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REVIEW

Unstimulated cortisol secretory activity in everyday life and its relationship with fatigue and chronic fatigue syndrome: A systematic review and subset meta-analysis☆

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Summary The hypothalamic—pituitary—adrenal (HPA) axis is a psychoneuroendocrine regulator of the stress response and immune system, and dysfunctions have been associated with outcomes in several physical health conditions. Its end product, cortisol, is relevant to fatigue due to its role in energy metabolism. The systematic review examined the relationship between different markers of unstimulated salivary cortisol activity in everyday life in chronic fatigue syndrome (CFS) and fatigue assessed in other clinical and general populations. Search terms for the review related to salivary cortisol assessments, everyday life contexts, and fatigue. All eligible studies (n = 19) were reviewed narratively in terms of associations between fatigue and assessed cortisol markers, including the cortisol awakening response (CAR), circadian profile (CP) output, and diurnal cortisol slope (DCS). Subset meta-analyses were conducted of case—control CFS studies examining group differences in three cortisol outcomes: CAR output; CAR increase; and CP output. Meta-analyses revealed an attenuation of the CAR increase within CFS compared to controls (d = —.34) but no statistically significant differences between groups for other markers. In the narrative review, total cortisol output (CAR or CP) was rarely associated with fatigue in any population; CAR increase and DCS were most relevant. Outcomes reflecting within-day change in cortisol levels (CAR increase; DCS) may be the most relevant to fatigue experience, and future research in this area should report at least one such marker. Results should be considered with caution due to heterogeneity in one meta-analysis and the small number of studies.

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1. Introduction

The repeated assessment of salivary cortisol has enabled the examination of hypothalamic–pituitary–adrenal (HPA) axis activity and its relationship with various psychosocial and somatic experiences in everyday life with high levels of ecological validity (Kirschbaum and Hellhammer, 1989; Schlotz, 2011). Fatigue is a relatively common somatic experience, experienced by up to 40% of the general population (Wessely et al., 1997; Ricci et al., 2007; van't Leven et al., 2010) and considered the primary motive for 6.5% of general practitioner visits and a discreet symptom in 19% (Cullen et al., 2002). Fatigue is prevalent in many clinical populations (e.g., Barnes and Bruera, 2002; Sullivan and Dworkin, 2003; Krupp et al., 2010), and is frequently described as having a detrimental impact on daily living (Hewlett et al., 2005; Lerdal et al., 2007). Chronic fatigue syndrome (CFS) is thought to conceivably represent the extreme end of a fatigue continuum (Pawlikowska et al., 1994). CFS is characterized by profound and persistent fatigue lasting at least six months, coexisting with several other symptoms such as muscular pain and short-term memory loss (Fukuda et al., 1994). However, some have suggested CFS may be qualitatively and quantitatively different to chronic fatigue per se, including fatigue secondary to distinct conditions such as multiple sclerosis or cancer (Wessely, 2001).

The relevance of hypocortisolism to bodily disorders such as CFS has previously been hypothesized (Heim et al., 2000; Fries et al., 2005). Cortisol secretory activity (CSA) is relevant to fatigue due to cortisol's regulatory role in energy metabolism, the high prevalence of fatigue in conditions characterized by low cortisol levels (such as Addison's disease), and the relative efficacy of glucocorticoid treatments in alleviating short-term fatigue (McKenzie et al., 1998; Cleare et al., 1999; Sapolsky et al., 2000; Khani and Tayek, 2001). In an influential study of HPA axis activity in CFS by Demitrack et al. (1991), significantly reduced 24 h urinary free cortisol, attenuated evening plasma cortisol levels, reduced cortisol responses to adrenocorticotropic hormone (ACTH) administration, and blunted ACTH responses to oral corticotrophin releasing hormone (CRH) were reported in CFS versus controls. Prior to this, Poteliakhoff (1981) had also demonstrated attenuated plasma cortisol levels in individuals experiencing chronic fatigue.

Since these early findings, relevant studies have accumulated and published reviews have generally described an attenuation of CSA in CFS (Cleare, 2003; Tak et al., 2011; Papadopoulos and Cleare, 2012). However, this is far from unequivocal, and there are several studies observing no attenuation of CSA or, indeed, raised CSA in CFS (Wood et al., 1998; Inder et al., 2005; Papadopoulos et al., 2009). As such, whether CSA contributes to the etiology of CFS is currently unknown. In addition, despite its potential relevance to fatigue experienced in other populations, no review has yet examined the relationship between CSA and fatigue other than in CFS.

The cortisol awakening response (CAR) describes a surge in cortisol levels upon awakening (Wilhelm et al., 2007), and has two components: (1) the total cortisol output within this period and (2) the dynamic response, usually referring to the change in cortisol output from waking to peak levels (Clow et al., 2004). Typically, total cortisol output is estimated by computing the area under the curve from baseline 0 (AUC_G) using constituent assessments, and the dynamic response by the area under the curve from a baseline defined as cortisol level at waking (AUC_I) (Pruessner et al., 2003) or a variant of cortisol peak-level minus waking-level calculation. A previous review of CAR studies detailed that each component

may be differentially associated with various psychosocial factors (Chida and Steptoe, 2009).

The diurnal cortisol slope (DCS) models the declining pattern of CSA throughout the rest of the day, following the CAR (Adam and Kumari, 2009). An estimation of total cortisol output may also be calculated for the complete circadian rhythm (or profile) using AUC_G or mean cortisol levels. However, a review advised that circadian AUC_G should predominantly be used to complement other measures of CSA as, although it provides "unique information" about average levels of cortisol, it neglects diurnal variation (Adam and Kumari, 2009, p. 1431).

Examining the relationship between fatigue and CSA in real world contexts with high ecological validity is warranted given the impact fatigue has on the quality of life of those who experience it (Repping-Wuts et al., 2008). Laboratory environments can confound cortisol measurements due to the novelty stress of first-time laboratory or hospital visits, as well as physiological reactivity induced by the venipuncture procedure itself in serum sampling (Schlotz, 2011). Urinary sampling for cortisol is sometimes utilized in research designs, but offers only a summary index of cortisol production over a period of time (Schlotz, 2011). When incorporating strategic salivary cortisol assessments, studies abiding by research traditions such as ambulatory assessment (Ebner-Priemer and Kubiak, 2010; Trull and Ebner-Priemer, 2013) or ecological momentary assessment (Stone and Shiffman, 1994) can acquire frequent and fairly rapid repeated measures of circulating free cortisol. The present review examined studies of different CSA markers operationalized by saliva sampling in everyday life and their respective relationships with fatigue in (1) CFS; (2) other clinical groups; and (3) nonclinical populations.

2. Method

2.1. Search strategy

Systematic searches were made using the MEDLINE (Ebsco); PsycINFO (Ebsco); Embase (Ovid); Web of Science (ISI Web of Knowledge); and CINAHL (Ebsco) electronic databases (between database start and 1st June, 2012). Reference lists of similar review articles were hand-searched for potentially relevant articles. Search strings were created as follows: (1) "*fatigue*", (2) "*saliva**" and "*cortisol*", and (3) "*circadian*" or "*diurnal*" or "*basal*" or "*daily*" or "*everyday*" or "*daytime*" or "*slope*" or "*profile*" or "*morning*" or "*awaken**" or "*evening*" or "*waking*" or "wake" (where * indicates truncation). Conference proceedings, dissertations, and theses were not included. No review protocol was published.

2.2. Study selection and criteria for inclusion

Articles were included if they met the following criteria: (1) adult population ($\geq$18 years); (2) published in English; (3) analyzing original data; (4) ambulatory design, featuring salivary cortisol assessments on at least one occasion per day (fixed-occasion if only one); and (5) fatigue measured as an outcome or predictor variable, using (i) an established scale, defined as gaining at least partial inclusion in the Whitehead review of unidimensional and multidimensional measures of fatigue (Whitehead, 2009); (ii) momentary assessments; or (iii) a population with a recognized diagnosis of CFS (meeting Fukuda et al. (1994) or Sharpe et al. (1991) criteria). Exclusion criteria for this review were: (1) studies of HPA axis reactivity to pharmacologic, physiologic, or psychosocial stimulation, unless qualifying data was provided prior to stimulation; (2) randomized controlled trials, unless providing qualifying baseline data; (3) inclusion of pregnant women; (4) inclusion of sleep-deprived or shift workers; and (5) inclusion of participants taking steroidal medications at the time of the study.

2.3. Data extraction

After removal of duplicate records, titles and abstracts were screened for obvious departures from review criteria, followed by full-text screening of those remaining. The following data were extracted: (1) author; (2) year; (3) definition of fatigue, if given; (4) study design (case/control, etc.); (5) participant characteristics (population; number; age; gender; criteria for inclusion/exclusion); (6) number and timing of cortisol assessments; (7) number of sampling days; (8) method of maximizing compliance, if any; (9) saliva sampling procedure; (10) behavioral instructions around saliva sampling; (11) cortisol assay used; (12) chosen fatigue measure; (13) facets of fatigue experience measured (for example, physical or mental fatigue components); (14) variables controlled in the analyses; (15) mean/SD of cortisol assessments and/or computations; (16) mean/SD of fatigue measures; (17) statistical analysis used; (18) results and conclusions. Where incomplete or unclear information was reported, attempts were made to contact the study authors by email for verification. Where salivary cortisol data was unavailable, the study was excluded. Study screening and data extraction was completed by DP.

2.4. Assessment of study quality

Study quality was assessed by a scale developed by the authors, as no appropriate tool existed in the research area focusing on the acknowledged methodological concerns in studies of salivary cortisol assessment in everyday life (Hansen et al., 2008; Adam and Kumari, 2009; Schlotz, 2011). Quality tools used in related systematic reviews were examined, such as in reviews of studies of HPA axis activity in functional somatic disorders (Tak et al., 2011) and of CAR studies (Chida and Steptoe, 2009), and features of both were incorporated where appropriate. As well as discussions between the authors, we also consulted three independent experts in the research area at different stages of the formulation of the scale. Each expert was emailed with a version of the scale and asked to comment on each specific item and to identify any oversights on our part.

The final scale items and scoring options are detailed in Table 1. A maximum score of 16 was possible for each study. For the purposes of this review, the study quality scale was applied independently by two authors (DP and WS), with discrepancies resolved by discussion.

Table 1 Scale to assess methodological quality of everyday life salivary cortisol studies.

(1) Is the population defined with inclusion and exclusion criteria?
- Medication use, disease status, psychiatric morbidity; all 3 stated (2)
- Medication use, disease status, psychiatric morbidity; 2 stated (1)
- None or one stated, or not clearly stated (0)

(2) Are the methods for salivary cortisol assessment clearly described and appropriate?
- Two or more assessment days, repeated assessments within days with assessment times reported, saliva sampling method, storage conditions, type of assay performed; all 5 stated (2)
- Repeated assessments within days with assessment times reported, saliva sampling method, storage conditions, type of assay performed; 3—4 stated (1)
- Less than 3 stated or not appropriate (0)

(3) Is adherence to the sampling protocol controlled?
- Electronic monitoring or prompting, with deviations from protocol observed and controlled, including the objectively observed time of awakening (3)
- As above, but without objectively observing the time of awakening (2)
- Electronic prompting, but deviations from protocol not observed and controlled; OR self-reported sampling times, with deviations observed and controlled (1)
- No appropriate controls, or not stated (0)

(4) If there are early-morning (before 1000 h) salivary measures within the design, were all requested at a time relative to the actual waking time (i.e., upon awakening, or awakening plus 30 min, etc.) OR more than 60 min after awakening?
- Yes, or no pre-1000 h measure included (2)
- No, but awakening time assessed and statistically controlled (1)
- No, or not clearly reported (0)

(5) Were missing cortisol assessments dealt with appropriately in the analyses?
- No missing data; OR principled[a] missing data technique used when estimating parameters (3)
- Parameters based on non-complete but adequate data to provide reliable estimates[b] (2)
- Ad hoc[a] missing data technique used (1)
- No method of dealing with missingness reported, or inappropriate (0)

(6) Is the outcome cortisol measurement clearly presented (verbally, graphically or both) with appropriate units?
- Central tendencies, and measures of dispersion presented for each fixed time-point and all computed cortisol estimates (e.g., AUC) (2)
- Central tendency and measures of dispersion presented for either fixed time-point or computed cortisol estimates (1)
- Outcome not clearly presented (0)

(7) Does the study provide appropriate control/adjustment for confounding variables in the relevant analysis?[c]
- Age, gender, socio-economic status, menstrual cycle,[d] body mass index, smoking, depression, medication,[e] physical exercise, eating shortly before sampling saliva, stressor experience, 6—11 stated (in CAR studies, then also consider waking time, brushing teeth during CAR measurement period, drinking anything other than water during CAR measurement period, sampling day (weekend/weekday), 9—15 stated) (2)
- Age, gender, socio-economic status, menstrual cycle,[d] body mass index, smoking, depression, medication,[e] physical exercise, eating shortly before sampling saliva, stressor experience, 3—5 stated (in CAR studies, +waking time, brushing teeth during CAR measurement period, drinking anything other than water during CAR measurement period, sampling day (weekend/weekday), 6—8 stated) (1)
- Age, gender, socio-economic status, menstrual cycle,[d] body mass index, smoking, depression, medication,[e] physical exercise, eating shortly before sampling saliva, stressor experience, 0—2 stated (in CAR studies, +waking time, brushing teeth during CAR measurement period, drinking anything other than water during CAR measurement period, sampling day (weekend/weekday), 0—5 stated) (0)

[a] Principled missing data techniques refer to likelihood-based and Bayesian estimation methods, and multiple imputation. Ad hoc missing data techniques refer to case deletion or single imputation methods.

[b] To be considered an adequate level of data, must have >2 completed assessments for daytime cortisol estimations and >1 assessment for the CAR. Where cases were deleted due to insufficient completed assessments, a comparison of characteristics of included and excluded cases should be made. Not meeting these criteria should result in a score of 0.

[c] Only score for analysis relevant to the review. If study includes any of the confounders as exclusion criteria in participant recruitment, consider these controlled. If potential confounders are compared between groups (with or without explicit matching procedure) and no difference found ($p > .05$), consider that these variables have been controlled for if they are omitted from subsequent analyses. Person-level, day-level, or assessment-level control and adjustment is acceptable.

[d] In male-only studies, menstrual cycle redundant and 6—10 (9—15) required for a score of 2. Requirements for 1 or 0 points unchanged.

[e] Medication includes hormone replacement therapy, contraceptives, steroids, psychotropic drugs, etc. Accept if study controls for one or all of these.

2.5. Data synthesis

The heterogeneity of designs and populations between qualifying studies led to a narrative review being conducted. Three meta-analyses were also carried out within a subset of studies which had cross-sectional CFS case—control designs. These examined differences between CFS and control groups for CAR total output (meta-analysis 1); CAR dynamic response (meta-analysis 2); and circadian cortisol output (meta-analysis 3). It has been argued that where constituent study characteristics are similar, meta-analysis represents the most appropriate synthesis method even where the number of studies is very small (Valentine et al., 2010).

Standardized mean differences (SMD) were calculated in all cases using AUC_G and AUC_I computations, depending on the aim. Cohen's *d* was the preferred SMD measure due to a tendency for group sizes to be quite different (McGrath, 2006). Where studies computed AUC on more than one day, but did not compute between-day AUC mean and SDs, the decision was made a priori to use only Day 1 data for the meta-analyses. All cortisol values were converted to nmol/L units beforehand, and SDs calculated from confidence intervals where necessary. A random-effects model was considered most appropriate given it assumes varying effect sizes between studies, and it permits inferences that generalize beyond those studies included here (Field and Gillett, 2010). Where appropriate, Cochrane's *Q* and the I^2 statistic were calculated to check for heterogeneity between studies. Where significant mean effect sizes were found, Rosenthal's Fail Safe N (FSN) (Rosenthal, 1979) was used to check for any evidence of publication bias. Analyses were carried out using Review Manager software (The Nordic Cochrane Centre, The Cochrane Collaboration, Version 5.1, 2011), and bespoke meta-analysis syntax to compute FSN (Field and Gillett, 2010) using SPSS (IBM SPSS Statistics, Version 20, 2011).

3. Results

3.1. Search and study selection

The study selection process is detailed in Fig. 1. Searches revealed 514 potentially-relevant papers, and we identified and removed 277 duplicate records of the same report. Following screening and application of selection criteria, data from 19 papers was extracted. Of note, the studies by Nater et al. (2008) and Heim et al. (2009) appeared to be relevant multiple reports of the same study, but testing different hypotheses. We were unable to verify duplicate samples with the authors. We retained Nater et al. (2008) as this report appeared to more closely match the purpose of this review.

Eight studies implementing cross-sectional case—control designs in CFS were selected for the subset meta-analyses (Strickland et al., 1998; Young et al., 1998; Gaab et al., 2002; Roberts et al., 2004; Jerjes et al., 2005; Nater et al., 2008; Papadopoulos et al., 2009; Rahman et al., 2011), and are summarized in Table 2. Two studies qualified for meta-analysis 1 (Gaab et al., 2002; Nater et al., 2008), two for meta-analysis 2 (Roberts et al., 2004; Nater et al., 2008), and three for meta-analysis 3 (Young et al., 1998; Nater et al., 2008; Papadopoulos et al., 2009). Other markers of CSA, such as DCS, were discussed in the narrative review. Seven studies of clinical populations other than CFS qualified (Dekkers et al., 2000; Bower et al., 2005; McLean et al., 2005; Barroso et al., 2006; Bay and Xie, 2009; Sudhaus et al., 2009; Gold et al., 2011); see Table 3. Three nonclinical population studies were also included (Lindeberg et al., 2008; Kumari et al., 2009; Eek et al., 2012); see Table 4. For clarity, all saliva samples provided upon awakening are henceforth referred to as T0, T30 (30 min after awakening), and so on.

3.2. Study quality

Quality Scale item scores for each study are presented in the supplementary material and the total score in the final column of Tables 2—4. Respective study populations and salivary cortisol assessments were generally well-defined and reported within the studies reviewed. Several studies failed to incorporate any method toward maximizing adherence to the sampling design, and several potentially confounded data by ignoring actual waking time when requesting early-morning samples. One potential source of bias apparent in the majority of studies reviewed was the omission of any analytical plan for dealing with missing assessments. The median score for the Quality Scale was 7 out of 16, with scores for CFS studies ranging from 3 to 11, and for other populations from 4 to 14.

3.3. Chronic fatigue syndrome studies

Eight case—control studies were selected, incorporating 636 participants. All studies where fatigue severity was measured revealed statistically significant differences in fatigue scores between groups. One additional qualifying study did not incorporate a control group and used a fatigue measure to distinguish levels of fatigue within their CFS population (Torres-Harding et al., 2008). Comorbid psychiatric disorders were present within the CFS group in six out of the nine studies included.

Three studies assessed the CAR (Gaab et al., 2002; Roberts et al., 2004; Nater et al., 2008). In meta-analysis 1, across both studies measuring CAR AUC_G (Gaab et al., 2002; Nater et al., 2008) (CFS $n = 96$, healthy control $n = 131$) the mean between-group effect size was $d = .27$ (95% CI, −.58, 1.12) with no significant overall effect ($Z = .62$, $p = .53$). Fig. 2(i) reflects this, showing that, although the study by Gaab et al. (2002) showed a higher CAR AUC_G in CFS, this was not replicated in the study by Nater et al. (2008). However, meta-analysis 1 likely reflected a heterogeneous sample of studies ($I^2 = 83\%$; Cochran's $Q\ \chi^2 = 6.06$, $p = .01$).

In meta-analysis 2, which examined CAR AUC_I, across both studies (Roberts et al., 2004; Nater et al., 2008) (CFS $n = 131$, healthy control $n = 145$) the mean between-group effect size was $d = -.34$ (95% CI, −.58, −.09) and revealed a significant overall effect ($Z = 2.72$, $p = .006$, FSN = 4). Both studies individually found a significant between-group difference for AUC_I (see Fig. 2(ii)) reflecting an attenuated cortisol response to awakening in CFS from T0. Meta-analysis 2 did not reflect heterogeneity ($I^2 = 0\%$; Cochran's $Q\ \chi^2 = .21$, $p = .65$).

Four studies examined group differences in the circadian cortisol profile (Young et al., 1998; Gaab et al., 2002; Jerjes et al., 2005; Papadopoulos et al., 2009). Three of these (Young et al., 1998; Gaab et al., 2002; Papadopoulos

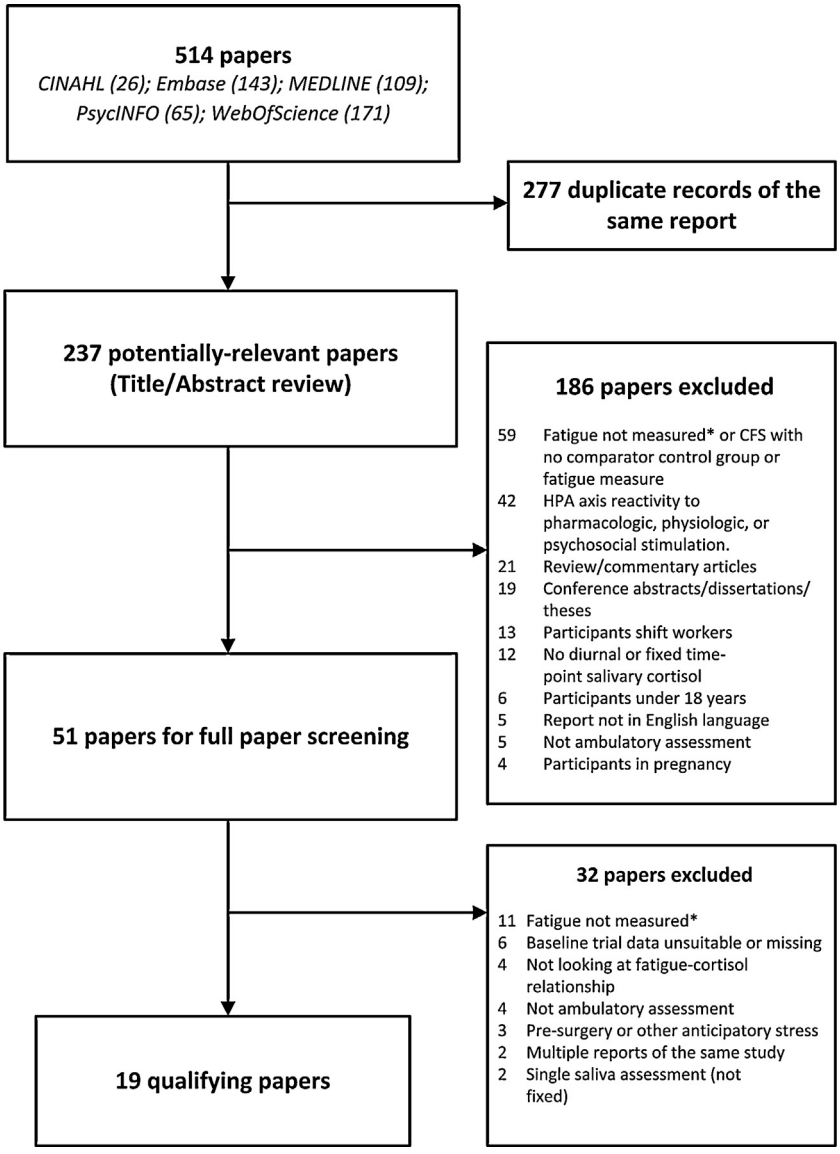


Figure 1 Flow chart of study screening and exclusion process. * indicates fatigue that was not assessed by a measure meeting full or partial inclusion in Whitehead (2009) review.

et al., 2009) estimated total cortisol output (AUC_G) and were entered into meta-analysis 3. The remaining paper (Jerjes et al., 2005) carried out cosinor rhythm analysis. Across all three studies (CFS $n = 61$, healthy control $n = 63$) the mean between-group effect size was $d = 3.18$ (95% CI, .38, 5.98), reflecting a significant overall effect ($Z = 2.23$, $p = .03$). Fig. 2(iii) depicts this. Heterogeneity was high ($I^2 = 97\%$; Cochran's Q $\chi^2 = 64.12$, $p < .001$), and one study (Papadopoulos et al., 2009) provided outlying results. The study by Papadopoulos et al. (2009) was excluded in a subsequent meta-analysis (Fig. 2(iv)) where heterogeneity between studies was rejected ($I^2 = 0\%$; Cochran's Q $\chi^2 = .54$, $p = .46$). The remaining studies (CFS $n = 43$, healthy controls $n = 43$) reflected a mean effect size of $d = .01$ (95% CI, −.43, .42) with no significant overall effect ($Z = .03$, $p = .98$).

Only one of the CFS case–control studies examined cortisol variability within the whole day, using cosinor analysis to perform individual and population mean computations as detailed in the relevant column of Table 2 (Jerjes et al., 2005). MESOR (midline estimate statistic of rhythm), defined as the rhythm-adjusted mean cortisol, was shown to be significantly lower in the CFS group than the control group. Amplitude, which was defined as half the difference between daytime cortisol peak and nadir, was also lower in CFS than healthy controls.

Examination of fixed time-based group comparisons in the case–control studies were mixed, with one study revealing lower CSA in the CFS group at every assessment (T0, 0900 h, 1200 h, 1500 h, 1800 h) except 2100 h, where there was no difference (Jerjes et al., 2005). Another study observed lower levels of CSA in the CFS group only at 2100 h (and not at 1100 h: the only other assessment) (Strickland et al., 1998). In the remaining study performing such comparisons, no statistically significant differences were observed between groups at any assessment (T30, 1200 h, 1800 h, 2200 h) (Rahman et al., 2011).

Table 2 Characteristics of CFS case–control and cross-sectional studies.

Study	Design	Sample: *N* (% female), mean age (SD)	Psychiatric comorbidity	Saliva sampling protocol	Basal cortisol computations	Main findings	Quality score[a] (16)
Gaab et al. (2002)	Case–control, cross-sectional	*CFS*: 21 (52), 36.0 years (4.5); *control*: 21 (52), 35.2 years (4.5).	1 CFS had current episode of major depression (MD); 7 CFS history of MD; 4 CFS history of anxiety disorder.	Days: 2; assessments: 9 (T0, T15, T30, T45, T60, 0800 h, 1100 h, 1500 h, 2000 h).	CAR (AUC_G); circadian profile (AUC_G).	No difference between groups on any basal cortisol measure. Graphical representation does seem to suggest flatter CARs in CFS than controls, although not statistically tested.	8
Jerjes et al. (2005)	Case–control, cross-sectional	*CFS*: 15 (53), 35 years (7.9); *control*: 20 (50), 33 years (11.3).	Individuals with current major depression or anxiety disorders excluded.	Days: 1; assessments: 6 (T0 (0600 h), 0900 h, 1200 h, 1500 h, 1800 h, 2100 h).	Circadian profile ("goodness of fit" to cosinor curve, midline estimate statistic of rhythm (MESOR), amplitude, acrophase); fixed time point.	Evidence for reduced basal cortisol secretory activity in CFS compared to controls, in terms of both MESOR and amplitude (half the cortisol peak minus nadir). Lower cortisol levels observed at all time points, except 2100.	6
Nater et al. (2008)	Case–control, cross-sectional	*CFS*: 75 (77), 43.9 years (SD not given); *control*: 110 (75), 44.8 years (SD not given).	21.3% of CFS group fulfilled diagnostic criteria for MD.	Days: 1; assessments: 3 (T0, T30, T60).	CAR (AUC_G, AUC_I, slope, peak-waking).	Evidence that CFS may be associated with an attenuated CAR, but effect only present in women (overall associations shown actually represent that shown in females; no association apparent in men). AUC_I, slope, and peak minus waking levels all attenuated in female participants.	11
Papadopoulos et al. (2009)	Case–control, cross-sectional	*CFS*: 18 (56), 39.1 years (8.2); *control*: 20 (65), 39.5 years (11.4).	9 CFS with comorbid depression.	Days: 1[b]; assessments: 4 (0800 h, 1200 h, 1600 h, 2000 h).	Circadian profile (AUC_G).	Basal cortisol output significantly higher in CFS compared to controls (CFS with and without comorbid depression both raised compared to controls).	6
Rahman et al. (2011)	Case–control, cross-sectional	*CFS*: 15 (87), 32.5 years (11.1); *control*: 15 (67), 35.6 years (13.9).	MD and psychosis excluded.	Days: 1; assessments: 4 (T30 (to have occurred 0600–0800 h), 1200 h, 1800 h, 2200 h).	Fixed time points only.	No difference at any time point.	11

Table 2 (*Continued*)

Study	Design	Sample: *N* (% female), mean age (SD)	Psychiatric comorbidity	Saliva sampling protocol	Basal cortisol computations	Main findings	Quality score[a] (16)
Roberts et al. (2004)	Case–control, cross-sectional	*CFS*: 56 (63), 39.4 years (11.0); *control*: 35 (60), 34.9 years (12.8).	22 CFS with comorbid depression.	Days: 1; assessments: 5 (T0, T10, T20, T30, T60).	CAR (AUC_I).	Lower CAR in CFS group compared to controls.	9
Strickland et al. (1998)	Case–control, cross-sectional	*CFS*: 14 (100), 36 years (11); *depressed*: 26 (100), 34 (6); *control*: 131 (100), 34 years (7).	10 CFS mild or moderate depressive episodes.	Days: 2; assessments: 2 (1100 h, 2100 h).	Fixed time points (morning, evening).	No difference in 1100 cortisol between groups (trend for lower cortisol in CFS). CFS without comorbid depression significantly lower cortisol at 1100 than controls. Cortisol lower for CFS at 2100 than both controls and depressed group.	8
Torres-Harding et al. (2008)	Cross-sectional	*CFS*: 108 (83), men = 39.6 (11.5); women = 43.9 (11.4).	Not stated, but individuals with psychiatric disorder and taking antidepressants clearly present within sample.	Days: 1; assessments: 5 (T0, T45, 0900 h, 1600 h, 2100 h).	Circadian profile (mean day cortisol, slope, physician classification of profile as "normal" or "abnormal").	No relationship between level of fatigue within CFS and mean cortisol or diurnal slope. Those with "abnormal" cortisol profiles had higher fatigue severity than those with "normal" profiles.	3
Young et al. (1998)	Case–control, cross-sectional	*CFS*: 22 (45), 39 years (8.8); *control*: 22 (45), 38 years (8.0).	Current depressive or anxiety disorder excluded. 2 CFS definite history of MD, 10 CFS probable history of MD.	Days: 1; assessments: 4 (0800 h, 1200 h, 1600 h, 2000 h).	Circadian profile (AUC_G).	No difference between groups.	6

[a] See quality scale items and respective scores in supplementary material for further information.
[b] Additional measurement day in study but was post-administration of dexamethasone.

Table 3 Characteristics of clinical population studies.

Study	Design	Sample population, *N* (% female), mean age (SD)[a]	Saliva sampling protocol	Basal cortisol computations	Fatigue measure	Main findings	Quality score[b] (16)
Barroso et al. (2006)	Cross-sectional	*HIV-positive*, 40 (28), 39.45 years (SD not given).	Days: 1; assessments: 3 (0700 h, 1500 h, 2200 h).	None. Only visual slope trends.	HIV-Related Fatigue Scale.	An upwards cortisol slope over the day ($n = 5$) had highest levels of fatigue (not empirically tested).	4
Bay and Xie (2009)	Cross-sectional	*Mild-to-moderate traumatic brain injury*, 75 (48), mean age and SD not reported.	Days: 1; assessments: 4 (0800 h, 1200 h, 1600 h, 2200 h).	Circadian profile (AUC_G).	Fatigue subscale of the Profile of Mood States.	AUC_G did not predict concurrent fatigue (it did not contribute to their regression model of fatigue alongside other covariates).	6
Bower et al. (2005)	Cross-sectional	*Breast cancer survivors*, 29 (100), fatigued = 58.2 years; not fatigued = 61.8 years (SDs not given).	Days: 2; assessments: 4; (T0 (not while still in bed), 1200 h, 1700 h, 2200 h).	Circadian profile (AUC_G, mean cortisol across days, diurnal slope).	Fatigue subscale of RAND SF-36.	Higher levels of fatigue were assoc. with flatter cortisol slopes, possibly as a consequence of reduced cortisol decline in the evening.	8
Dekkers et al. (2000)	Cross-sectional	*Rheumatoid arthritis (recently diagnosed)*, 25 (76), 55.2 years (SD not given).	Days: 2; assessments: 9 (T0, T15, T30, T45, 1000 h, 1200 h, 1430 h, 1700 h, 1930 h).	CAR (slope); circadian profile (AUC_G, intra-individual standard deviation).	Momentary fatigue ("I feel tired"; 1—5).	Steeper (more positive) responses to waking associated with higher levels of fatigue. Negative correlation between cortisol at T0 and fatigue level at any point in the day. All other tests not significant.	7
Gold et al. (2011)	Cross-sectional	*Multiple sclerosis (relapsing-remitting)*, 44 (100), 35.8 years (0.7).	Days: 2[c]; assessments: 9 (T0, T15, T30, T45, T60, 1100 h, 1500 h, 2000 h, 2200).	CAR (AUC_G); circadian profile (AUC_G).	Modified Fatigue Impact Scale; Fatigue Severity Scale.	No evidence of a relationship between any markers of basal CSA and level of fatigue.	7

Table 3 (*Continued*)

Study	Design	Sample population, *N* (% female), mean age (SD)[a]	Saliva sampling protocol	Basal cortisol computations	Fatigue measure	Main findings	Quality score[b] (16)
McLean et al. (2005)	Cross-sectional	*Fibromyalgia*, 16 (100), 43 years (9).	Days: 2; assessments: 5 (T0, T60, 5 h after waking, late afternoon (1500—1600 h), 30 min before bed).	Fixed time points only.	Momentary fatigue (wording unavailable; 1—100).	No evidence of a relationship between momentary fatigue and concurrent levels of circulating cortisol at any time point.	14
Sudhaus et al. (2009)	Cross-sectional	*Acute and chronic lower back pain (ALBP; CLBP)*, two groups: ALBP = 19 (63), 39.8 years (12.3); CLBP = 24 (71) 38.3 years (11.4).	Days: 2; assessments: 5 (T0, T15, T30, T45, T60).	CAR (AUC_G).	General Fatigue Scale of the Multi-dimensional Fatigue Inventory.	CAR AUC_G correlated with fatigue in positive direction in ALBP and negative direction in CLBP. Within the CLBP group, highly fatigued individuals had blunted CAR compared to those with low fatigue.	10

[a] *N*, sex, age, and cortisol computations reported or used in relevant analyses (patient group in all cases).
[b] See quality scale items and respective scores in supplementary material for further information.
[c] A third day was post-administration of dexamethasone.

Table 4 Characteristics of general population studies.

Study	Design	Sample population, *N* (% female); mean age (SD)	Saliva sampling protocol	Basal cortisol computations	Fatigue measure	Main findings	Quality score[a] (16)
Eek et al. (2012)	Cross-sectional	*Workers*, 581 (61); 46.3 years (10.7).	Days: 1; assessments: 3 (T0, T30, 2100 h).	CAR (morning peak, % increase between T0 and T30, mean of T0 and T30); circadian profile (mean cortisol, evening minus morning peak). Fixed time points.	Swedish Occupational Fatigue Inventory.	% increase in CAR positively associated with lack of energy, lack of motivation, and physical exertion subscales of the SOFI-20. Physical exertion also negatively associated with T0. Associations stronger in women than in men (all associations mentioned above not significant in male-only analyses).	5
Kumari et al. (2009)	Cross-sectional and longitudinal: (1) Phase 6 (P6; 2001); (2) Phase 7 (P7; 2003—2004); (3) Phase 8 (P8; 2006)	*Whitehall II cohort*, 4299, "Fatigued" = (22.3% female); 61.4 years (SD not given); "Not fatigued" = (34.2% female); 59.8 years (SD not given).	Days: 1; assessments: 6 (T0, T30, T2.5 h, T8 h, T12 h, bedtime). Measured at P7 only.	CAR (T30 minus T0); circadian profile (slope, using all samples except T30); fixed time points.	Vitality subscale of SF-36 (cut-off = 50). Fatigue measured at all phases.	Longitudinal (P6/P7): fatigue at P6 not predictive of any cortisol measures at P7. Cross-sectional (P7): no difference in CAR between fatigued and not fatigued groups. T0, T30, and slope all lower or flatter in fatigued group (but T0 cortisol association accounted for by other health measures). Bedtime cortisol higher in fatigued group. Longitudinal (P7/P8): those with flatter slopes at P7 more likely to report persistent fatigue across both P7 and P8, or new fatigue in P8 for those without fatigue at P7.	9

Table 4 (*Continued*)

Study	Design	Sample population, *N* (% female); mean age (SD)	Saliva sampling protocol	Basal cortisol computations	Fatigue measure	Main findings	Quality score[a] (16)
Lindeberg et al. (2008)	Cross-sectional	*Workers*, 78 (73); "Exhausted" = 45 years (8); "Not exhausted" = 46 years (9).	Days: 1; assessments: 3 (T0, T30, 2100 h).	Circadian profile (peak minus nadir, mean cortisol); fixed time point.	Vitality subscale of SF-36[b] (cut-off = 16).	Significant negative correlation between vitality score and peak-nadir cortisol score, and peak-nadir lower in fatigued group. No difference in mean cortisol or cortisol at each time point between groups.	7

[a] See quality scale items and respective scores in supplementary material for further information.
[b] Inverted SF-36 (fatigue measured in positive direction, such that higher scores indicate higher levels of fatigue).

One CFS study without a control group measured levels of fatigue within the sample (Torres-Harding et al., 2008). The study found no relationship between fatigue and either the daily mean cortisol computation or the DCS. However, using a classification approach, a physician categorized participant circadian cortisol profiles as "normal" or "abnormal" (based on "expected" ranges of cortisol profiles), and found that "abnormal" profiles were associated with higher levels of fatigue severity. "Abnormal" profiles did not reflect a specific type of cortisol growth trend but did contain at least one of the following features: (1) "cortisol patterns or results exhibiting divergent peak times"; (2) "decreases in cortisol level followed by sudden increases"; or (3) "general attenuation of cortisol pattern" (Torres-Harding et al., 2008, p. 166). The validity of this classification is unknown, and has not been replicated to the best of our knowledge.

3.4. Fatigue and cortisol secretory activity in other clinical groups

Table 3 shows the characteristics of each of the studies incorporating clinical populations. Previous evidence has suggested a high prevalence of fatigue in each of the conditions represented here: multiple sclerosis (Lerdal et al., 2003); rheumatoid arthritis (Belza, 1995); fibromyalgia (White et al., 2000); chronic lower back pain (Fishbain et al., 2004); traumatic brain injury (Oullet and Morin, 2006); and HIV (Breitbart et al., 1998). Most studies recruited healthy control groups, but the relationship between CSA and fatigue within the control group was not reported in any study.

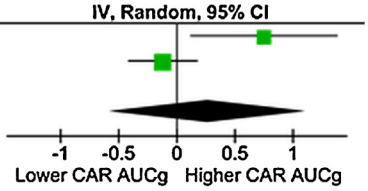
The CAR was examined in three of the seven studies (Dekkers et al., 2000; Sudhaus et al., 2009; Gold et al., 2011). All of these studies computed CAR AUC_G, while one also operationalized individual CAR dynamic responses as regression slope parameters (Dekkers et al., 2000). Only one study found a relationship between fatigue level and AUC_G (Sudhaus et al., 2009). In this study, the chronic lower back pain group had associations between greater fatigue and attenuated CAR output, but the acute lower back pain group showed the opposite: greater fatigue was associated with elevated CAR output. A median split on the Multidimensional Fatigue Inventory (MFI; Smets et al., 1995) showed there were CSA differences between high and low fatigue only within the chronic pain group, with an attenuated CAR AUC_G in those categorized as high fatigue compared to low fatigue. In the remaining two studies, CAR AUC_G was not associated with fatigue level (Dekkers et al., 2000; Gold et al., 2011).

As mentioned, the CAR dynamic response was assessed in only one study (people with rheumatoid arthritis). Higher slope parameters (steeper cortisol responses to awakening) were associated with greater levels of daytime fatigue, but not daytime fatigue variability (Dekkers et al., 2000). Momentary fatigue assessments were incorporated in this study to compute these variables. The authors also performed time-lagged associations between fixed momentary assessments, finding correlations of T0 cortisol with fatigue at any assessment during the day at around $r = -.35$, with successive cortisol assessments up until 1000 h becoming less negatively correlated with fatigue. These time-lagged analyses imply that increased CSA within the first hour of awakening, particularly precisely upon awakening, may be

(i)

Study or Subgroup	CFS Mean	SD	Total	Healthy Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Gaab et al.	86.8	6.5	21	82.3	5.2	21	44.7%	0.75 [0.12, 1.38]
Nater et al.	15.6	6.9	75	16.4	6.4	110	55.3%	-0.12 [-0.41, 0.17]
Total (95% CI)			96			131	100.0%	0.27 [-0.58, 1.12]

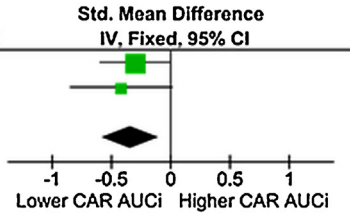
Heterogeneity: Tau² = 0.32; Chi² = 6.06, df = 1 (P = 0.01); I² = 83%
Test for overall effect: Z = 0.62 (P = 0.53)



(ii)

Study or Subgroup	CFS Mean	SD	Total	Healthy Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Nater et al.	2.48	5.37	75	4.22	6.08	110	67.7%	-0.30 [-0.59, -0.00]
Roberts et al.	70.7	241.6	56	172.5	240	35	32.3%	-0.42 [-0.85, 0.01]
Total (95% CI)			131			145	100.0%	-0.34 [-0.58, -0.09]

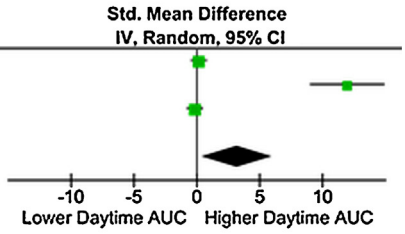
Heterogeneity: Chi² = 0.21, df = 1 (P = 0.65); I² = 0%
Test for overall effect: Z = 2.72 (P = 0.006)



(iii)

Study or Subgroup	Case Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Gaab et al.	27.4	1.6	21	27.1	2.1	21	36.7%	0.16 [-0.45, 0.76]
Papadopoulos et al.	115.3	7.9	18	42.8	3.3	20	26.6%	11.96 [9.05, 14.87]
Young et al.	137.8	20.7	22	141	18.2	22	36.7%	-0.16 [-0.75, 0.43]
Total (95% CI)			61			63	100.0%	3.18 [0.38, 5.98]

Heterogeneity: Tau² = 5.46; Chi² = 64.12, df = 2 (P < 0.00001); I² = 97%
Test for overall effect: Z = 2.23 (P = 0.03)



(iv)

Study or Subgroup	CFS Mean	SD	Total	Healthy Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Gaab et al.	27.4	1.6	21	27.1	2.1	21	48.8%	0.16 [-0.45, 0.76]
Young et al.	137.8	20.7	22	141	18.2	22	51.2%	-0.16 [-0.75, 0.43]
Total (95% CI)			43			43	100.0%	-0.01 [-0.43, 0.42]

Heterogeneity: Tau² = 0.00; Chi² = 0.54, df = 1 (P = 0.46); I² = 0%
Test for overall effect: Z = 0.03 (P = 0.98)

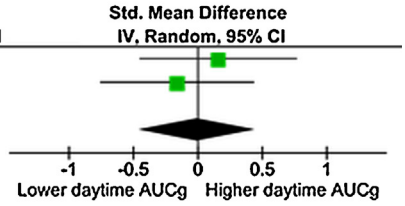


Figure 2 Forest plots for (i) CAR estimated total cortisol output; (ii) CAR estimated dynamic response; and circadian profile total cortisol output in CFS (iii) with, and (iv) without Papadopoulos et al. (2009) paper.

related to how fatigue is experienced throughout the rest of the day in rheumatoid arthritis.

Five of the seven studies examined at least one facet of the circadian cortisol profile (Dekkers et al., 2000; Bower et al., 2005; McLean et al., 2005; Bay and Xie, 2009; Gold et al., 2011) and one study characterized circadian cortisol profiles into different "cortisol trends" using visual categorizations after having problems having saliva samples from their HIV population analyzed (Barroso et al., 2006). No study found any relationship between total estimated cortisol output over the day and fatigue. Bower et al. (2005) found no differences in cortisol AUC_G or mean cortisol between those categorized as fatigued (score < 50) or not fatigued (score > 70) by the energy/fatigue subscale of the RAND SF-36 (Hays et al., 1993). Gold et al. (2011) found that cortisol AUC_G was not a significant predictor of cross-sectional fatigue. Bay and Xie (2009) also observed that cortisol AUC_G did not make a significant contribution to a statistical model of fatigue.

In terms of CSA daily variability, Bower et al. (2005) reported that higher levels of fatigue severity were associated with a flatter DCS. Those within the fatigued group had a flatter DCS than those who were not fatigued, with approximately 25% of between-subject DCS variation accounted for by fatigue group. Dekkers et al. (2000) found that the intra-individual standard deviation of cortisol ("daytime cortisol variability") was not associated with level of fatigue.

The only study in an HIV population had participants' saliva samples refused by the planned analysis laboratory (Barroso et al., 2006). The alternative laboratory required samples be diluted 16 times, which led the authors to render only primitive analyses appropriate. Cortisol profiles were categorized into different trends: (1) "normal downward trend"; (2) "afternoon fall"; (3) "afternoon peak"; (4)

"upward trend". Although no statistical testing was conducted between groups, it was apparent that those with a "normal downward trend" had the lowest ratings of fatigue on the Fatigue Severity Index, computed from the intensity and consequences subscale of the HIV-Related Fatigue Scale (Barroso and Lynn, 2002).

Two studies looked at associations between fixed-occasion salivary cortisol assessments and momentary fatigue (Dekkers et al., 2000; McLean et al., 2005). Neither showed any associations between cortisol and concurrent fatigue, although lagged associations, as detailed previously, were apparent in the rheumatoid arthritis study (Dekkers et al., 2000). Bower et al. (2005) found that between "fatigued" and "not fatigued" participants, there were differences in salivary cortisol levels only in the evening, with cortisol levels marginally higher in the fatigued group at 1700 h and reached significance at 2200 h.

3.5. Fatigue and cortisol secretory activity in nonclinical populations

Three studies examined the relationship between fatigue and CSA in nonclinical populations (Lindeberg et al., 2008; Kumari et al., 2009; Eek et al., 2012). Table 4 depicts study characteristics for each. Two studies examined facets of the CAR in relation to fatigue (Kumari et al., 2009; Eek et al., 2012). Eek et al. (2012) computed mean cortisol between T0 and T30 as an estimation of CAR output, and computed a percentage increase from T0 to T30 as a marker of the dynamic cortisol response to waking. The study found no correlation between CAR output and fatigue on five subscales (lack of energy; physical exertion; physical discomfort; lack of motivation; sleepiness) of the Swedish Occupational Fatigue Inventory (SOFI; Åhsberg et al., 1997). However, positive associations between the CAR dynamic response and three of the SOFI subscales (lack of energy; physical exertion; lack of motivation) were found, but in subsequent analyses these were found to be present in female participants only. Conversely, Kumari et al. (2009) operationalized the CAR dynamic response by calculating peak (T30) minus nadir (T0), and categorized participants into two groups based on a cut-off of 50 on the vitality subscale of the SF-36 (Ware and Sherbourne, 1992). No differences were found for CAR peak minus nadir between the fatigued and not fatigued groups.

In the third study, salivary assessments were made at T0, T30, and 2100 h (Lindeberg et al., 2008). Participants were split into two groups based on a cut-off of 16 on the vitality subscale of the SF-36. There were no differences in daily mean CSA between groups, but the more fatigued group did have significantly lower peak minus nadir values (flatter cortisol profiles). In addition, the study found a negative correlation between vitality score and peak minus nadir values such that they became smaller, and cortisol profiles flatter, with increasing fatigue (vitality scores were inverted such that higher scores indicated more fatigue). Eek et al. (2012) did not find any associations between fatigue and mean cortisol level or peak minus nadir cortisol values. However, Kumari et al. (2009) found the DCS was flatter in the more fatigued group.

All three studies examined associations between fatigue and salivary cortisol at fixed assessment time points (Lindeberg et al., 2008; Kumari et al., 2009; Eek et al., 2012). Kumari et al. (2009) observed lower cortisol levels in the more fatigued group at T0 and T30, and higher cortisol levels at bedtime, with no differences for any of the fixed afternoon assessments (T2.5 h; T8 h; T12 h). Eek et al. (2012) found a negative correlation between the physical exertion subscale of the SOFI scale and cortisol at T0 (in females only), but no associations with any other subscale or at any other time point. No differences were found between groups at any occasion (T0, T30, nor 2100 h) in the study by Lindeberg et al. (2008).

Only one study included in this review had a longitudinal facet to its design (Kumari et al., 2009), and was a large epidemiological study that recruited from the Whitehall II cohort (see Marmot and Brunner, 2005) categorizing each individual as fatigued or not fatigued, as already outlined, at Phase 6 (2001), Phase 7 (2003/2004), and Phase 8 (2006). Salivary cortisol assessments were made only at Phase 7. The study revealed no association between Phase 6 levels of fatigue and Phase 7 CAR peak minus nadir or slope parameter. As has been stated, cross-sectional associations at Phase 7 were apparent, but the between-group differences for T0 cortisol disappeared once health measures were included in the model. A flatter DCS at Phase 7 was associated with persistent fatigue through Phases 7 and 8, as well as predictive of the onset of new fatigue at Phase 8.

4. Discussion

In this review, we included 19 studies published before June 2012 which examined the relationship between fatigue experience and different markers of unstimulated (basal) CSA in everyday life, using salivary cortisol ambulatory assessments. We found an attenuation of cortisol diurnal variability to be important in relation to fatigue in most constituent studies. Measures of total cortisol output, which discard information about diurnal variability (Adam and Kumari, 2009), were rarely associated with fatigue in those studies reviewed. These findings were supported by three meta-analyses of CFS case—control studies, and by a narrative synthesis of remaining clinical and nonclinical studies; although conclusions were less clear in the non-CFS clinical subpopulation.

4.1. Chronic fatigue syndrome

Evidence from eight case—control studies and one case-only study indicated decreased within-person CAR and circadian cortisol variation within CFS. An attenuation of diurnal variability concurs with the most recent review of endocrine dysfunction in CFS (Papadopoulos and Cleare, 2012). However, the present review differs in suggesting that CSA markers that neglect cortisol variability, such AUC_G, have limited relevance to CFS; published reviews have thus far proposed at least modest reductions in total cortisol output in CFS (Cleare, 2003; Tak et al., 2011; Papadopoulos and Cleare, 2012).

A lack of qualifying studies prevents overly-robust conclusions being drawn but, taken together with the narrative synthesis, these observations would seem consistent and could inform the sorts of cortisol markers computed in future empirical studies in CFS. The research area requires more

studies that incorporate prudent steps to maximizing participant adherence to study designs to fully validate these findings, as this is a particular weakness in those studies reviewed here. Consensus on how best to operationalize CSA has not yet been reached. Studies continue to report various models of cortisol activity from constituent assessments, as was demonstrated by two of the nonclinical studies which had the same one-day salivary cortisol assessment design (T0; T30; 2100 h). Despite both wanting to test associations between fatigue and cortisol levels, each computed different markers of CSA and came to opposing conclusions (Lindeberg et al., 2008; Eek et al., 2012). The heterogeneity of CSA measurement is not a criticism exclusive to CFS research, and is apparent in other populations and, indeed, outside of the sphere of fatigue research.

Childhood trauma may contribute to the etiology of CFS. One study has identified childhood maltreatment as a risk factor for CFS, and this relationship may be mediated by HPA axis activity (Heim et al., 2009). Indeed, Heim et al. found only those with CFS who had experienced childhood trauma had an attenuated CAR compared to controls.

Finally, latent class analysis performed in a study of individuals with CFS has identified up to five subgroups in CFS, indicating that CFS is likely to be an umbrella term (Cella et al., 2011). Earlier work by Jason et al. (2005) argued that not employing subtypes in CFS research may be contributing to general inconsistencies in findings within this population. Future studies of salivary cortisol in CFS may benefit from performing subgroup analyses based upon variables such as depression, sleep quality, gender, and pain sensitivity.

4.2. Other clinical and nonclinical groups

AUC_G measures were associated with fatigue in only the study of CSA in lower back pain (Sudhaus et al., 2009), finding associations in alternate directions depending on having chronic (negative association) or acute (positive association) lower back pain (Sudhaus et al., 2009). The authors speculated upon reasons for this differential association: (1) when fatigue accompanies pain, daily activities become more stressful and there is increased CSA in acute pain via the HPA axis stress response and (2) when this stress evolves to become more chronic, this reflects in the HPA axis dysfunction (hypocortisolism) that was observed in the chronic lower back pain group.

Contrary to the apparent trend in CFS studies, two studies found larger increases upon awakening were associated with greater fatigue (Dekkers et al., 2000; Eek et al., 2012). In rheumatoid arthritis, Dekkers et al. (2000) argued that this potentially reflected an "adaptive response of the HPA system" to the fatigue experienced by elevating morning cortisol levels to facilitate higher energy availability (Dekkers et al., 2000, p. 367). Eek et al. (2012) found a similar relationship with fatigue in a nonclinical population, but secondary analyses revealed this to exist only in women. No association between the awakening response and fatigue level was found in a similar analysis with a different nonclinical population (Kumari et al., 2009).

There was evidence of reduced CSA diurnal variability in fatigued individuals in cross-sectional analyses with nonclinical populations. The one longitudinal study we included indicated that fatigue severity did not predict CSA 2—3 years later, but that some facets of CSA (flattened diurnal slope and low waking cortisol) were predictive of concurrent fatigue, and persistent or new fatigue 2—3 years later (Kumari et al., 2009). These findings suggest that changes in basal CSA may occur prior to the onset of (or early in the process of developing) fatigue; a position which would appear at odds with the argument made in the rheumatoid arthritis study that the HPA axis may become more active in order to facilitate increased energy metabolism when experiencing fatigue (Dekkers et al., 2000).

4.3. Relevant salivary cortisol markers in fatigue research

In relation to fatigue experience, the relative importance of within-day cortisol variability compared to estimations of total cortisol output was apparent across all populations. A significant association between fatigue and total cortisol output was only apparent within an outlying study in CFS (Papadopoulos et al., 2009), suggesting that this facet of CSA is not relevant to everyday fatigue experience: chronic or otherwise. In a review of psychosocial factors and the CAR, it was determined that AUC_I, rather than AUC_G, likely represents a "more appropriate measure for assessing HPA activation following waking in relation to psychosocial factors" (Chida and Steptoe, 2009, p. 275). Further, estimates of total cortisol output may be less important than measures of circadian rhythm or variability as outcomes as these latter types may be prominent indicators of regulatory competence (Sephton and Spiegel, 2003). Taken together, this suggests future studies in this field should observe at least one marker of CSA variability, rather than exclusively make comparisons of fixed occasion cortisol levels or estimates of total cortisol output.

In terms of causality, it was not possible to draw firm conclusions due to the lack of longitudinal ambulatory studies that have been conducted thus far. It would seem from the one study available that a flattened DCS may predict future fatigue (Kumari et al., 2009), which complements evidence that cortisol replacement therapy can reduce short-term fatigue in CFS (McKenzie et al., 1998; Cleare et al., 1999). However, there have been suggestions in previous reviews that HPA axis activity (or dysfunction) may not be at the core of CFS, but instead occur as a result of certain behavioral changes associated with the illness (Cleare, 2004). Inferences from two studies (Dekkers et al., 2000; Sudhaus et al., 2009), where CSA variability was actually increased in relation to fatigue, implied that fatigue may precipitate an adaptive or maladaptive alteration in HPA axis activity. It is not yet possible to discern with any certainty whether specific characteristics of CSA may trigger fatigue experience, or vice versa.

4.4. Limitations

We acknowledge several limitations of our review. A lack of published studies, incomplete reporting, and heterogeneous CSA measures all contributed to a small number of studies included in each meta-analysis. Each study also contained relatively few participants so, for both these reasons, interpretations should be taken with caution. There are now a plethora of different markers of CSA that can be computed

from constituent assessments and reported, and despite some efforts to suggest reporting consensus (for example, Clow et al., 2004) the variety of approaches to analysis create difficulties in making between-study comparisons in reviews such as we report here. Some studies chose to examine only fixed occasion assessments, rather than compute other potentially more informative markers of CSA such as a variant of the AUC or DCS. The issue of consensus in the reporting of cortisol markers is something that should be addressed in HPA axis research with a degree of urgency (Clow et al., 2010).

Psychiatric comorbidity was also present within some study samples, which is particularly important within CFS where a recent study has reported comorbidities of depression and/or anxiety disorders in around half of CFS patients (Cella et al., 2013), and previous reports of psychiatric comorbidities have been as high as 75% (Wessely et al., 1996). Salivary cortisol may present at higher levels in depressed individuals than those without depression (Knorr et al., 2010), and Papadopoulos et al. (2009) felt that latent mild or moderate depression with their CFS sample may have contributed toward their unexpected outlying results. Future research should focus on longitudinal designs, where possible, as there is a paucity of this type of evidence available and may contribute to understanding the direction of causality between fatigue and CSA.

It is also important to note that the bidirectional relationship between the immune system and the HPA axis has not been considered within this review. It is likely that variations in immune activity will be relevant to the experience of fatigue in all populations, whether that be directly or indirectly via changes in HPA axis function (Bansal et al., 2012).

4.5. Conclusions

In conclusion, this review suggests that attenuation of CSA variability, in terms of dynamic responses to waking and variations in circadian activity, is the most relevant facet of CSA within fatigued individuals across all populations. The review was unable to unequivocally support the hypocortisolism hypothesis in CFS, although it would seem that smaller increases in cortisol after awakening are apparent within this clinical group. Longitudinal evidence was minimal, and therefore no robust conclusions could be drawn regarding causality in the association of fatigue experience with unstimulated CSA.

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Conflict of interest

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.psyneuen.2013.07.004.

References

Adam, E.K., Kumari, M., 2009. Assessing salivary cortisol in large-scale, epidemiological research. Psychoneuroendocrinology 34, 1423—1436.

Åhsberg, E., Garnberale, F., Kjellberg, A., 1997. Perceived quality of fatigue during different occupational tasks. Development of a questionnaire. Int. J. Ind. Ergonom. 20, 121—135.

Bansal, A.S., Bradley, A.S., Bishop, K.N., Kiani-Alikhan, S., Ford, B., 2012. Chronic fatigue syndrome, the immune system and viral infection. Brain Behav. Immun. 26, 24—31.

Barnes, E.A., Bruera, E., 2002. Fatigue in patients with advanced cancer: a review. Int. J. Gynecol. Cancer 12, 424—428.

Barroso, J., Burrage, J., Carlson, J., Carlson, B.W., 2006. Salivary cortisol values in HIV-positive people. J. Assoc. Nurses AIDS Care 17, 29—36.

Barroso, J., Lynn, M.R., 2002. Psychometric properties of the HIV-Related Fatigue Scale. J. Assoc. Nurses AIDS Care 13, 66—75.

Bay, E., Xie, Y., 2009. Psychological and biological correlates of fatigue after mild-to-moderate traumatic brain injury. West. J. Nurs. Res. 31, 731—747.

Belza, B.L., 1995. Comparison of self-reported fatigue in rheumatoid arthritis and controls. J. Rheumatol. 22, 639—643.

Bower, J.E., Ganz, P.A., Dickerson, S.S., Petersen, L., Aziz, N., Fahey, J.L., 2005. Diurnal cortisol rhythm and fatigue in breast cancer survivors. Psychoneuroendocrinology 30, 92—100.

Breitbart, W., McDonald, M.V., Rosenfeld, B., Monkman, N.D., Passik, S., 1998. Fatigue in ambulatory AIDS patients. J. Pain Symptom Manage. 15, 159—167.

Cella, M., Chalder, T., White, P.D., 2011. Does the heterogeneity of chronic fatigue syndrome moderate the response to cognitive behaviour therapy? An exploratory study. Psychother. Psychosom. 80, 353—358.

Cella, M., White, P.D., Sharpe, M., Chalder, T., 2013. Cognitions, behaviours and co-morbid psychiatric diagnoses in patients with chronic fatigue syndrome. Psychol. Med. 43, 375—380.

Chida, Y., Steptoe, A., 2009. Cortisol awakening response and psychosocial factors: a systematic review and meta-analysis. Biol. Psychol. 80, 265—278.

Cleare, A.J., 2003. The neuroendocrinology of chronic fatigue syndrome. Endocr. Rev. 24, 236—252.

Cleare, A.J., 2004. The HPA axis and the genesis of chronic fatigue syndrome. Trends Endocrinol. Metab. 15, 55—59.

Cleare, A.J., Heap, E., Malhi, G.S., Wessely, S., O'Keane, V., Miell, J., 1999. Low-dose hydrocortisone in chronic fatigue syndrome: a randomised crossover trial. Lancet 353, 455—458.

Clow, A., Hucklebridge, F., Stalder, T., Evans, P., Thorn, L., 2010. The cortisol awakening response: more than a measure of HPA axis function. Neurosci. Biobehav. Rev. 35, 97—103.

Clow, A., Thorn, L., Evans, P., Hucklebridge, F., 2004. The awakening cortisol response: methodological issues and significance. Stress 7, 29—37.

Cullen, W., Kearney, Y., Bury, G., 2002. Prevalence of fatigue in general practice. Ir. J. Med. Sci. 171, 10—12.

Dekkers, J.C., Geenen, R., Godaert, G.L.R., van Doornen, L.J.P., Bijlsma, J.W.J., 2000. Diurnal courses of cortisol, pain, fatigue,

negative mood, and stiffness in patients with recently diagnosed rheumatoid arthritis. Int. J. Behav. Med. 7, 353—371.
Demitrack, M.A., Dale, J.K., Straus, S.E., Laue, L., Listwak, S.J., Kruesi, M.J.P., Chrousos, G.P., Gold, P.W., 1991. Evidence for impaired activation of the hypothalamic—pituitary—adrenal axis in patients with chronic fatigue syndrome. J. Clin. Endocrinol. Metab. 73, 1224—1234.
Ebner-Priemer, U.W., Kubiak, T., 2010. The decade of behavior revisited: future prospects for ambulatory assessment. Eur. J. Psychol. Assess. 26, 151—153.
Eek, F., Karlson, B., Garde, A.H., Hansen, Å.M., Ørbæk, P., 2012. Cortisol, sleep, and recovery — some gender differences but no straight associations. Psychoneuroendocrinology 37, 56—64.
Field, A., Gillett, R., 2010. How to do a meta-analysis. Br. J. Math. Stat. Psychol. 63, 665—694.
Fishbain, D.A., Cutler, R.B., Cole, B., Lewis, J., Smets, E., Rosomoff, H.L., Rosomoff, R.S., 2004. Are patients with chronic low back pain or chronic neck pain fatigued? Pain Med. 5, 187—195.
Fries, E., Hesse, J., Hellhammer, J., Hellhammer, D.H., 2005. A new view on hypocortisolism. Psychoneuroendocrinology 30, 1010—1016.
Fukuda, K., Straus, S., Hickie, I., Sharpe, M., Dobbins, J., Komaroff, A., 1994. The chronic fatigue syndrome: a comprehensive approach to its definition and study. Ann. Intern. Med. 121, 953—959.
Gaab, J., Huster, D., Peisen, R., Engert, V., Schad, T., Schurmeyer, T.H., Ehlert, U., 2002. Low-dose dexamethasone suppression test in chronic fatigue syndrome and health. Psychosom. Med. 64, 311—318.
Gold, S.M., Kruger, S., Ziegler, K.J., Krieger, T., Schulz, K.H., Otte, C., Heesen, C., 2011. Endocrine and immune substrates of depressive symptoms and fatigue in multiple sclerosis patients with comorbid major depression. J. Neurol. Neurosurg. Psychiatry 82, 814—818.
Hansen, Å.M., Garde, A.H., Persson, R., 2008. Sources of biological and methodological variation in salivary cortisol and their impact on measurement among healthy adults: a review. Scand. J. Clin. Lab. Invest. 68, 448—458.
Hays, R.D., Sherbourne, C.D., Mazel, R.M., 1993. The RAND 36-item health survey 1.0. Health Econ. 2, 217—227.
Heim, C., Ehlert, U., Hellhammer, D.H., 2000. The potential role of hypocortisolism in the pathophysiology of stress-related bodily disorders. Psychoneuroendocrinology 25, 1—35.
Heim, C., Nater, U.M., Maloney, E., Boneva, R.S., Jones, J.F., Reeves, W.C., 2009. Childhood trauma and risk for chronic fatigue syndrome: association with neuroendocrine dysfunction. Arch. Gen. Psychiatry 66, 72—80.
Hewlett, S., Cockshott, Z., Byron, M., Kitchen, K., Tipler, S., Pope, D., Hehir, M., 2005. Patients' perceptions of fatigue in rheumatoid arthritis: overwhelming, uncontrollable, ignored. Arthritis Care Res. 53, 697—702.
Inder, W.J., Prickett, T.C.R., Mulder, R.T., 2005. Normal opioid tone and hypothalamic—pituitary—adrenal axis function in chronic fatigue syndrome despite marked functional impairment. Clin. Endocrinol. (Oxf.) 62, 343—348.
Jason, L., Corradi, K., Torres-Harding, S., Taylor, R., King, C., 2005. Chronic fatigue syndrome: the need for subtypes. Neuropsychol. Rev. 15, 29—58.
Jerjes, W.K., Cleare, A.J., Wessely, S., Wood, P.J., Taylor, N.F., 2005. Diurnal patterns of salivary cortisol and cortisone output in chronic fatigue syndrome. J. Affect. Disord. 87, 299—304.
Khani, S., Tayek, J.A., 2001. Cortisol increases gluconeogenesis in humans: its role in the metabolic syndrome. Clin. Sci. 101, 739—747.
Kirschbaum, C., Hellhammer, D.H., 1989. Salivary cortisol in psychobiological research: an overview. Neuropsychobiology 22, 150—169.
Knorr, U., Vinberg, M., Kessing, L.V., Wetterslev, J., 2010. Salivary cortisol in depressed patients versus control persons: a systematic review and meta-analysis. Psychoneuroendocrinology 35, 1275—1286.
Krupp, L.B., Serafin, D.J., Christodoulou, C., 2010. Multiple sclerosis-associated fatigue. Expert Rev. Neurother. 10, 1437—1447.
Kumari, M., Badrick, E., Chandola, T., Adam, E.K., Stafford, M., Marmot, M.G., Kirschbaum, C., Kivimaki, M., 2009. Cortisol secretion and fatigue: associations in a community based cohort. Psychoneuroendocrinology 34, 1476—1485.
Lerdal, A., Celius, E.G., Moum, T., 2003. Fatigue and its association with sociodemographic variables among multiple sclerosis patients. Mult. Scler. 9, 509—514.
Lerdal, A., Gulowsen Celius, E., Krupp, L., Dahl, A.A., 2007. A prospective study of patterns of fatigue in multiple sclerosis. Eur. J. Neurol. 14, 1338—1343.
Lindeberg, S.I., Eek, F., Lindbladh, E., Östergren, P.-O., Hansen, Å.M., Karlson, B., 2008. Exhaustion measured by the SF-36 vitality scale is associated with a flattened diurnal cortisol profile. Psychoneuroendocrinology 33, 471—477.
Marmot, M., Brunner, E., 2005. Cohort profile: the Whitehall II study. Int. J. Epidemiol. 34, 251—256.
McGrath, R.E., 2006. When effect sizes disagree: the case of r and d. Psychol. Methods 11, 386—401.
McKenzie, R., O'Fallon, A., Dale, J., Demitrack, M., Sharma, G., Deloria, M., Garcia-Borreguero, D., Blackwelder, W., Straus, S.E., 1998. Low-dose hydrocortisone for treatment of chronic fatigue syndrome: a randomized controlled trial. JAMA 280, 1061—1066.
McLean, S.A., Williams, D.A., Harris, R.E., Kop, W.J., Groner, K.H., Ambrose, K., Lyden, A.K., Gracely, R.H., Crofford, L.J., Geisser, M.E., Sen, A., Biswas, P., Clauw, D.J., 2005. Momentary relationship between cortisol secretion and symptoms in patients with fibromyalgia. Arthritis Rheum. 52, 3660—3669.
Nater, U.M., Maloney, E., Boneva, R.S., Gurbaxani, B.M., Lin, J.-M., Jones, J.F., Reeves, W.C., Heim, C., 2008. Attenuated morning salivary cortisol concentrations in a population-based study of persons with chronic fatigue syndrome and well controls. J. Clin. Endocrinol. Metab. 93, 703—709.
Oullet, M., Morin, C., 2006. Fatigue following traumatic brain injury: frequency, characteristics, and associated factors. Rehabil. Psychol. 51, 140—149.
Papadopoulos, A., Cleare, A.J., 2012. Hypothalamic—pituitary—adrenal axis dysfunction in chronic fatigue syndrome. Nat. Rev. Endocrinol. 8, 22—32.
Papadopoulos, A., Ebrecht, M., Roberts, A.D.L., Poon, L., Rohleder, N., Cleare, A.J., 2009. Glucocorticoid receptor mediated negative feedback in chronic fatigue syndrome using the low dose (0.5 mg) dexamethasone suppression test. J. Affect. Disord. 112, 289—294.
Pawlikowska, T., Chalder, T., Hirsch, S.R., Wallace, P., Wright, D.J.M., Wessely, S.C., 1994. Population based study of fatigue and psychological distress. Br. Med. J. 308, 763—766.
Poteliakhoff, A., 1981. Adrenocortical activity and some clinical findings in acute and chronic fatigue. J. Psychosom. Res. 25, 91—95.
Pruessner, J.C., Kirschbaum, C., Meinlschmid, G., Hellhammer, D.H., 2003. Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. Psychoneuroendocrinology 28, 916—931.
Rahman, K., Burton, A., Galbraith, S., Lloyd, A., Vollmer-Conna, U., 2011. Sleep—wake behavior in chronic fatigue syndrome. Sleep 34, 671—678.
Repping-Wuts, H., Uitterhoeve, R., van Riel, P., van Achterberg, T., 2008. Fatigue as experienced by patients with rheumatoid arthritis (RA): a qualitative study. Int. J. Nurs. Stud. 45, 995—1002.
Ricci, J.A., Chee, E., Lorandeau, A.L., Berger, J., 2007. Fatigue in the U.S. workforce: prevalence and implications for lost productive work time. J. Occup. Environ. Med. 49, 1—10.

Roberts, A.D.L., Wessely, S., Chalder, T., Papadopoulos, A., Cleare, A.J., 2004. Salivary cortisol response to awakening in chronic fatigue syndrome. Br. J. Psychiatry 184, 136—141.

Rosenthal, R., 1979. The file drawer problem and tolerance for null results. Psychol. Bull. 86, 638—641.

Sapolsky, R.M., Romero, L.M., Munck, A.U., 2000. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. Endocr. Rev. 21, 55—89.

Schlotz, W., 2011. Ambulatory psychoneuroendocrinology: assessing salivary cortisol and other hormones in daily life. In: Mehl, M.R., Conner, T.S. (Eds.), Handbook of Research Methods for Studying Daily Life. Guilford Press, New York, NY.

Sephton, S., Spiegel, D., 2003. Circadian disruption in cancer: a neuroendocrine—immune pathway from stress to disease? Brain Behav. Immun. 17, 321—328.

Sharpe, M.C., Archard, L.C., Banatvala, J.E., Borysiewicz, L.K., Clare, A.W., David, A., Edwards, R.H., Hawton, K.E., Lambert, H.P., Lane, R.J., et al., 1991. A report — chronic fatigue syndrome: guidelines for research. J. R. Soc. Med. 84, 118—121.

Smets, E.M.A., Garssen, B., Bonke, B., De Haes, J.C.J.M., 1995. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. J. Psychosom. Res. 39, 315—325.

Stone, A.A., Shiffman, S., 1994. Ecological momentary assessment (EMA) in behavioral medicine. Ann. Behav. Med. 16, 199—202.

Strickland, P., Morriss, R., Wearden, A., Deakin, B., 1998. A comparison of salivary cortisol in chronic fatigue syndrome, community depression and healthy controls. J. Affect. Disord. 47, 191—194.

Sudhaus, S., Fricke, B., Stachon, A., Schneider, S., Klein, H., von During, M., Hasenbring, M., 2009. Salivary cortisol and psychological mechanisms in patients with acute versus chronic low back pain. Psychoneuroendocrinology 34, 513—522.

Sullivan, P.S., Dworkin, M.S., 2003. Prevalence and correlates of fatigue among persons with HIV infection. J. Pain Symptom Manage. 25, 329—333.

Tak, L.M., Cleare, A.J., Ormel, J., Manoharan, A., Kok, I.C., Wessely, S., Rosmalen, J.G.M., 2011. Meta-analysis and meta-regression of hypothalamic—pituitary—adrenal axis activity in functional somatic disorders. Biol. Psychol. 87, 183—194.

Torres-Harding, S., Sorenson, M., Jason, L., Reynolds, N., Brown, M., Maher, K., Fletcher, M.A., 2008. The associations between basal salivary cortisol and illness symptomatology in chronic fatigue syndrome. J. Appl. Biobehav. Res. 13, 157—180.

Trull, T.J., Ebner-Priemer, U., 2013. Ambulatory assessment. Annu. Rev. Clin. Psychol. 9, 151—176.

Valentine, J.C., Pigott, T.D., Rothstein, H.R., 2010. How many studies do you need? J. Educ. Behav. Stat. 35, 215—247.

van't Leven, M., Zielhuis, G.A., van der Meer, J.W., Verbeek, A.L., Bleijenberg, G., 2010. Fatigue and chronic fatigue syndrome-like complaints in the general population. Eur. J. Public Health 20, 251—257.

Ware, J.E., Sherbourne, C.D., 1992. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med. Care 30, 473—483.

Wessely, S., 2001. Chronic fatigue: symptom and syndrome. Ann. Intern. Med. 134, 838—843.

Wessely, S., Chalder, T., Hirsch, S., Wallace, P., Wright, D., 1996. Psychological symptoms, somatic symptoms, and psychiatric disorder in chronic fatigue and chronic fatigue syndrome: a prospective study in the primary care setting. Am. J. Psychiatry 153, 1050—1059.

Wessely, S., Chalder, T., Hirsch, S., Wallace, P., Wright, D., 1997. The prevalence and morbidity of chronic fatigue and chronic fatigue syndrome: a prospective primary care study. Am. J. Public Health 87, 1449—1455.

White, K., Speechley, M., Harth, M., Ostbye, T., 2000. Co-existence of chronic fatigue syndrome with fibromyalgia syndrome in the general population: a controlled study. Scand. J. Rheumatol. 29, 44—51.

Whitehead, L., 2009. The measurement of fatigue in chronic illness: a systematic review of unidimensional and multidimensional fatigue measures. J. Pain Symptom Manage. 37, 107—128.

Wilhelm, I., Born, J., Kudielka, B.M., Schlotz, W., Wüst, S., 2007. Is the cortisol awakening rise a response to awakening? Psychoneuroendocrinology 32, 358—366.

Wood, B., Wessely, S., Papadopoulos, A., Poon, L., Checkley, S., 1998. Salivary cortisol profiles in chronic fatigue syndrome. Neuropsychobiology 37, 1—4.

Young, A.H., Sharpe, M., Clements, A., Dowling, B., Hawton, K.E., Cowen, P.J., 1998. Basal activity of the hypothalamic—pituitary—adrenal axis in patients with the chronic fatigue syndrome (neurasthenia). Biol. Psychiatry 43, 236—237.