual abuse in female patients with fibromyalgia. *Journal of Clinical Rheumatology* 4, 301–306.
- Caseras X, Mataix-Cols D, Giampietro V, Rimes KA, Brammer M, Zelaya F, Chalder T, Godfrey EL (2006). Probing the working memory system in chronic fatigue syndrome: a functional magnetic resonance imaging study using the n-back task. *Psychosomatic Medicine* 68, 947–955.
- Caseras X, Mataix-Cols D, Rimes KA, Giampietro V, Brammer M, Zelaya F, Chalder T, Godfrey E (2008). The neural correlates of fatigue: an exploratory imaginal fatigue provocation study in chronic fatigue syndrome. *Psychological Medicine* 38, 941–951.
- Catley D, Kaell AT, Kirschbaum C, Stone AA (2000). A naturalistic evaluation of cortisol secretion in persons with fibromyalgia and rheumatoid arthritis. *Arthritis Care and Research* 13, 51–61.
- CDC (2012a). *Chronic Fatigue Syndrome (CFS) Case Definition*. Centers for Disease Control and Prevention (www.cdc.gov/cfs/case-definition/index.html). Accessed 2 July 2013.
- CDC (2012b). *Fibromyalgia*. Centers for Disease Control and Prevention (www.cdc.gov/arthritis/basics/fibromyalgia.htm). Accessed 2 July 2013.

- Cella M, White PD, Sharpe M, Chalder T** (2013). Cognitions, behaviours and co-morbid psychiatric diagnoses in patients with chronic fatigue syndrome. *Psychological Medicine* **43**, 375–380.
- Chartier MJ, Walker JR, Naimark B** (2009). Health risk behaviors and mental health problems as mediators of the relationship between childhood abuse and adult health. *American Journal of Public Health* **99**, 847–854.
- Chen LP, Murad MH, Paras ML, Colbenson KM, Sattler AL, Goranson EN, Elamin MB, Seime RJ, Shinozaki G, Prokop LJ, Zirakzadeh A** (2010). Sexual abuse and lifetime diagnosis of psychiatric disorders: systematic review and meta-analysis. *Mayo Clinic Proceedings* **85**, 618–629.
- Cho HJ, Skowera A, Cleare A, Wessely S** (2006). Chronic fatigue syndrome: an update focusing on phenomenology and pathophysiology. *Current Opinion in Psychiatry* **19**, 67–73.
- Chou KL** (2013). Chronic fatigue and affective disorders in older adults: evidence from the 2007 British National Psychiatric Morbidity Survey. *Journal of Affective Disorders* **145**, 331–335.
- Ciccone DS, Elliott DK, Chandler HK, Nayak S, Raphael KG** (2005). Sexual and physical abuse in women with fibromyalgia syndrome: a test of the trauma hypothesis. *Clinical Journal of Pain* **21**, 378–386.
- Clark C, Goodwin L, Stansfeld SA, Hotopf M, White PD** (2011). Premorbid risk markers for chronic fatigue syndrome in the 1958 British birth cohort. *British Journal of Psychiatry* **199**, 323–329.
- Cleare AJ** (2004). The HPA axis and the genesis of chronic fatigue syndrome. *Trends in Endocrinology and Metabolism* **15**, 55–59.
- Crofford LJ, Pillemer SR, Kalogeras KT, Cash JM, Michelson D, Kling MA, Sternberg EM, Gold PW, Chrousos GP, Wilder RL** (1994). Hypothalamic-pituitary-adrenal axis perturbations in patients with fibromyalgia. *Arthritis and Rheumatism* **37**, 1583–1592.
- Crofford LJ, Young EA, Engleberg NC, Korszun A, Brucksch CB, McClure LA, Brown MB, Demitrack MA** (2004). Basal circadian and pulsatile ACTH and cortisol secretion in patients with fibromyalgia and/or chronic fatigue syndrome. *Brain, Behavior, and Immunity* **18**, 314–325.
- Danese A, McEwen BS** (2012). Adverse childhood experiences, allostasis, allostatic load, and age-related disease. *Physiology and Behaviour* **106**, 29–39.
- Danese A, Moffitt TE, Harrington H, Milne BJ, Polanczyk G, Pariante CM, Poulton R, Caspi A** (2009). Adverse childhood experiences and adult risk factors for age-related disease: depression, inflammation, and clustering of metabolic risk markers. *Archives of Pediatrics and Adolescent Medicine* **163**, 1135–1143.
- Danese A, Moffitt TE, Pariante CM, Ambler A, Poulton R, Caspi A** (2008). Elevated inflammation levels in depressed adults with a history of childhood maltreatment. *Archives of General Psychiatry* **65**, 409–415.
- Danese A, Pariante CM, Caspi A, Taylor A, Poulton R** (2007). Childhood maltreatment predicts adult inflammation in a life-course study. *Proceedings of the National Academy of Sciences USA* **104**, 1319–1324.
- Di Giorgio A, Hudson M, Jerjes W, Cleare AJ** (2005). 24-hour pituitary and adrenal hormone profiles in chronic fatigue syndrome. *Psychosomatic Medicine* **67**, 433–440.
- Epstein SA, Kay G, Clauw D, Heaton R, Klein D, Krupp L, Kuck J, Leslie V, Masur D, Wagner M, Waid R, Zisook S** (1999). Psychiatric disorders in patients with fibromyalgia: a multicenter investigation. *Psychosomatics* **40**, 57–63.
- Finestone HM, Stenn P, Davies F, Stalker C, Fry R, Koumanis J** (2000). Chronic pain and health care utilization in women with a history of childhood sexual abuse. *Child Abuse and Neglect* **24**, 547–556.
- Fuite J, Vernon SD, Broderick G** (2008). Neuroendocrine and immune network re-modeling in chronic fatigue syndrome: an exploratory analysis. *Genomics* **92**, 393–399.
- Goldberg RT, Pachas WN, Keith D** (1999). Relationship between traumatic events in childhood and chronic pain. *Disability and Rehabilitation* **21**, 23–30.
- Griep EN, Boersma JW, de Kloet ER** (1993). Altered reactivity of the hypothalamic-pituitary-adrenal axis in the primary fibromyalgia syndrome. *Journal of Rheumatology* **20**, 469–474.
- Gunnar MR, Vazquez DM** (2001). Low cortisol and a flattening of expected daytime rhythm: potential indices of risk in human development. *Development and Psychopathology* **13**, 515–538.
- Häuser W** (2005). Fibromyalgia in the legal procedures of the German sozialgericht – psychosocial risk factors and predictors of health care utilization [in German]. *Psychotherapy, Psychosomatik, Medizinische Psychologie* **55**, 72–78.
- Häuser W, Kosseva M, Uceyler N, Klose P, Sommer C** (2011). Emotional, physical, and sexual abuse in fibromyalgia syndrome: a systematic review with meta-analysis. *Arthritis Care and Research (Hoboken)* **63**, 808–820.
- Heath NM, Chesney SA, Gerhart JI, Goldsmith RE, Luborsky JL, Stevens NR, Hobfoll SE** (2013). Interpersonal violence, PTSD, and inflammation: potential psychogenic pathways to higher C-reactive protein levels. *Cytokine* **63**, 172–178.
- Heim C, Mletzko T, Purselle D, Musselman DL, Nemeroff CB** (2008a). The dexamethasone/corticotropin-releasing factor test in men with major depression: role of childhood trauma. *Biological Psychiatry* **63**, 398–405.
- Heim C, Nater UM, Maloney E, Boneva R, Jones JF, Reeves WC** (2009). Childhood trauma and risk for chronic fatigue syndrome: association with neuroendocrine dysfunction. *Archives of General Psychiatry* **66**, 72–80.
- Heim C, Nemeroff CB** (2002). Neurobiology of early life stress: clinical studies. *Seminars in Clinical Neuropsychiatry* **7**, 147–159.
- Heim C, Newport DJ, Bonsall R, Miller AH, Nemeroff CB** (2001). Altered pituitary-adrenal axis responses to

- provocative challenge tests in adult survivors of childhood abuse. *American Journal of Psychiatry* **158**, 575–581.
- Heim C, Newport DJ, Mletzko T, Miller AH, Nemeroff CB** (2008b). The link between childhood trauma and depression: insights from HPA axis studies in humans. *Psychoneuroendocrinology* **33**, 693–710.
- Heim C, Wagner D, Maloney E, Papanicolaou DA, Solomon L, Jones JF, Unger ER, Reeves WC** (2006). Early adverse experience and risk for chronic fatigue syndrome: results from a population-based study. *Archives of General Psychiatry* **63**, 1258–1266.
- Heins MJ, Knoop H, Lobbetael J, Bleijenberg G** (2011). Childhood maltreatment and the response to cognitive behavior therapy for chronic fatigue syndrome. *Journal of Psychosomatic Research* **71**, 404–410.
- Henningsen P, Zipfel S, Herzog W** (2007). Management of functional somatic syndromes. *Lancet* **369**, 946–955.
- Hepgul N, Pariante CM, Dipasquale S, DiForti M, Taylor H, Marques TR, Morgan C, Dazzan P, Murray RM, Mondelli V** (2012). Childhood maltreatment is associated with increased body mass index and increased C-reactive protein levels in first-episode psychosis patients. *Psychological Medicine* **42**, 1893–1901.
- Imbierowicz K, Egle UT** (2003). Childhood adversities in patients with fibromyalgia and somatoform pain disorder. *European Journal of Pain* **7**, 113–119.
- Johnson SK, DeLuca J, Natelson BH** (1999). Chronic fatigue syndrome: reviewing the research findings. *Annals of Behavioral Medicine* **21**, 258–271.
- Johnson SK, Schmalzing KB, Dmochowski J, Bernstein D** (2010). An investigation of victimization and the clinical course of chronic fatigue syndrome. *Journal of Health Psychology* **15**, 351–361.
- Kawatani J, Mizuno K, Shiraishi S, Takao M, Joudoi T, Fukuda S, Watanabe Y, Tomoda A** (2011). Cognitive dysfunction and mental fatigue in childhood chronic fatigue syndrome – a 6-month follow-up study. *Brain and Development* **33**, 832–841.
- Kempke S, Luyten P, Claes S, Van Wambeke P, Bekaert P, Goossens L, Van Houdenhove B** (2013). The prevalence and impact of early childhood trauma in chronic fatigue syndrome. *Journal of Psychiatric Research* **47**, 664–669.
- Kosseva M, Schild S, Wilhelm-Schwenk R, Biewer W, Häuser W** (2010). Comorbid depression mediates the association of childhood/adolescent maltreatment and fibromyalgia syndrome. A study with patients from different clinical settings [in German]. *Schmerz* **24**, 474–484.
- Kroenke K, Mangelsdorff AD** (1989). Common symptoms in ambulatory care: incidence, evaluation, therapy, and outcome. *American Journal of Medicine* **86**, 262–266.
- Lampe A, Doering S, Rumpold G, Solder E, Krismer M, Kantner-Rumplmair W, Schubert C, Sollner W** (2003). Chronic pain syndromes and their relation to childhood abuse and stressful life events. *Journal of Psychosomatic Research* **54**, 361–367.
- Lovinger BL, Shirtcliff EA, Muller D, Alonso C, Coe CL** (2012). Delineating psychological and biomedical profiles in a heterogeneous fibromyalgia population using cluster analysis. *Clinical Rheumatology* **31**, 677–685.
- Lommel K, Kapoor S, Bamford J, Melguizo MS, Martin C, Crofford L** (2009). Juvenile primary fibromyalgia syndrome in an inpatient adolescent psychiatric population. *International Journal of Adolescent Medicine and Health* **21**, 571–579.
- Low LA, Schweinhardt P** (2012). Early life adversity as a risk factor for fibromyalgia in later life. *Pain Research and Treatment* **2012**, 140832.
- Lyall M, Peakman M, Wessely S** (2003). A systematic review and critical evaluation of the immunology of chronic fatigue syndrome. *Journal of Psychosomatic Research* **55**, 79–90.
- Maes M, Twisk FN** (2010). Chronic fatigue syndrome: Harvey and Wessely's (bio)psychosocial model versus a bio (psychosocial) model based on inflammatory and oxidative and nitrosative stress pathways. *BMC Medicine* **8**, 35.
- Maes M, Twisk FNM, Ringel K** (2012). Inflammatory and cell-mediated immune biomarkers in myalgic encephalomyelitis/chronic fatigue syndrome and depression: inflammatory markers are higher in myalgic encephalomyelitis/chronic fatigue syndrome than in depression. *Psychotherapy and Psychosomatics* **81**, 286–295.
- Malleson PN, al-Matar M, Petty RE** (1992). Idiopathic musculoskeletal pain syndromes in children. *Journal of Rheumatology* **19**, 1786–1789.
- Maniglio R** (2009). The impact of child sexual abuse on health: a systematic review of reviews. *Clinical Psychology Review* **29**, 647–657.
- Masuda A, Nozoe SI, Matsuyama T, Tanaka H** (1994). Psychobehavioral and immunological characteristics of adult people with chronic fatigue and patients with chronic fatigue syndrome. *Psychosomatic Medicine* **56**, 512–518.
- May-Chahal C, Cawson P** (2005). Measuring child maltreatment in the United Kingdom: a study of the prevalence of child abuse and neglect. *Child Abuse and Neglect* **29**, 969–984.
- McBeth J, Silman AJ** (2001). The role of psychiatric disorders in fibromyalgia. *Current Rheumatology Reports* **3**, 157–1564.
- McLean SA, Williams DA, Stein PK, Harris RE, Lyden AK, Whalen G, Park KM, Liberzon I, Sen A, Gracely RH, Baraniuk JN, Clauw DJ** (2006). Cerebrospinal fluid corticotropin-releasing factor concentration is associated with pain but not fatigue symptoms in patients with fibromyalgia. *Neuropsychopharmacology* **31**, 2776–2782.
- Morris G, Maes M** (2012). Increased nuclear factor-kappaB and loss of p53 are key mechanisms in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). *Medical Hypotheses* **79**, 607–613.
- NICE** (2007). *Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (or Encephalopathy). Diagnosis and Management of CFS/ME in Adults*. National Institute for Health and Clinical Excellence (NICE) Clinical Guidelines No. 53. Royal College of General Practitioners (UK): London.
- Nicolson NA, Davis MC, Kruszewski D, Zautra AJ** (2010). Childhood maltreatment and diurnal cortisol patterns in women with chronic pain. *Psychosomatic Medicine* **72**, 471–480.

- Okifuji A, Turk DC, Sherman JJ** (2000). Evaluation of the relationship between depression and fibromyalgia syndrome: why aren't all patients depressed? *Journal of Rheumatology* **27**, 212–219.
- Pace TW, Mletzko TC, Alagbe O, Musselman DL, Nemeroff CB, Miller AH, Heim CM** (2006). Increased stress-induced inflammatory responses in male patients with major depression and increased early life stress. *American Journal of Psychiatry* **163**, 1630–1633.
- Pae CU, Masand PS, Marks DM, Krulewicz S, Han CS, Peindl K, Mannelli P, Patkar AA** (2009). History of early abuse as a predictor of treatment response in patients with fibromyalgia: a post-hoc analysis of a 12-week, randomized, double-blind, placebo-controlled trial of paroxetine controlled release. *World Journal of Biological Psychiatry* **10**, 435–441.
- Pariante CM** (2009). Chronic fatigue syndrome and the immune system: 'findings in search of meanings'. *Brain, Behavior, and Immunity* **23**, 325–326.
- Pariante CM, Lightman SL** (2008). The HPA axis in major depression: classical theories and new developments. *Trends in Neurosciences* **31**, 464–468.
- Pereda N, Guilera G, Fornis M, Gomez-Benito J** (2009). The prevalence of child sexual abuse in community and student samples: a meta-analysis. *Clinical Psychology Review* **29**, 328–338.
- Post RM, Altshuler LL, Leverich GS, Frye MA, Suppes T, McElroy SL, Keck PE Jr., Nolen WA, Kupka RW, Grunze H, Rowe M** (2013). Role of childhood adversity in the development of medical co-morbidities associated with bipolar disorder. *Journal of Affective Disorders* **147**, 288–294.
- Raison CL, Lin JM, Reeves WC** (2009). Association of peripheral inflammatory markers with chronic fatigue in a population-based sample. *Brain, Behavior, and Immunity* **23**, 327–337.
- Reeves WC, Lloyd A, Vernon SD, Klimas N, Jason LA, Bleijenberg G, Evengard B, White PD, Nisenbaum R, Unger ER** (2003). Identification of ambiguities in the 1994 chronic fatigue syndrome research case definition and recommendations for resolution. *BMC Health Services Research* **3**, 25.
- Roberts AD, Papadopoulos AS, Wessely S, Chalder T, Cleare AJ** (2009). Salivary cortisol output before and after cognitive behavioural therapy for chronic fatigue syndrome. *Journal of Affective Disorders* **115**, 280–286.
- Roberts ADL, Wessely S, Chalder T, Papadopoulos A, Cleare AJ** (2004). Salivary cortisol response to awakening in chronic fatigue syndrome. *British Journal of Psychiatry* **184**, 136–141.
- Ruiz-Perez I, Plazaola-Castano J, Caliz-Caliz R, Rodriguez-Calvo I, Garcia-Sanchez A, Ferrer-Gonzalez MA, Guzman-Ubeda M, del Rio-Lozano M, Lopez-Chicheri Garcia I** (2009). Risk factors for fibromyalgia: the role of violence against women. *Clinical Rheumatology* **28**, 777–786.
- Sanders P, Korf J** (2008). Neuroaetiology of chronic fatigue syndrome: an overview. *World Journal of Biological Psychiatry* **9**, 165–171.
- Sareen J, Henriksen CA, Bolton SL, Affi TO, Stein MB, Asmundson GJ** (2013). Adverse childhood experiences in relation to mood and anxiety disorders in a population-based sample of active military personnel. *Psychological Medicine* **43**, 73–84.
- Sigurdardottir S, Halldorsdottir S** (2013). Repressed and silent suffering: consequences of childhood sexual abuse for women's health and well-being. *Scandinavian Journal of Caring Sciences* **27**, 422–432.
- Smith BW, Papp ZZ, Tooley EM, Montague EQ, Robinson AE, Cosper CJ** (2010). Traumatic events, perceived stress and health in women with fibromyalgia and healthy controls. *Stress and Health* **26**, 83–93.
- Solomon L, Nisenbaum R, Reyes M, Papanicolaou DA, Reeves WC** (2003). Functional status of persons with chronic fatigue syndrome in the Wichita, Kansas, population. *Health and Quality of Life Outcomes* **1**, 48.
- Sommer C, Häuser W, Burgmer M, Engelhardt R, Gerhold K, Petzke F, Schmidt-Wilcke T, Spath M, Tolle T, Uceyler N, Wang H, Winkelmann A, Thieme K** (2012). Etiology and pathophysiology of fibromyalgia syndrome [in German]. *Schmerz* **26**, 259–267.
- Strickland P, Morriss R, Wearden A, Deakin B** (1998). A comparison of salivary cortisol in chronic fatigue syndrome, community depression and healthy controls. *Journal of Affective Disorders* **47**, 191–194.
- Susman EJ** (2006). Psychobiology of persistent antisocial behavior: stress, early vulnerabilities and the attenuation hypothesis. *Neuroscience and Biobehavioural Reviews* **30**, 376–389.
- Taylor RR, Jason LA** (2001). Sexual abuse, physical abuse, chronic fatigue, and chronic fatigue syndrome: a community-based study. *Journal of Nervous and Mental Disease* **189**, 709–715.
- Tietjen GE, Brandes JL, Peterlin BL, Eloff A, Dafer RM, Stein MR, Drexler E, Martin VT, Hutchinson S, Aurora SK, Recober A, Herial NA, Utley C, White L, Khuder SA** (2010). Childhood maltreatment and migraine (Part III). Association with comorbid pain conditions. *Headache* **50**, 42–51.
- Van Houdenhove B, Egle U, Luyten P** (2005). The role of life stress in fibromyalgia. *Current Rheumatology Reports* **7**, 365–370.
- Van Houdenhove B, Neerinx E, Lysens R, Vertommen H, Van Houdenhove L, Onghena P, Westhovens R, D'Hooghe MB** (2001). Victimization in chronic fatigue syndrome and fibromyalgia in tertiary care: a controlled study on prevalence and characteristics. *Psychosomatics* **42**, 21–28.
- Walen HR, Oliver K, Groessl E, Cronan TA, Rodriguez VM** (2001). Traumatic events, health outcomes, and health care use in patients with fibromyalgia. *Journal of Musculoskeletal Pain* **9**, 19–38.
- Walker EA, Keegan D, Gardner G, Sullivan M, Bernstein D, Katon WJ** (1997). Psychosocial factors in fibromyalgia compared with rheumatoid arthritis: II. Sexual, physical, and emotional abuse and neglect. *Psychosomatic Medicine* **59**, 572–577.

- Wallace DJ** (2006). Is there a role for cytokine based therapies in fibromyalgia. *Current Pharmaceutical Design* **12**, 17–22.
- Weissbecker I, Floyd A, Dedert E, Salmon P, Sephton S** (2006). Childhood trauma and diurnal cortisol disruption in fibromyalgia syndrome. *Psychoneuroendocrinology* **31**, 312–324.
- Wessely S** (1998). The epidemiology of chronic fatigue syndrome. *Epidemiologia e Psichiatria Sociale* **7**, 10–24.
- Wessely S, Powell R** (1989). Fatigue syndromes: a comparison of chronic 'postviral' fatigue with neuromuscular and affective disorders. *Journal of Neurology, Neurosurgery and Psychiatry* **52**, 940–948.
- Wolfe F** (1997). The relation between tender points and fibromyalgia symptom variables: evidence that fibromyalgia is not a discrete disorder in the clinic. *Annals of the Rheumatic Diseases* **56**, 268–271.