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Review article

Meta-analysis and meta-regression of hypothalamic-pituitary-adrenal axis activity in functional somatic disorders

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ABSTRACT

Dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis is the most investigated biological risk marker in functional somatic disorders (FSDs), such as chronic fatigue syndrome (CFS), fibromyalgia (FM), and irritable bowel syndrome (IBS). Our aim was to assess whether there is an association between basal hypocortisolism and FSD and to identify potential moderators of this association. Meta-analysis on 85 studies revealed that although basal cortisol levels were generally lower in FSD subjects compared to controls, this association did not reach statistical significance (SMD −0.07, 95% CI −0.17 to 0.04, $p = 0.241$). However, when the three FSD were assessed separately, statistically significant basal hypocortisolism was observed in CFS subjects compared to controls (SMD −0.14, 95% CI −0.28 to 0.00, $p = 0.047$), but not in FM or IBS. When all potential moderators were entered into a meta-regression analysis, only type of FSD and female gender were significant independent predictors of basal hypocortisolism. In conclusion, we did not find evidence to consider all three main FSD as hypocortisolemic disorders, as significant reduction in basal cortisol compared to healthy controls was only found in CFS and in females with FM, but not in IBS.

Contents

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1. Introduction

Functional somatic disorders (FSDs) are syndromes of related physical complaints without known underlying conventional organic pathology. The main three disorders are chronic fatigue syndrome (CFS), fibromyalgia (FM), and irritable bowel syndrome (IBS); other examples include temporomandibular joint dysfunction, multiple chemical sensitivity and chronic pelvic pain (Wessely et al., 1999). Different FSD share a lot of similarities, for example in case definition and reported symptoms, but also in non-symptom specific associations such as sex, prognosis and response to treatment (Wessely et al., 1999). However, there are also disease-specific characteristics, including specific infections and premorbid levels of distress that may differentially precipitate FSD (Moss-Morris and Spence, 2006). Shared factors might underlie general susceptibility for the development of any FSD, whereas factors specific to individual FSD might shape their final manifestation (Aggarwal et al., 2006; Kato et al., 2009).

HPA axis dysfunction, the most widely investigated biological factor in the etiology of FSD, is one potential shared factor, as alterations in this stress responsive system have been reported for all main FSD (Tak and Rosmalen, 2007). A potential etiological link between the HPA axis and FSD emerges from the potential of HPA axis underactivity to increase symptoms through mechanisms such as increasing pain perception and causing fatigue (Lariviere and Melzack, 2000; Heim et al., 2000; Fries et al., 2005; Fabian et al., 2009). Some even already refer to FSD as hypocortisolemic disorders (Fries, 2008). However, narrative reviews conclude that findings on cortisol levels in CFS, FM, and IBS subjects compared to healthy controls are inconsistent: as well as mild hypocortisolism, normal or increased cortisol levels have also been reported (Mayer et al., 2001; Geenen et al., 2002; Cleare, 2003; Tak and Rosmalen, 2007). It remains to be elucidated why the presence of HPA axis alterations varies both within and among FSD. Moreover, if FSD are really characterized by HPA axis dysfunction, its position in the etiological pathway, if causally linked at all, is still elusive (Tak and Rosmalen, 2010). The idea of HPA axis dysfunction as a mediator between psychosocial stress and FSD has often been advanced, which is supported by the observation that retrospective psychosocial stress has been consistently associated with FSD (Barsky and Borus, 1999; van Houdenhove et al., 2005; Aggarwal et al., 2006; Deary et al., 2007) and has the capacity to induce hypocortisolism in the long-term (Ehlert et al., 2001; Miller et al., 2007; McEwen, 2007). However, HPA axis alterations could also be a consequence of factors such as concurrent stress, sleep disturbances, alcohol use, smoking, obesity, medication use, co-morbid depressive disorder, or physical inactivity (Geenen et al., 2002; Cleare, 2003). Twenty years of research has given rise to conflicting findings, suggesting a need for a systematic meta-analysis of previous research.

The primary purpose of this meta-analysis is to quantify the association between basal HPA axis function and FSD. We hypothesize that FSD are characterized by basal hypocortisolism. Additionally, we hypothesize that HPA axis dysfunction is a shared factor for all main three FSD (i.e., CFS, FM and IBS) and basal hypocortisolism therefore manifests irrespective of the diagnostic label of CFS, FM, or IBS. A second goal is to identify potential moderators of the association between HPA axis dysfunction and FSD, including gender, medication use, co-morbid depressive disorder, and physical inactivity.

2. Methods

2.1. Search strategy

We restricted our meta-analysis to CFS, FM and IBS because exploring literature searches only yielded a sufficient number of primary studies for those three FSD. Relevant articles were identified by searching the databases of Medline, Embase, and PsycINFO (January 1960–November 2009). A search string was formulated for searching Medline. The first component consisted of chronic fatigue syndrome, fibromyalgia, irritable bowel syndrome, and synonyms. The second component consisted of the terms hypothalamic-pituitary-adrenal axis, cortisol, and synonyms. Searching Embase and PsycINFO, terms included in our search were adapted according to the thesaurus of the respective database and explosion of the search terms was applied. Reference lists of original articles and related reviews were hand searched for additional citations. The search was conducted without language restrictions.

2.2. Screening and selection procedure

Title and abstract of the articles were screened by two independent reviewers on three inclusion criteria: (1) case–control studies; (2) cases are adults with CFS, FM, or IBS according to international consensus criteria for the respective FSD available at the time of the study (Center for Disease Control and Prevention Criteria for CFS (Fukuda et al., 1994), American College of Rheumatology Criteria for FM (Wolfe et al., 1990), Rome Criteria for IBS (Drossman, 2006); (3) measurement of HPA axis. Discrepancies were resolved by consensus. Full text articles were acquired and screened on the following exclusion criteria: (a) duplicate reports of the same subjects (original authors were contacted to detect overlap of cases or controls), (b) HPA axis not measured under baseline conditions, (c) no HPA axis data of healthy controls presented, (d) no extractable data or statements on HPA axis function, or (e) not original research.

2.3. Data extraction

From every included paper, name of first author, year of publication, type of FSD, number and age of participants, potential moderators (see Section 2.4) and baseline cortisol levels in either serum, saliva, or urine were extracted. Data extracted from studies using dexamethasone suppression was extracted only before administration of any challenge agent. Previous meta-analyses on HPA axis activity in psychobiological studies lend support to the comparability of cortisol assays in either saliva, blood, or urine (Meewisse et al., 2007; Michaud et al., 2008). When multiple measurements during the day were performed, the measurement closest to 0800 h was selected as the morning measurement and the measurement closest to 1600 h was selected as the afternoon measurement. Non-invasive cortisol measurement in saliva is more naturalistic than measurement after a venipuncture. Moreover, the unbound, biologically active fraction of cortisol in saliva is a more relevant indicator compared to the total (bound and unbound fraction) cortisol that is measured in serum. Furthermore, available evidence suggests that morning levels are related to the experience of symptoms later in the day (Adam et al., 2006; Kumari et al., 2009; Fabian et al., 2009). For the primary meta-analysis combining various types of assays, the hierarchy of the selected measurement was therefore as follows: morning samples were preferred above afternoon samples, saliva was preferred above serum and serum was preferred above 24-h urinary free cortisol (24-h UFC) (Kirschbaum and Hellhammer, 1994; Meewisse et al., 2007). If data were not extractable, i.e., no appropriate units and measures of dispersion or test statistics were provided, authors were

contacted and asked for additional information. For 10 studies, authors supplied additional outcome information that was not presented in the original publication (Elsenbruch et al., 2002, 2004; Zarkovic et al., 2003; Posserud et al., 2004; Bohmelt et al., 2005; Klingmann et al., 2008; Meeus et al., 2008; Nater et al., 2008a,b; Chang et al., 2009). To allow pooling across studies that used different types of HPA axis measurement, we calculated a standardized mean difference (SMD) of basal cortisol levels, which is an effect size measure based on the difference between mean values of FSD subject and healthy control groups divided by the pooled standard deviation (also referred to as Cohen's d) for each study (Rosenthal and DiMatteo, 2001). All data extraction was done by two independent reviewers. In case of missing data, conservative effect sizes were estimated. The SMD of three studies only stating that cortisol levels in FSD patients were not significantly different from controls was therefore set at 0.00 (Yatham et al., 1995; Strickland et al., 1998; Malt et al., 2002). As introducing such conservative effect sizes may yield an underestimated summary effect size that underestimates the real value, the summary effect size was calculated without these three studies in the primary analysis but with those studies in a sensitivity analysis.

2.4. Coding of moderator variables

A second aim of this study was to assess sources of heterogeneity to explain differences between studies. In order to minimize the number of covariates investigated, we followed recommendations to select those justified through scientific rationale, and specify them in advance (Higgins and Thompson, 2004; Freedland et al., 2009). Therefore we composed *a priori* a panel of variables that are most important potential sources of heterogeneity to be tested in moderator analyses, including type of FSD (either CFS, FM, or IBS), gender (based on median split of % females), medication use (exclusion or discontinuation of medication that affects the HPA axis, notably corticosteroids, oral contraceptives, estrogen replacement therapy, and antidepressants), co-morbid depressive disorder (exclusion of participants meeting diagnostic criteria for a depressive disorder) and physical activity (selection of matched physically inactive healthy controls). Some variables that might be theoretically important were rarely addressed in the original studies, including concurrent stress ($N = 13$), sleep disturbances ($N = 13$), and childhood trauma ($N = 5$), while others did not have enough variability between studies to enable the construction of different relevant subgroups, such as age, body mass index, smoking, and duration and severity of the FSD. Those variables could therefore not be tested in moderator analyses. Variables such as somatic co-morbidity and characteristics of HPA axis measurement may introduce noise in cortisol measurements but were not considered likely to essentially bias the results.

2.5. Quality assessment

To assess methodological study quality, we adapted a quality tool already developed for autonomic nervous system studies in FSD (Tak et al., 2009) according to the specific characteristics of HPA axis studies (Table 1). Based on nine items in the three key domains selection of participants, measurement of HPA axis, assessment of confounders (see Appendix A for background and references), a judgment of quality was made by two independent reviewers. We tested interrater reliability by calculating the kappa coefficient (Landis and Koch, 1977). The maximum attainable quality score for a study was 18 points.

2.6. Statistical analyses

Meta-analyses were carried out by an independent statistician in STATA 10.0 (StataCorp, College Station, TX) using the user-contributed command METAN (Bradburn et al., 1998). Each study's SMD was weighted by its inverse variance and an accompanying 95% confidence interval (95% CI) was calculated. Given the previously found conflicting findings (Cleare, 2003; Tak and Rosmalen, 2007), the random effects model that allows for between-study variation of effect sizes was considered more plausible *a priori*. Therefore, random effects models were fitted and presented in the forest plot. The *Q*-test was performed to examine whether there was more heterogeneity in the effect sizes than could be expected from chance alone (DerSimonian and Laird, 1986). Additionally, we calculated the I^2 statistic, expressing the percentage of total variation that can be attributed to heterogeneity rather than chance. We then performed subgroup analyses to examine whether the summary effect size (weighted mean SMD) was moderated by an *a priori* defined set of variables. Meta-regression was performed with SMD as outcome variable and potentially moderating variables as predictor variables to assess their independent contributions. Regression coefficients and 95% confidence intervals (95% CIs) were calculated. Sensitivity analyses taking into account missing values and study quality were performed. The influence of methodological study quality was studied by comparing the summary effect size in low versus high quality studies based on a median split. Publication bias was visually evaluated by a funnel plot and quantified by Egger's test (Egger et al., 1997). We planned to perform a trim and fill procedure as an additional sensitivity analysis (Duval and Tweedie, 2000). All *p*-values less than 0.05 were considered statistically significant.

Table 1
Quality tool to assess methodological quality of hypothalamic-pituitary-adrenal (HPA)-axis function studies in functional somatic disorders.

Appropriate selection of participants

1. Has the disease of the cases been reliably assessed and validated?
   According to international criteria by a physician (2)
   Not according to international criteria or assessor not clearly established (1)
   Self-report or not clearly stated (0)
2. Have all controls been recruited from the same population as the cases?
   Controls from same population as cases (2)
   Selected population, such as hospital staff or students (1)
   Not clearly stated (0)
3. Is the population defined with in- and exclusion criteria?
   Medication use, somatic morbidity, psychiatric morbidity, 3 stated (2)
   Medication use, somatic morbidity, psychiatric morbidity, 1–2 stated (1)
   None stated or not clearly stated (0)
4. Are disease characteristics presented (length and severity of functional somatic disorder)?
   Duration of disease and severity of disorder are stated (2)
   Only duration or only severity is stated (1)
   None stated (0)

Appropriate quantification of HPA axis function

5. Is assessor of HPA axis blind for disease status?
   Yes (2)
   Not clearly stated (0)
6. Are methods for assessment of HPA axis function clearly stated*?
   Time of day, behavior shortly prior to measurement, storage conditions, type of assay performed, repeated measurements, assessing compliance, 5–6 stated (2)
   Time of day, behavior shortly prior to measurement, storage conditions, type of assay performed, repeated measurements, assessing compliance, 3–4 stated (1)
   Time of day, behavior shortly prior to measurement, storage conditions, type of assay performed, repeated measurements, assessing compliance, 1–2 or none stated (0)
7. Is outcome HPA axis measurement clearly described and presented?
   Central tendency and measures of dispersion stated in appropriate units (2)
   Only central tendency but no measures of dispersion stated in appropriate units (1)
   Outcome not clearly stated (0)

Appropriate control for confounding

8. Are potential confounders assessed?[a]
   Age, gender, body mass index, smoking, depression, medication, physical exercise, 5–7 stated (2)
   Age, gender, body mass index, smoking, depression, medication, physical exercise, 3–4 stated (1)
   Age, gender, body mass index, smoking, depression, medication, physical exercise, 1–2 or none stated (0)
9. Are the analyses adjusted for potential confounders?[b]
   Age, gender, body mass index, smoking, depression, medication, physical exercise, 5–7 stated (2)
   Age, gender, body mass index, smoking, depression, medication, physical exercise, 3–4 stated (1)
   Age, gender, body mass index, smoking, depression, medication, physical exercise, 1–2 or none stated (0)

[a] In case of exclusion at item 3, consider confounder as assessed.
[b] In case of exclusion at item 3 or no significant difference between cases and controls at item 8 consider confounder as adjusted for.

3. Results

3.1. Search results and study characteristics

In total, we included 82 references, in which 85 case–control comparisons between FSD subjects and healthy controls were made (see Appendix B). Four of those 85 comparisons did not provide means and standard deviations and were therefore not included in the primary meta-analysis (Yatham et al., 1995;

Table 2
Characteristics of the included studies in the meta-analysis.

Study	Type of FSD	*N* of cases	% *F* cases	Mean age cases	Mean duration (months)	*N* of con	% *F* con	Mean age con	Quality (points)	Cortisol saliva	Cortisol blood	Cortisol urine
Altemus et al. (2001)	CFS	19	68	39.7	44	19	68	38.9	13		x	
Bohmelt et al. (2005)	IBS	25	56	43.5	NR	24	56	38.4	12	x		
Burr et al. (2009)	IBS	30	100	30	NR	31	100	32	10		x	
Calis et al. (2004)	FM	22	100	38.7	NR	15	100	36.5	11		x	
Catley et al. (2000)	FM	21	86	47.9	47	22	86	46.6	15	x		
Chang et al. (2009)	IBS	41	100	39.9	NR	25	100	33	12		x	
Cleare et al. (2001b)	CFS	37	68	33.8	43	28	68	32.4	13		x	x
Cleare et al. (2001a)	CFS	121	64	39.5	65	64	64	33.9	12			x
Cleare et al. (1995)	CFS	10	40	36.5	NR	25	40	35	12		x	
Crofford et al. (2004)	CFS	15	73	35	36	15	73	35.1	15		x	x
Crofford et al. (2004)	FM	13	100	49.8	212	12	100	51	15		x	x
Crofford et al. (1994)	FM	12	100	39.5	74	11	100	39.6	9		x	x
Demitrack et al. (1991)	CFS	19	53	36.4	86	20	53	39.4	9		x	x
Dickhaus et al. (2003)	IBS	15	60	39	NR	14	60	35	12		x	
Dinan et al. (2006)	IBS	21	67	34.6	NR	21	67	30.2	11		x	
Dinan et al. (1997)	CFS	14	80	38	NR	14	80	36.5	8		x	
Elsenbruch et al. (2006)	IBS	17	76	42	NR	12	76	39	12		x	
Elsenbruch et al. (2004)	IBS	14	100	47.7	169	14	100	40	13		x	
Elsenbruch et al. (2002)	IBS	24	100	34	NR	17	100	36.4	12	x		
Elsenbruch et al. (2001)	IBS	24	100	32.8	160	20	100	32.5	14	x		
Eriksson et al. (2008)	IBS	80	91	NR	NR	21	91	NR	7		x	
Fukudo et al. (1998)	IBS	10	50	23.8	NR	10	50	20.7	7		x	
Gaab et al. (2002)	CFS	21	52	36	67	21	52	35.2	15	x		
Giske et al. (2008)	FM	19	100	37	120	19	100	NR	13		x	
Griep et al. (1998)	FM	40	90	43	128	14	90	38.1	15		x	x
Griep et al. (1993)	FM	18	100	38.3	114	18	100	36.8	17		x	
Griep (2000)	FM	20	90	43.7	126	14	90	38.1	15		x	x
Griep (2000)	CFS	12	75	43.4	196	14	75	38.1	15		x	x
Gur et al. (2004)	CFS	62	100	32.6	51	46	100	31.5	12		x	
Gur et al. (2004)	FM	68	100	31.4	48	46	100	31.5	12		x	
Gursel et al. (2001)	FM	20	100	41.3	51	20	100	42.7	9		x	
Hamilos et al. (1998)	CFS	7	86	43	NR	7	86	44.8	8		x	x
Hudson and Cleare (1999)	CFS	20	60	37	NR	20	60	36	14		x	
Inder et al. (2005)	CFS	12	NR	NR	NR	11	NR	NR	9		x	x
Izgi et al. (2005)	CFS	20	70	37.6	NR	15	70	36.5	9		x	
Izquierdo-Alvarez et al. (2008)	FM	47	100	53	NR	58	100	45.5	5			x
Jerjes et al. (2006)	CFS	28	50	34	25	27	50	32.6	12			x
Jerjes et al. (2005)	CFS	15	53	35	32	20	53	33	17	x		
Kaufmann et al. (2008)	FM	22	77	53.1	NR	22	77	51	10		x	
Kilkens et al. (2005)	IBS	14	57	31.5	NR	14	57	32.5	11		x	
Kirnap et al. (2001)	FM	16	81	37.3	NR	16	81	36.9	9		x	
Klerman et al. (2001)	FM	10	100	39.7	NR	12	100	33.3	13		x	
Klingmann et al. (2008)	FM	93	100	51.4	NR	100	100	44.4	6	x		
Light et al. (2009)	FM	25	100	46.4	NR	31	100	40.6	9		x	
Macedo et al. (2008)	FM	27	85	49.4	NR	29	85	50.1	11	x	x	
MacHale et al. (1998)	CFS	30	63	44.2	62	15	63	41.1	12		x	
Maes et al. (1998)	FM	14	79	51	NR	17	79	41.8	8			x
Malt et al. (2002)	FM	22	100	45	NR	13	100	43	7		x	
McLean et al. (2005)	FM	20	80	43	NR	16	80	39	13	x		
Meeus et al. (2008)	CFS	31	68	45	NR	31	68	44	7	x		
Moorkens et al. (2000)	CFS	29	69	39.1	18	9	69	32.4	9		x	
Morriss et al. (2007)	CFS	9	50	46	NR	9	50	45.2	15		x	
Nater et al. (2008b)	CFS	24	79	49.6	151	36	79	49.9	14	x		
Nater et al. (2008a)	CFS	75	77	43.9	90	110	77	44.8	17	x		
Ottenweller et al. (2001)	CFS	17	100	34.4	NR	14	100	34.4	6		x	
Paiva et al. (2002)	FM	20	100	44.6	NR	10	100	47	7		x	
Patacchioli et al. (2001)	IBS	55	61	33.3	NR	28	61	33.7	10	x		
Posserud et al. (2004)	IBS	25	72	43.6	NR	24	72	35.9	7		x	
Racciatti et al. (2001)	CFS	36	56	38.3	88	20	56	34.2	8		x	
Riedel et al. (2002)	FM	13	100	49	NR	13	100	50.1	8		x	
Riedel et al. (1998)	FM	16	81	46.3	NR	17	81	39.9	8		x	
Roberts et al. (2004)	CFS	56	63	39.4	56	35	63	34.9	16	x		
Roberts-Thomson et al. (1988)	IBS	14	NR	47	NR	15	NR	40	3		x	x
Rowbottom et al. (1998)	CFS	16	63	40.1	NR	16	63	40.5	5		x	
Scott et al. (2000)	CFS	19	63	33.8	NR	10	63	27.6	8		x	
Scott et al. (1999b)	CFS	15	53	40.6	NR	11	53	35.8	9		x	
Scott et al. (1999a)	CFS	13	38	38.9	60	13	38	39.4	10		x	
Scott et al. (1998)	CFS	20	65	32.9	NR	20	65	28.2	6		x	
Scott et al. (1998)	CFS	14	57	38.7	58	14	57	33.1	8		x	
Scott et al. (1998)	CFS	13	62	36.2	57	13	62	31	9		x	
Scott et al. (1998)	CFS	21	67	36.1	NR	15	67	33.4	9			x
Shufflebotham et al. (2009)	IBS	11	100	34.4	NR	10	100	31.2	8		x	
Strickland et al. (1998)	CFS	14	100	36	NR	131	100	34	8	x		
Torpy et al. (2000)	FM	13	100	44.9	NR	8	100	45.8	8		x	x
van Denderen et al. (1992)	FM	10	100	40.6	NR	10	100	40.6	7		x	

Table 2 (*Continued*)

Study	Type of FSD	*N* of cases	% *F* cases	Mean age cases	Mean duration (months)	*N* of con	% *F* con	Mean age con	Quality (points)	Cortisol saliva	Cortisol blood	Cortisol urine
van Rensburg et al. (2001)	CFS	15	67	NR	NR	15	67	NR	5		x	
Videlock et al. (2009)	IBS	44	57	40.4	NR	39	54	37.3	10	x		
Visser et al. (2001)	CFS	59	67	38	NR	54	67	38	8		x	
Walter et al. (2006)	IBS	24	85	41	NR	15	85	42	11	x		
Wingenfeld et al. (2007)	FM	15	100	47.9	185	20	100	37.9	12		x	
Wood et al. (1998)	CFS	10	60	34.9	37	10	60	34.2	11	x		
Yatham et al. (1995)	CFS	11	73	NR	NR	11	73	NR	4		x	
Young et al. (1998)	CFS	22	45	39	30	22	45	38	11	x		x
Zarkovic et al. (2003)	CFS	9	67	35	23	39	67	37.8	12		x	

Abbreviations: CFS, chronic fatigue syndrome; con, controls; F, female; FM, fibromyalgia; FSD, functional somatic disorder; IBS, irritable bowel syndrome; NR, not reported.

Strickland et al., 1998; Malt et al., 2002; Burr et al., 2009). Table 2 lists the 85 available comparisons, which together included 2148 FSD subjects and 1988 healthy controls. Forty studies reported on CFS (1010 cases; 1039 controls), 27 studies on FM (650 cases; 595 controls), and 18 studies on IBS (488 cases; 354 controls). Median number of FSD subjects was 20 (range 7–121); median number of controls was 17 (range 7–131). The average mean age of FSD subjects was 40 years (range 24–53); the average mean age of controls was 38 years (range 21–51). Median duration of the FSD was 62 months (range 18–212).

3.2. Overall comparison cortisol and FSD

Fig. 1 shows a forest plot of the SMD of baseline cortisol level in FSD subjects compared to healthy controls in each of the included studies. Meta-analysis revealed that cortisol levels were generally lower in FSD subjects compared to controls, but this association did not reach statistical significance (81 studies, SMD −0.07, 95% CI −0.17 to 0.04, $p = 0.241$). As expected, statistically significant heterogeneity in effect sizes across those studies was present (*Q*-test $\chi^2 = 201$, $p < 0.0001$, $I^2 = 60\%$).

Next, we performed separate meta-analyses to address the effect of the diurnal rhythm of the HPA axis on the association between cortisol and FSD. No statistically significant differences in cortisol between FSD subjects and controls in the morning measurements (60 studies, SMD −0.10, 95% CI −0.22 to 0.02, $p = 0.107$) or afternoon measurement (35 studies, SMD 0.01, 95% CI −0.14 to 0.17, $p = 0.868$) were found. In contrast, the summary effect size for 24-h UFC revealed statistically significant lower cortisol output in FSD subjects compared to controls (19 studies, SMD −0.42, 95% CI −0.67 to −0.18, $p = 0.001$). Statistically significant heterogeneity in the effect sizes was present for all analyses (*Q*-test for morning measurements $\chi^2 = 129$, $p < 0.001$, $I^2 = 54\%$; *Q*-test for afternoon measurements $\chi^2 = 69$, $p < 0.001$, $I^2 = 51\%$; *Q*-test for 24-h UFC measurements $\chi^2 = 49$, $p < 0.001$, $I^2 = 63\%$).

3.3. Moderator analyses

3.3.1. Type of FSD

We first tested whether the type of FSD influenced the summary effect size regarding cortisol levels. Statistically significant hypocortisolism was found in CFS subjects compared to controls (38 studies, SMD −0.14, 95% CI −0.28 to 0.00, $p = 0.047$). Lower cortisol levels were also found in FM subjects compared to controls; however, this difference was not statistically significant (26 studies, SMD −0.10, 95% CI −0.30 to 0.11, $p = 0.359$). Higher baseline cortisol levels were observed compared to controls in IBS patients; however, this difference was not statistically significant (17 studies, SMD 0.14, 95% CI −0.10 to 0.38, $p = 0.263$). For all three FSD, significant heterogeneity in effect sizes was present (*Q*-test for CFS $\chi^2 = 73$, $p < 0.001$, $I^2 = 49\%$; *Q*-test for FM $\chi^2 = 71$, $p < 0.001$, $I^2 = 65\%$; *Q*-test for IBS $\chi^2 = 40$, $p < 0.001$, $I^2 = 60\%$).

3.3.2. Gender

We divided the studies based on a median split of percentage female FSD subjects. Studies with relatively few (<77%) females did not find a difference in cortisol between FSD subjects and controls (40 studies, SMD −0.01, 95% CI −0.17 to 0.14, $p = 0.868$). Although not reaching statistical significance, studies with relatively many (≥77%) females tended to find lower cortisol in FSD subjects compared to controls (41 studies, SMD −0.11, 95% CI −0.26 to 0.04, $p = 0.132$). A post hoc exploratory analysis only including studies restricted to females, showed significant hypocortisolism in FSD female subjects compared to female controls (24 studies, SMD −0.21, 95% CI −0.37 to −0.05, $p = 0.009$). This effect was mainly accounted for by studies in FM (17 studies, SMD −0.24, 95% CI −0.42 to −0.06, $p = 0.008$) and CFS (2 studies, SMD −0.37, 95% CI −0.82 to 0.08, $p = 0.109$), but not IBS (5 studies, SMD −0.04, 95% CI −0.47 to 0.39, $p = 0.851$).

3.3.3. Medication use

The summary effect size approached statistical significance in studies in which medication use potentially affecting the HPA axis (corticosteroids, oral contraceptives, estrogen replacement therapy, antidepressants) was excluded (34 studies, SMD −0.16, 95% CI −0.33 to 0.06, $p = 0.059$), whereas there was no difference between FSD subjects and controls in studies which medication use was either not excluded or not stated as exclusion criterion (47 studies, SMD 0.08, 95% CI −0.13 to 0.15, $p = 0.910$).

3.3.4. Co-morbid depressive disorder

In studies that excluded co-morbid depressive disorder there was no difference in cortisol between FSD subjects and controls (33 studies, SMD 0.03, 95% CI −0.14 to 0.20, $p = 0.730$), whereas in studies that did not exclude co-morbid depressive disorder or did not state whether co-morbid depressive disorder was an exclusion criterion there was borderline statistically significant lower cortisol in FSD subjects compared to controls (48 studies, SMD −0.13, 95% CI −0.27 to 0.01, $p = 0.071$).

3.3.5. Physical inactivity

Only a minority of the studies ascertained that physical activity level in FSD subjects was comparable with controls when assessing cortisol levels (13 studies, SMD −0.05, 95% CI −0.24 to 0.14, $p = 0.608$). In studies that did not specifically address physical activity levels, however, the summary effect size regarding cortisol was essentially the same (68 studies, SMD −0.07, 95% CI −0.19 to 0.06, $p = 0.281$).

3.4. Meta-regression

Meta-regression, taking the independent effects of all above mentioned moderators into account (Table 3), demonstrates that type of FSD is a statistically significant moderator of the summary effect size, with the largest difference between CFS and IBS. A neg-

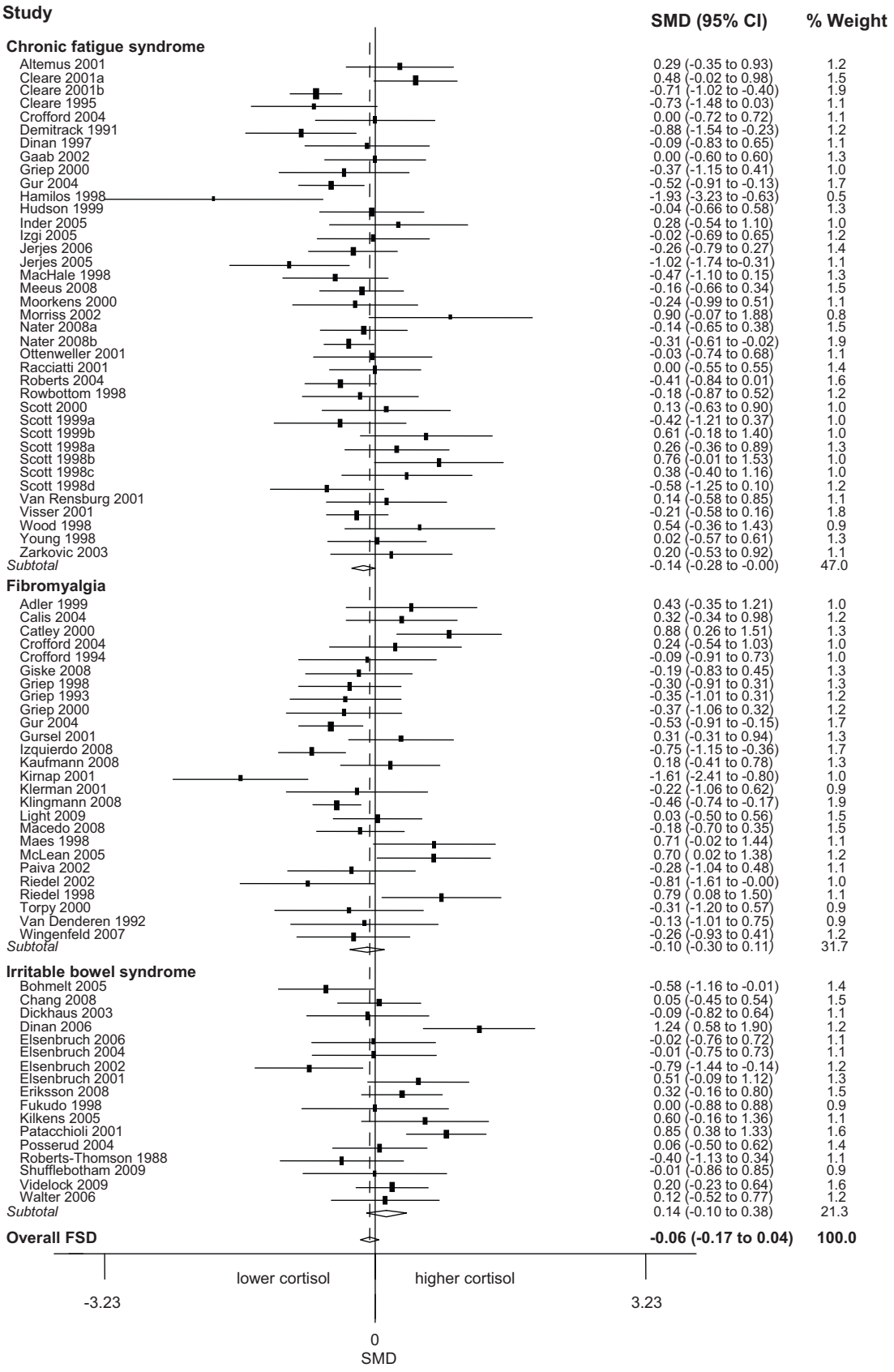

Fig. 1. Forest plot of the association between cortisol and functional somatic disorders. This forest plot demonstrates standardized mean differences (SMDs) and 95% confidence intervals (95% CI) of the included studies and the summary effect size of the association between baseline cortisol and functional somatic disorders (FSDs).

Table 3
Meta-regression with effect size as dependent variable and different potential moderators of the effect size as independent variables.

	Coefficient	95% CI	*t*	*p*-value
Type of FSD[a]				
FM	0.25	−0.10 to 0.60	1.44	0.156
IBS	0.39	0.08 to 0.70	2.52	0.014*
Percentage females[b]	−0.01	−0.02 to 0.00	−2.00	0.049*
Medication use not excluded	0.15	−0.08 to 0.37	1.31	0.193
Exclusion of co-morbid depressive disorder	0.19	−0.04 to 0.41	1.64	0.106
Controls not matched on physical inactivity	−0.15	−0.47 to 0.17	−0.93	0.356
Adjusted r^2	0.14			

Abbreviations: FSD, functional somatic disorder; CFS, chronic fatigue syndrome; FM, fibromyalgia; IBS, irritable bowel syndrome.
[a] CFS is the reference category; overall significance of FSD is $F_{(2,72)} = 3.22$, $p = 0.046$.
[b] Percentage females is entered as a continuous variable in this regression model.
* Denotes the coefficient is significant at 0.05 level.

ative direction of the regression coefficient in this meta-regression indicates that presence of the moderator is associated with more hypocortisolism in FSD compared to controls. Percentage of females is also a significant moderator of the summary effect size, such that including females leads to more marked hypocortisolism in FSD subjects compared to controls. The other moderators did not have an independent statistically significant contribution; however, the directions of the regression coefficients suggest that not matching physical activity levels results in more marked hypocortisolism in FSD subjects compared to controls; not excluding medication use results in less hypocortisolism in FSD subjects compared to controls; and excluding subjects with co-morbid depressive disorder leads to less hypocortisolism in FSD subjects compared to controls. In a model with those five moderators, explained variance of the summary effect size is 14%. Post hoc, we tested whether differences in type of assay could explain the differences in cortisol findings between the three FSD. Adding type of assay to the meta-regression did not essentially change the results.

3.5. Sensitivity analyses

3.5.1. Missing values

Imputing conservative effect sizes (SMD = 0.00) for four studies that only stated that cortisol levels in FSD subjects were not significantly different from controls did not essentially change the overall summary effect size (85 studies, SMD −0.06, 95% CI −0.17 to 0.04, $p = 0.238$).

3.5.2. Methodological study quality

Out of the maximum of 18 points, mean quality score was 10 (range 3–17). The interrater reliability of methodological study quality was good ($\kappa = 0.82$). Based on a median split (low quality = less than 10 points, high quality = 10 points or more), the summary effect size for low quality studies (35 studies, SMD −0.13, 95% CI −0.30 to 0.03, $p = 0.108$) was larger but not statistically different from the summary effect size of high quality studies (46 studies, SMD −0.02, 95% CI −0.16 to 0.13, $p = 0.836$). Furthermore, heterogeneity in both quality subgroups was comparable (*Q*-test $\chi^2 = 74$, $p < 0.001$, $I^2 = 54\%$ and *Q*-test $\chi^2 = 127$, $p < 0.001$, $I^2 = 64\%$, respectively).

3.5.3. Publication bias

Finally, we tested whether publication bias could have affected the results. In discordance with the funnel plot from which no visual asymmetry is apparent (Fig. 2), Egger's test suggested that there was significant funnel plot asymmetry ($p = 0.011$). However, after performing the trim and fill procedure, no studies were trimmed or filled, indicating absence of substantial publication bias.

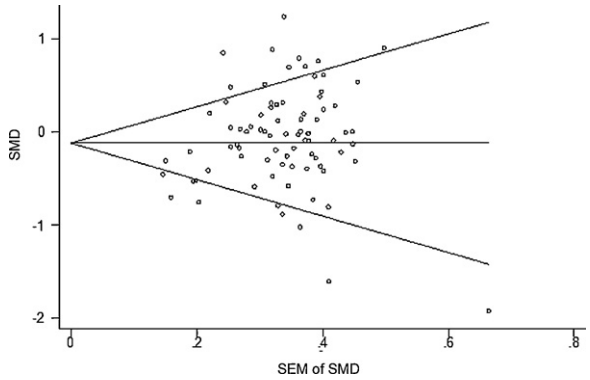

Fig. 2. Funnel plot showing the correlation between the standardized mean difference (SMD) and its standard error (SEM) with pseudo 95% confidence limits.

4. Discussion

The aims of this study were to assess whether FSD are characterized by HPA axis alterations and, if present, to examine by which variables this association is moderated. A meta-analysis of 85 studies demonstrated that baseline cortisol levels were not significantly different in FSD subjects as a whole compared to healthy controls, but were significantly lower in CFS when FSD were considered separately. Female gender, medication use, and presence of co-morbid depressive disorder were moderators of this association. However, meta-regression indicated that the only independent statistically significant factors explaining heterogeneity in effect sizes of cortisol were type of FSD and female gender. It is important to note that the magnitude of the effect size in CFS and FM is comparable, with a wider confidence interval for FM studies possibly related to a lower total number of subjects. In studies composed of exclusively female patients, hypocortisolism is also significant in FM. Thus, hypocortisolism is found in CFS and possibly FM, but not in IBS.

Several explanations can be offered to clarify why, in contrast to our hypothesis, hypocortisolism is only present in CFS and FM but not in IBS.

A first explanation is that this finding demonstrates that CFS and FM are etiologically more alike than CFS or FM with IBS (Aaron et al., 2000; Sullivan et al., 2002). If CFS and FM indeed share hypocortisolism as a causal risk factor, this might also contribute to the experience of fatigue and widespread pain, which are prominent features of both conditions, but not of IBS. This explanation is, however, not fully compatible with the often advanced idea of HPA axis dysfunction as a mediator between psychosocial stress and FSD, since there are no indications that chronic psychosocial stress is differentially associated with the three FSD.

Another explanation is that cortisol levels in IBS patient may differ from those observed in FM and CFS because of the type of studies which are performed in IBS patients. Baseline cortisol measurements in IBS subjects are often performed before sigmoidoscopy or rectal extensions, both stressful procedures which may elicit acute anticipatory stress responses with a hyperactive HPA axis (Walter et al., 2006; Miller et al., 2007).

A third explanation is that cortisol alterations are not FSD-specific, but are instead specific for certain subgroups among FSD which have the highest prevalence in CFS. A subgroup may be formed by subjects with co-morbid depressive disorder which indeed has a higher prevalence in CFS compared to IBS (Henningsen et al., 2003). Given the association of depressive disorder with elevated cortisol levels (Burke et al., 2005; Vreeburg et al., 2009a), we expected that a meta-analysis restricted to studies excluding participants with depressive disorder would lead to more marked hypocortisolism in FSD subjects. In contrast, however,

meta-analysis of studies that did not exclude co-morbid depressive disorder showed more marked hypocortisolism in FSD subjects compared to controls, whereas meta-analysis of studies that did exclude co-morbid depressive disorder did not show any differences between FSD subjects and controls. Although a potentially counterintuitive result, it could be explained by FSD patients experiencing more atypical features of depression (American Psychiatric Association, 1994), given that atypical depression is characterized by hypocortisolism (Gold et al., 1995; Antonijevic, 2006). Alternatively, excluding patients with co-morbid depressive disorder may lead to the exclusion of the more severe cases of FSD, which might reduce the chance of finding HPA axis disturbances. Females could constitute another relevant subgroup across different FSD. Although only reaching statistical significance in exploratory analysis, lower cortisol levels in FSD subjects are predominantly found in studies which included a larger proportion of women. This effect is especially apparent in FM studies (effect size in FM studies with only females is two to three times as large as in the total group of FM studies), but not in IBS studies, whereas the number of CFS studies was too low to draw conclusions. However, in a high quality, large population-based study of CFS subjects and controls included in this meta-analysis, attenuated morning salivary cortisol concentrations were only found in female CFS subjects but not in male CFS subjects (Nater et al., 2008a). Future studies are advised to consider gender as a moderator of the association between HPA axis activity and FSD, as meta-regression also indicates that a difference in percentage of included female subjects accounts for differences in cortisol levels between FSD.

Finally, FSD-specific cortisol alterations may arise from differences in behavioral consequences of the FSD, such as changes in medication use, physical activity, sleeping pattern, working status, or smoking habits (Luger et al., 1987; Badrick et al., 2007; Ambrogio et al., 2008; Vreeburg et al., 2009b). The importance of considering medication use was confirmed by our meta-analysis, although the information that could be obtained from the original studies is too general to draw firm conclusions on the exact influence of oral contraceptives, corticosteroids, estrogen replacement therapy, and antidepressants separately. Although we are not aware of studies directly assessing differences in medication use between FSD, the prevalence of antidepressant use may differ by FSD due to differences in co-morbidity with depressive disorder (Henningsen et al., 2003), or by a differential evidence base for antidepressant use for indication other than depressive disorder (e.g., pain) (Henningsen et al., 2007; Uceyler et al., 2008). We also examined the effect of physical inactivity in our meta-analysis. Given the nature of their symptoms, CFS and FM subjects might avoid physical exercise to a larger degree than IBS subjects do. Although this may theoretically explain differences between the FSD, we found no support for a role of physical inactivity in explaining differences in cortisol levels. However, it should be recognized that the robustness of this analysis is limited, as only a few studies – in particular in CFS – took this potential moderator into account. Moreover, information on physical inactivity was usually based on self-report, while using an objective method to assess physical inactivity (actigraphy), only a subgroup of the CFS patients can be labeled as persistently inactive (van der Werf et al., 2000). Although some studies have indeed shown that hypocortisolism in FSD is reversible by treatment (Bonifazi et al., 2006; Roberts et al., 2009b), these studies have not specifically examined whether these alterations are related to reducing adverse behavioral consequences.

It should be noted that all these mechanisms are probably not mutually exclusive in their contribution to differences in cortisol levels in FSD, and future studies are needed to determine which explanation carries most weight in whom.

Some limitations of this meta-analysis specifically and this research field in general should be recognized.

First, this research field lacks a gold standard how best to study the HPA axis. Several different measurement procedures are available, interpretation of which is not always unambiguous, making the research field prone to focusing on isolated false positive findings. In this meta-analysis, for example, we observed the importance of time of day of the measurement, as hypocortisolism in FSD seem especially present in the morning samples (although not reaching statistical significance in the overall-analysis), but not in afternoon samples. This relative importance of morning cortisol levels is underlined by the finding of statistically significant lower cortisol 24-h UFC in FSD subjects compared to controls, to which morning urine is important because the amount of cortisol excreted following the morning peak of HPA axis activity makes a substantial contribution to the total amount of cortisol excreted in a day (Edwards et al., 2001). These findings suggest that future studies on HPA axis activity in FSD could at least obtain the cortisol awakening response or a morning cortisol sample. Furthermore, when (salivary) cortisol levels are collected in ambulatory settings, subjects' adherence to sampling schedules might be another potentially important confounder, as it has been shown that patients are somewhat more compliant than healthy volunteers resulting in resulting in flatter cortisol slopes in the latter (Broderick et al., 2004). This may have resulted in an underestimation of real differences in salivary cortisol between cases and controls.

Second, this study contains a systematic and quantitative analysis of robust alterations in basal cortisol levels only. Although spontaneous cortisol secretion has been considered most relevant for understanding disease processes (Nicolson, 2007), systematically analyzing HPA axis dysfunction after challenge tests might help to gain a more complete picture of the HPA axis in FSD. The rationale behind stimulating the HPA axis is that the level of the underlying pathophysiology (i.e., dysfunction of the hypothalamus, pituitary, or adrenals) and more subtle alterations may become visible. However, baseline and stress measurements may reflect different processes and should not be lumped together. To be able to interpret subtle alterations in HPA axis functioning appropriately in the process of somatization, it is essential that their different meanings will be further elucidated. The low number of available studies assessing the HPA axis after challenge tests in combination with the abundance of different tests does not allow reliable meta-analysis at this time.

Another limitation is that some variables that might theoretically be important moderators could not be tested in this meta-analysis because they were seldom measured in the included studies. For example, acute psychosocial stress and psychosocial stress in the past are rarely addressed, but both have an impact on cortisol levels (Dickerson and Kemeny, 2004; Meewisse et al., 2007; Miller et al., 2007; Michaud et al., 2008). In this perspective, one relevant stressor might be physical or emotional maltreatment during youth, as it has recently been found that decreased cortisol responses to awakening are observed only in those individuals with CFS who reported exposure to childhood trauma but not in individuals without such exposure (Heim et al., 2009). Another example of an often mentioned potential moderator that could not be tested is sleep disturbance (Buckley and Schatzberg, 2005). However, while subjects with FSD perceive and report sleeping disturbances significantly more often than control subjects, objective sleeping abnormalities are often absent (Elsenbruch et al., 1999; Majer et al., 2007).

We conclude that FSD cannot be collectively referred to as hypocortisolemic disorders, as this meta-analysis only confirmed the presence of lower cortisol levels in subjects with CFS and in females with FM, but not in IBS. Because this meta-analysis only included the main three FSD, we cannot draw conclusions on the cortisol status of patients with other FSD.

Given the likely multifactorial etiology of FSD, HPA axis dysfunction may be of clinical relevance, especially because there are indications for the existence of subgroups in which effects sizes are substantially larger. Although it is important to realize that predictors of remission might differ from predictors of disease onset, randomized controlled trials have shown that low-dose cortisol replacement therapy can produce short-term reductions in fatigue and other features of CFS (McKenzie et al., 1998; Cleare et al., 1999). It should be noted, however, that although pharmacologically raising levels of cortisol can temporarily alleviate symptoms, it is not recommended as treatment in CFS. Reasons for caution are potentially dangerous side effects, a rapid loss of efficacy upon discontinuation and the observation that only a minority of patients gain benefit (Cleare, 2004). A recent study shows that hypocortisolism and a flattened diurnal release of cortisol are associated with a poorer response to cognitive behavioral therapy in CFS (Roberts et al., 2009a). This implies that a patient's neuroendocrine profile may be relevant in choosing the optimal treatment strategy.

This meta-analysis provides a robust assessment of the presence of HPA axis activity alterations in FSD and the role of several potential moderators of this relationship. Several sensitivity analyses confirmed the validity of the findings. Due to the large extent of reliance on cross-sectional case–control studies in this field, however, important questions about the role of cortisol alterations in FSD remain (Tak and Rosmalen, 2010; Rosmalen, 2010). Cross-sectional studies are unable to shed light on the important question as to whether observed endocrine disturbances are primary and causal, secondary and consequential, or epiphenomenal and causally unrelated to CFS. Nevertheless, knowledge about moderators derived from those cross-sectional studies in combination with the criteria listed in the quality tool should inform the conduct of well-designed prospective studies and aid further progress in this field.

Conflict of interest

All authors declare that there are no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.biopsycho.2011.02.002.

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