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Association between light exposure patterns and multidimensional health outcomes in individuals with myalgic encephalomyelitis/chronic fatigue syndrome: findings from an observational cross-sectional cohort study

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† These authors contributed equally to this work and share the senior authorship. **Running title:** Light exposure and illness severity in ME/CFS

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jesus.castro@vhir.org **Abstract**

Background: Light is a major environmental factor regulating circadian rhythms, sleep-
wake cycles, and mood-related behaviors. Patients with Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) often experience circadian disruption and poor sleep quality, which severely compromise their quality of life; however, the relationship between light exposure and illness severity remains largely unknown.

Methods: An observational cross-sectional cohort secondary study used collected data from 100 ME/CFS patients and 56 healthy controls to explore the impact of spontaneous light exposure on multidimensional health status and circulating biochemical parameters. Demographic and clinical features were assessed using validated patient-reported outcome measures. Light intensity, wrist temperature, and physical activity were continuously monitored at home over one week using wrist-worn actigraphy. Light intensity during predefined intervals and rhythmic variables of light cycle were calculated. Principal component analysis (PCA) was applied to reduce dimensionality of light variables. Multivariable analysis was performed adjusting for age, sex, body mass index, and physical activity.

Results: Following PCA of the light patterns, two components emerged across groups with high consistency: PC1 (explaining 61.7% of the total variance) reflected higher daytime light and rhythm stability, and PC2 (explaining 16.1%) represented nocturnal/early-morning light and rhythm instability. In ME/CFS patients, light variables were more extensively

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associated with clinical outcomes measures (FIS-40, PSQI and SF-36) than in healthy controls (all $p < 0.05$). Furthermore, PC2 was associated with higher levels of VCAM-1 and triglycerides, and lower serotonin concentrations (all $p < 0.05$). Four distinct light patterns were identified based on PCA scores: nocturnal light, healthy, adverse, and low diurnal light. ME/CFS patients exhibiting the healthy light pattern showed significantly lower fatigue, fewer sleep complaints, reduced autonomic dysfunction, and higher quality of life compared to those with the adverse light pattern (all $p < 0.05$). No significant differences were observed among healthy controls.

Conclusions: Light exposure patterns show distinct associations with symptom variability in ME/CFS compared to healthy controls. More stable daytime light appears to relate to better symptom profiles, whereas irregular exposure and nocturnal light are linked to poorer health outcomes. Although causality cannot be inferred, these findings highlight light exposure as a potentially modifiable, non-invasive target for behavioral interventions aimed at improving the quality of life in ME/CFS, representing a promising emerging for future translational research.

Keywords: chronobiology; circadian rhythm; light patterns; fatigue; non-restorative sleep; autonomic dysfunction; myalgic encephalomyelitis; chronic fatigue syndrome

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Background

Human behavior and physiology are regulated by circadian rhythms, whose primary synchronizer is the natural light-dark cycle. Accordingly, light plays a crucial role in human health and well-being beyond its visual function. The non-visual effects of light encompass influences on the circadian system, sleep quality, mood, cognitive performance, and broader physiological regulation [1]. Conversely, disruptions in light exposure patterns, such as insufficient daytime light or excessive exposure to artificial light at night (LAN) have been associated with sleep disturbances [2–7], cognitive

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impairments and mood disorders [4–6,8] and metabolic dysregulation [9–11]. Therefore, understanding how different light exposure profiles affect human health is essential for developing interventions aimed at improving health-related quality of life, particularly in vulnerable populations.

Myalgic encephalomyelitis, also referred to as chronic fatigue syndrome (ME/CFS), is a complex and debilitating multifaceted disorder characterized by persistent or relapsing fatigue lasting at least six months that is not alleviate by rest. It is frequently accompanied by post-exertional malaise, cognitive impairments, non-restorative sleep, autonomic dysfunction, and a broad spectrum of somatic symptoms that substantially impair daily functioning by more than 50% among sufferers [12]. Despite increasing recognition of the clinical and societal burden of ME/CFS, its underlying pathophysiological mechanisms remain poorly understood, and reliable biomarkers or environmental indicators of disease severity are still lacking [13].

Through the visual and non-visual pathways, light may influence both fatigue and quality of life directly via neural circuits regulating mood and alertness, and indirectly through the modulation of circadian rhythms. Disruption of these rhythms, often referred to as chronodisruption, has been increasingly recognized as a key mechanism linking abnormal light exposure to adverse health outcomes [14,15]. Individuals with ME/CFS frequently experience reduced exposure to natural daylight, often as a consequence of mobility limitations or prolonged periods spent indoors or bedbound [16]. Insufficient light exposure may further exacerbate these health and wellbeing challenges by contributing to fatigue, sleep disturbances, cognitive dysfunction (“brain fog”), alterations in neurotransmitter homeostasis, and reduced vitamin D biosynthesis [16–19]. However, the extent to which light exposure patterns are associated with symptom severity in ME/CFS remains largely unexplored.

Actigraphy, a non-invasive method for continuously monitoring rest–activity cycles, represents a valuable tool for assessing sleep and circadian rhythms

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in real-world settings [20–23]. Modern wrist-worn actigraphy can also capture ambient light intensity, enabling the simultaneous assessment of behavioral and environmental circadian inputs [24]. Thus, by integrating actigraphy-derived light exposure data with clinical outcomes, it is possible to investigate potential associations between objective light exposure patterns and subjective experiences of health status and quality of life in ME/CFS.

In previous studies, we demonstrated that overall light intensity was lower in ME/CFS patients than in healthy controls, likely reflecting reduced outdoor exposure and increased time spent indoors. Given the tight coupling between light exposure and physical activity, this observation is consistent with the lower activity levels typically reported in this population [25–27]. Building upon these findings, the current study constitutes a secondary analysis utilizing actigraphy-derived light exposure data, health outcomes measures, and circulating blood parameters from previous investigations to explore their potential association with light exposure patterns in individuals with ME/CFS [26–28].

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This study aimed to extend our prior findings by examining whether real-world light exposure may differentially relate to clinical and physiological outcomes measures in ME/CFS patients, independent of differences in overall light intensity. We hypothesize that more stable and well-defined light exposure patterns are associated with a lower symptom burden and better health-related quality of life in ME/CFS.

Methods

Study design, setting and participant recruitment

A unicenter, observational cross-sectional cohort secondary study included 100 ME/CFS patients (mean age: 49.5 ± 0.99 years; 80 females) and 56 matched healthy controls (mean age: 42.9 ± 1.78 years; 45 females) consecutively by a specialist clinic from the largest outpatient tertiary

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referral center (ME/CFS Unit, Vall d'Hebron University Hospital, Barcelona, Spain) between October 2020 and March 2022.

Individual with ME/CFS were eligible if they were aged ≥18 years and had a confirmed diagnosis of ME/CFS established according to the 2011 Canadian Consensus Criteria (also commonly referred to as ICC) [29]. Patient selection was based on consecutive enrollment, and exclusion criteria were applied as previously reported [27].

Healthy controls were eligible if they were aged ≥ 18 years and reported no history of autonomic and neurological symptoms, autoimmunity, cancer, cardiovascular, endocrine, or neuroimmune disorders, as well as no alcohol or drug dependence or regular use of medication, as previously reported [25]. Healthy volunteers were recruited through word-of-mouth from the same local community and did not meet case criteria for ME/CFS at the time of enrollment. All study participants were of Caucasian origin and resided in the same geographical area.

Ethics statement and consent to participate

After receiving verbal and written information on the study protocol, all participants gave signed informed consent prior to enrolment. The study was reviewed and approved by the local Vall d'Hebron University Hospital Institutional Ethical Committee on Human Research (reference number: PR/AG-201/2016). The study was carried out in accordance with the 2024 Declaration of Helsinki and with all the International Conference on Harmonization and Good Clinical Practice Guidelines. After providing consent, all participants underwent a clinical examination and experimental research protocols.

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Study procedures

Data collection

The data collection took place both in the office and at home. Demographics and clinical characteristics, outcome measures, actigraphy-derived data, and laboratory biochemical variables used in the present study were obtained from an existing dataset. The current analysis included participants with complete available data across all relevant items.

Detailed methodological procedures for participant recruitment, clinical evaluation, data acquisition, and laboratory blood processing have been previously reported. Nevertheless, a brief overview of the methodology is provided below for clarity.

Actigraphy-derived measures

Objective behavioral and environmental data were collected using wrist-worn actigraphy.

Participants were equipped with a wrist-worn ambulatory actigraphy device (*ActTrust®, Condor Instruments, São Paulo, Brazil*) factory-calibrated by the manufacturer, which continuously recorded data on motor activity (accelerometry), skin temperature (°C), and ambient light intensity (lux) at one-minute intervals at home over a seven-day period. A week continuous monitoring period was selected and deemed sufficient based on several well-established protocols in chronobiology [30], and the specific clinical constraints of the target population.

Participants were instructed to wear the wearable device continuously, except during activities involving water exposure (e.g., showering or swimming). Compliance with the wrist-worn actigraphy protocol was evaluated through visual inspection of double-plotted actigraphy graphs of activity (accelerometry), skin temperature (°C), and ambient light intensity (lux) for all datasets. Although the actigraphy records light intensity (lux), values were log-transformed prior to analysis using $\log_{10}$ (lux +0.01). This

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transformation is commonly applied in light exposure research, as the response of the circadian system to light follows a non-linear, approximately semi-logarithmic relationship [31,32]. The device recorded and stored data in its memory for subsequent analysis.

Actigraphy-derived circadian rhythm analysis

Data collection recorded during the summer months (June to September) and December was not used, to minimize potential bias related to seasonal variations in environmental conditions, particularly temperature and daylight exposure [25].

Rhythmic parameters for physical activity, skin temperature and light intensity were derived using cosine curve fitting (24-hour model), including mesor, amplitude, and acrophase. Non-parametric measures of circadian organization were also computed, including intradaily variability (IV) and interdaily stability (IS). Additional derived variables included M10 (10 consecutive hours of highest activity/light exposure), L5 (5 consecutive hours of lowest activity and light exposure), M5 and L10 for skin temperature (inverse rhythm) [26,33].

Moreover, ambient light intensity was stratified into five predefined time intervals across the 24-hour day. Mean light exposure was calculated for 02:00–06:00 hours (L_2– 6), 08:00–12:00 hours (L_8–12), 12:00–16:00 hours (L_12–16), 16:00–20:00 hours (L_16–20), and 20:00–24:00 hours (L_20–24). These intervals were selected to capture key phases of the light–dark cycle, including nocturnal exposure, morning light as a primary circadian entraining signal, and afternoon–evening exposure. This stratification allowed characterization of temporal patterns of light exposure relevant to circadian regulation.

Measures

After a week, participants attended a follow-up visit, during which they returned the actigraphy device and completed a set of validated self-reported

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outcome measures assessing their current health status one week after the initial clinical assessment. Changes in fatigue perception, sleep disturbances, anxiety and depression, autonomic dysfunction, and health-related quality of life were rated by each participant under the supervision of two trained investigators (J.A.-M and J.C.-M.) who oversaw compliance as already described [27].

Fatigue perception

Fatigue was evaluated using the Fatigue Impact Scale (FIS-40), a 40-item questionnaire with three subscales measuring the perceived impact of fatigue: cognitive (10 items), physical (10 items), and psychosocial functioning (20 items). Each item is scored from 0 (no fatigue) to 4 (severe fatigue). The total FIS-40 score is calculated by summing all 40 items (range 0–160), with higher scores reflecting greater functional limitations due to fatigue [34].

Sleep quality

Sleep disturbances were assessed using the self-administered 19-item Pittsburgh Sleep Quality Index (PSQI). The questionnaire evaluates seven components of sleep quality: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. Each component is scored from 0 (no sleep problems) to 3 (severe sleep problems). The global PSQI score ranges from 0 to 21, with scores above 5 indicating poorer sleep quality [35].

Anxiety and depression

Symptoms of anxiety and depression were measured using the Hospital Anxiety and Depression Scale (HADS), a validated 14-item self-report instrument comprising seven items for anxiety and seven for depression. Each item is scored from 0 to 3, resulting in subscale scores ranging from 0 to 21. Scores are interpreted as follows: 0–7 = normal, 8– 10 = mild, 11–14

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= moderate, and 15–21 = severe. The overall HADS score ranges from 0 (no symptoms) to 42 (severe anxiety and depression) [36].

Autonomic dysfunction

Participants completed the Composite Autonomic Symptom Scale (COMPASS-31), a 31item questionnaire assessing the frequency and severity of autonomic symptoms across six domains: orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder, and pupillomotor systems. Summing the domain scores produces a total COMPASS-31 score ranging from 0 to 100, with higher scores indicating more severe autonomic dysfunction [37].

Health-related quality of life

Health-related quality of life was measured using the 36-item Short Form Health Survey (SF-36), a self-report questionnaire evaluating both physical and mental functioning. The SF-36 includes eight subscales: physical functioning, physical role functioning, bodily pain, general health, vitality, social functioning, emotional role functioning, and mental health. Lower scores indicate a greater negative impact of health on an individual's daily functioning. The overall SF-36 scores range from 0 to 100, with higher scores indicating better health outcomes [38].

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Blood collection and processing

Biological data included biomarkers of endothelial dysfunction and inflammatory and laboratory biochemical variables. Detailed methodological procedures for participant recruitment, clinical assessment, data acquisition, and laboratory sample processing have been previously reported [27,28].

Briefly, fasting venous blood samples from each participant were originally collected under standardized conditions between 8:00 a.m. and 10:00 a.m., processed and stored in aliquots at −80°C until further assays. The present study used previously generated and stored biomarker data. Blood samples

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were available from a subset of study participants, including 64 ME/CFS patients and 41 matched healthy controls.

Measurement of circulating biochemical parameters

For the current analysis, previously quantified circulating endothelial biomarkers were retrieved, including soluble endothelin-1 (ET-1), thrombospondin-1 (TSP-1), vascular cell adhesion molecule-1 (VCAM-1), and intercellular adhesion molecule-1 (ICAM-1), as previously described [27,28]. In addition, laboratory biochemical variables were also included (such as levels of cortisol, serotonin, triglycerides (TG), total cholesterol (TChol), HDL-cholesterol (cHDL), LDL-cholesterol (cLDL), and non-HDL cholesterol (TChol−cHDL). Derived clinical lipid indices were also calculated, including the ratios TChol/cHDL, cLDL/cHDL, and TG/cHDL, as previously reported [26].

Statistical analysis

Continuous variables are displayed as the mean ± standard error (SD), while categorical variables are expressed as number of participants (percentages), unless otherwise indicated. Normality and homogeneity of variance were assessed using the Shapiro–Wilk and Levene's tests, respectively. For group comparisons involving continuous variables, either Student's *t*-test or one-way analysis of variance (ANOVA) followed by post-hoc tests were used as appropriate.

For this study, participants were subsequently categorized into two seasonal groups based on expected environmental light exposure: a longer-daylight season (March to May), which included 56% of ME/CFS patients and 40% of healthy controls, and a shorter-daylight season (October, November, January, and February), comprising the remaining participants. A one-way analysis of variance (ANOVA) of maximum recorded light intensity indicated a trend toward a seasonal effect on light exposure ($p = 0.09$). Accordingly, all subsequent statistical analyses included season as a mandatory covariate.

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To reduce dimensionality and identify key patterns of light exposure, a principal component analysis (PCA) with varimax rotation was applied to nine light-related variables (mean, amplitude, IV, IS, L_2-6, L_8-12, L_12-16, L_16-20, and L_20-24).

Two components with eigenvalues greater than 1 were retained and standardized factor scores were calculated for use in subsequent analyses. These PCA-derived components were included in regression models for each outcome variable. Each model included group (ME/CFS vs. healthy controls) as a between-subjects factor, the two light components as covariates, and their interaction terms to assess whether associations between light exposure and outcomes measures differed by group.

Associations among variables were examined using linear regression analyses. Models were estimated using the ordinary least squares (OLS) method to assess the relationship between dependent and independent variables. Correlations between variables were assessed using the Pearson correlation coefficient. Due to the exploratory nature of the analyses and the intercorrelation among outcome measures, no formal correction for multiple comparisons was applied. Cases with missing data were excluded from the corresponding analyses. Statistical significance was set at $p < 0.05$. Multicollinearity among predictors was assessed using tolerance and variance inflation factor (VIF) values, with thresholds of tolerance > 0.1 and VIF < 10 indicating acceptable levels. All analyses were adjusted for age, sex, body mass index (BMI), season, and activity (amplitude of the activity rhythm).

Based on the two light components derived from PCA (named as Light1 and Light2), study participants were classified into four light exposure patterns. For each component, values were dichotomized according to the sample median (above vs. below median), resulting in a 2×2 classification and four distinct exposure profiles. This approach was used to facilitate the interpretation of multivariate light exposure patterns while maintaining

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comparability across participants. Estimated marginal means were computed for each group through General Linear Models, and pairwise comparisons between light exposure patterns were performed using Fisher's least significant difference (LSD) adjustment. The LSD procedure was applied following a significant omnibus effect and was selected to preserve statistical power while allowing for targeted group comparisons in a moderate number of planned contrasts. Statistical significance was set at $p < 0.05$.

This categorical approach was used as a complementary analysis to models based on continuous PCA-derived variables, aiming to explore whether distinct combinations of light exposure characteristics were associated with differences in clinical outcomes measures. All analyses were performed using SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, NY, USA). Two-side *P*-value less than 0.05 was considered statistically significant.

Results

Participant characteristics

Most of the participants completed datasets. However, actigraphy-derived data was missing in 6 ME/CFS participants and in 3 healthy controls, and health outcomes measures were also missing in 1 ME/CFS participant and in 3 healthy controls.

ME/CFS differs from healthy controls in most of the variables, reflecting well-established clinical and biological distinctions among study participants. Though, these results are not the primary focus of the present study, they are therefore displayed in **Table 1** and summarized herewith. The healthy controls had a mean age of 42.9 ± 1.8 years, whereas the ME/CFS patients had a mean age of 49.5 ± 1.0 years. Body mass index (BMI) was also significantly higher in the ME/CFS patients (mean = 27.0 ± 0.5 kg/m^2) than in healthy controls (mean = 24.4 ± 0.6 kg/m^2), while the proportion of females was similar across groups (80% in both).

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Consistent with previous reports, subjective assessment scores differed significantly between groups. Individuals with ME/CFS showed higher scores on the FIS40, HADS, COMPASS-31, and PSQI, indicating greater perceived fatigue, psychological distress, autonomic dysfunction, and poorer sleep quality (all $p < 0.001$). In contrast, SF36 scores were lower in the ME/CFS patients, reflecting reduced health-related quality of life ($p < 0.0001$). Similarly, alterations in circulating biochemical parameters were shown, including higher levels of ET-1, TSP-1, VCAM-1, and blood lipid profiles in ME/CFS patients compared with healthy controls (all $p < 0.001$).

Group differences were also found in circadian-related variables. It can be observed the lower levels in both physical activity and light exposure in the ME/CFS group, as both variables use to be associated. Healthy controls exhibited higher activity rhythm values (mean, amplitude, and M10), whereas ME/CFS showed greater rhythm fragmentation (intradaily variability, IV). Temperature rhythm variables were largely comparable between groups, with the exception of higher IV in the ME/CFS patients. Light-related variables also differed significantly, with the ME/CFS group showing lower average light exposure, reduced amplitude, and greater fragmentation of the light–dark cycle. Additionally, light exposure during daytime intervals (L_8–12, L_12–16, and L_16–20) was significantly lower in ME/CFS than in healthy controls (all $p \leq 0.01$). **Figure 1** shows the rhythmic profile of the three actigraphy-derived variables: light, activity and skin temperature, showing clearly that physical activity and light intensity during the day are significantly different between ME/CFS and healthy controls (all $p < 0.001$).

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Association between light variables and outcome measures

This study aimed to investigate the associations between objective light exposure patterns and both subjective and biological outcomes measures among participants. Accordingly, subsequent analyses focus on examining correlation- and regression-based relationships between light exposure

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variables and clinical and biochemical measures, while accounting for group membership and relevant covariates.

A first approach to associating light variables with self-reported outcome measures (**Table S1**) was carried out separately for ME/CFS patients and healthy controls. However, in some cases, associations were found for light intensity while in others for variables of the light rhythm. Thus, to assess the main effect of light based on both light intensity and rhythmic variables, a PCA with varimax rotation was performed using nine light-related variables: mean, amplitude, IS and IV of the light-dark cycle and the mean light intensity in the five timing intervals (L_2-6, L_8-12, L_12-16, L_16-20, and L_20-24). As shown in **Figure 2A**, the rotated component matrix identified two orthogonal dimensions of light exposure, with eigenvalues greater than 1. These components accounted for 77.91% of the total variance: component 1 (named as Light1) explained 61.78%, and component 2 (named as Light2) explained 16.13%. Light1 included strong positive loadings from mean (0.820), amplitude (0.928), IS (0.891), L_12-16 (0.887), L_16-20 (0.855), and L_8-12 (0.749), while L_IV had a negative loading (−0.768), indicating that brighter days and more stable light exposure patterns are associated with Light1. On the other hand, Light2 had high loadings from L_2-6 (0.916) and L_20-24 (0.612), reflecting a nocturnal/evening light exposure pattern. Rotation converged in 3 iterations.

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These two components were saved as standardized factor scores and later used to explore differential effects on sleep and mood across disease and control groups. The consistency of the overall results was confirmed by separate PCA analyses in ME/CFS patients and healthy controls, which independently reproduced the same two-component structure.

Linear regression models were conducted to determine whether the two PCAderived light components differentially predicted sleep, psychological stress, and physiological outcomes measures across study participants (**Table 2**). The dependent variables included total and subscale scores from

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the FIS-40, HADS, PSQI, and SF-36 questionnaires. Each model included group (ME/CFS patients vs. healthy controls) as a between-subjects factor, the two light components (Light1 and Light2) as covariates, and their respective interaction terms (Light1 × Group and Light2 × Group) to assess whether the associations between light exposure and outcomes measures differed by group. Additionally, age, sex, BMI, season and activity (assessed by amplitude of the activity rhythm) were included as confounding variables.

As expected, group was a significant factor in all the regression models. However, the most important of this analysis is the association of the outcome measures with light exposure considering group interaction. A significant interaction between Light2 and group was observed in several models indicating that the association between light exposure and clinical outcomes measures differs between ME/CFS and healthy controls ($p < 0.001$) This is the case of overall FIS-40, HADS, PSQI and COMPASS-31, with positive associations and total SF-36 with negative associations. Moreover, the interaction group x Light2 was also significant for TSP-1, triglycerides and TG/cHDL ratio. The interaction between Light1 and the group only accounted for some domains of outcomes measures. The adjustments, with or without taking into account the activity amplitude, as was subsequently verified, did not substantially alter these results.

To confirm these findings, we also carried out partial correlations separately for both groups of participants (**Table S2**), also controlling for age, sex, BMI, season and the amplitude of the activity rhythm, showing that Light2 is associated with outcomes measures in the ME/CFS subjects but not in healthy controls. Thus, Light2 was positively associated within ME/CFS patients for total COMPASS-31 and some of their domains, and also with VCAM-1, triglycerides, TG/cHDL ratio, and was negatively associated with serotonin levels in the ME/CFS cohort (all $p < 0.05$).

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Classification of actigraphy-derived light exposure patterns

As a second approach, we assessed whether distinct light exposure profiles could be identified within the whole population (**Figures 2B and 2C**). We classified individuals based on their PCA-derived component scores. Groups were defined by dichotomizing Light1 and Light2 at their respective sample medians (above median = 1, below median = 0). This approach yielded four groups based on the resulting light exposure patterns:

Group A: Light1 = 1 and Light2 = 1 (both components above the median). This pattern may reflect higher overall light exposure with poorer temporal distribution (e.g., nocturnal light exposure or irregular schedules). It was designated the nocturnal light pattern.

Group B: Light1 = 1 and Light2 = 0 (higher daytime light exposure and lower nocturnal/temporal disruption). This pattern reflects more appropriate circadian timing of light exposure and was designated the healthy light pattern.

Group C: Light1 = 0 and Light2 = 1 (lower daytime light exposure and higher nocturnal/temporal disruption). This pattern may reflect reduced daytime exposure, increased nocturnal exposure, and disrupted rhythms. It was designated the adverse light pattern.

Group D: Light1 = 0 and Light2 = 0 (both components below the median). This group reflects overall low light exposure with relatively stable timing and was designated the low diurnal light exposure pattern.

Group A (nocturnal light) shows a similar proportion in healthy controls than in ME/CFS (18.5 vs. 18.7%). The most adaptive light profile (group B, healthy) is the most frequent in ME/CFS (31.3%), with a bit lower proportion in healthy controls (29.6%). Group C (adverse) is more common in healthy controls than in ME/CFS (33.3% vs. 24%). Finally, Group D (low diurnal light) is more common in ME/CFS than in healthy controls (26% vs. 18.5%).

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However, a chi-square test of independence did not show different distribution of individuals and light exposure profiles.

A series of univariate general linear models (GLM) were also conducted separately in ME/CFS and healthy controls to explore differences in subjective outcomes measures across the four light exposure patterns. It is of interest that activity (mean or amplitude) did not differ among these groups.

Estimated marginal means were computed for each light exposure pattern, adjusting for the covariates (**Figure 3**). In ME/CFS patients, a significant effect of light exposure patterns was shown for total FIS-40 score ($p = 0.008$), with healthy pattern showing significantly lower fatigue compared to the other groups (**Figure 3A**). Significant differences were also found for sleep quality (PSQI score; $p = 0.042$), where healthy group had better scores than adverse or low diurnal light (**Figure 3D**). For total SF-36 score, the overall effect was borderline significant, with healthy pattern showing higher health-related quality of life compared to nocturnal light and low diurnal light (**Figure 3E;** $p = 0.050$). Overall COMPASS-31 score showed differences between healthy and adverse patterns (**Figure 3C**; $p = 0.04$). No significant effects were found for total HADS scores in ME/CFS patients (**Figure 3B**). In healthy controls, no significant overall effects of light exposure patterns were found on any of the health-related outcomes measures, nor on laboratory biochemical variables.

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Discussion

This study is the first one, to our knowledge, that examine the role of exposure to environmental light in multidimensional health outcomes and physiological variables in ME/CFS. The findings of this study suggest that environmental light exposure is differentially associated with a range of health outcomes measures, with more consistent and pronounced associations shown in ME/CFS patients. These findings extend current knowledge by suggesting

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that environmental light may represent an underexplored but potentially relevant modulator of symptom expression in ME/CFS.

Circadian disruption and sleep abnormalities are well documented in individuals with ME/CFS, with consistent evidence of altered rest-activity patterns and impaired sleep quality contributing to symptom burden and reduced health-related quality of life [16,39,40]. However, although light is the primary environmental zeitgeber regulating circadian rhythms, its role as a spontaneously occurring, real-world exposure factor in ME/CFS has been largely unexplored. To our knowledge, no previous studies have examined naturalistic light exposure measured using wrist-worn actigraphy in relation to multidimensional health outcomes and circulating biochemical markers in ME/CFS.

The methodology used in this study is novel in that it characterizes environmental light exposure along two distinct dimensions derived from principal component analysis, integrating both light intensity and temporal stability of light exposure patterns. Using this data-driven construct, Light2 likely reflects a combination of environmental exposure and altered behavioral or circadian regulation and may serve as a proxy of circadian disruption. This component showed greater clinical relevance in ME/CFS than in healthy controls, suggesting that increased evening light exposure and/or greater circadian rhythm instability may be linked to worse clinical status in ME/CFS patients. This is important because not only mean light intensity, but also the stability of the light–dark rhythm appears be relevant in ME/CFS.

These findings indicate that the impact of light exposure is not uniform across the population, but may depend on underlying physiological or pathological conditions. In particular, light exposure during biologically sensitive phases may contribute to symptom exacerbation in more vulnerable individuals, potentially through mechanisms related to circadian misalignment.

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Nevertheless, although the present study identified associations between light exposure patterns and both questionnaire-based outcomes and biochemical markers, these findings do not establish directionality and, thus, reverse causation cannot be excluded. Individuals with more severe ME/CFS symptoms may adopt behaviors that influence light exposure patterns, including increased nighttime awakenings and greater use of artificial light during the biological night. Moreover, it is also plausible that higher symptom burden leads to reduced daytime activity and increased time spent indoors or bedbound, resulting in diminished exposure to natural daylight and a consequent alteration of the overall light–dark exposure profile.

We acknowledge that physical activity is a multidimensional behavior and that actigraphy-derived amplitude may not fully capture short-term fluctuations, pacing strategies, and/or post-exertional malaise variability. Therefore, residual confounding cannot be entirely excluded given the observational and cross-sectional design of the study. Within this context, light exposure should be interpreted not only as a potential environmental exposure but also as a proxy of behavioral adaptations to illness and circadian disruption associated with illness severity, rather than as an independent causal determinant.

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This study also proposes a new approach to classify spontaneous patterns of light exposure in the ME/CFS population. A data-driven classification was applied to characterize individual light exposure profiles by combining the two principal components into four groups based on median splits. This novel approach enabled the identification of distinct patterns integrating light intensity, timing, and rhythm stability as potential variables.

The classification of individuals into four groups was intended to facilitate visualization and hypothesis generation for the development of targeted lifestyle or chronotherapeutic interventions. Combining two orthogonal dimensions into a 2×2 framework allowed us to explore whether specific combinations of daytime stability (Light1) and nocturnal exposure (Light2)

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were associated with multidimensional health outcomes in ME/CFS patients compared to healthy controls.

Although the distribution of individuals across the four profiles was comparable between ME/CFS and healthy controls, as indicating different profiles that can be found in the real-world, the clinical relevance of these patterns differed between groups. The group with healthy light profile was consistently associated with more favorable clinical outcomes in the ME/CFS patients, including lower physical fatigue and anxiety/depression symptoms, fewer autonomic symptoms, reduced sleep complaints, and better quality of life, especially compared with the adverse light profile. It may be that in ME/CFS, altered circadian regulation or increased sensitivity to environmental cues may amplify the physiological and behavioral consequences of suboptimal light exposure. The identification of maladaptive light exposure patterns associated with worse fatigue, sleep quality, and health perception in ME/CFS provides preliminary evidence that behavioral and environmental modifications may represent feasible strategies for symptom management in the condition.

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The absence of consistent associations between light exposure patterns and clinical outcomes in healthy controls may partly reflect the lower variability and generally favorable range of outcome measures in this group, limiting the ability to detect meaningful associations. Differences in sample size between groups may also have contributed to greater statistical power in the patient analyses. In contrast, individuals with ME/CFS showed a broader distribution of symptom severity and physiological measures, which likely increased statistical sensitivity to detect associations. However, importantly, the significant group × light exposure interaction observed in the combined analysis indicates that the relationship between light exposure patterns and clinical outcomes differs between ME/CFS patients and healthy controls.

It is of interest that L_2-6 was associated with circulating triglycerides and VCAM-1 levels This is consistent with previous evidence linking abnormal

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light exposure and circadian disruption to adverse metabolic profiles and increased cardiometabolic risk, including dyslipidemia [41,42]. In particular, light exposure during the biological night (light at night, LAN) has been associated with altered lipid metabolism, including elevated cholesterol and LDL levels, [43], potentially mediated through circadian misalignment of metabolic pathways [10,44,45].

From a mechanistic perspective, light–dark cycles represent the primary environmental zeitgeber for the circadian system, acting via intrinsically photosensitive retinal ganglion cells (ipRGCs), which project to the suprachiasmatic nucleus and other brain regions involved in sleep, neuroendocrine, and autonomic regulation [31,46,47]. Exposure to light at night can suppress melatonin and shift circadian phase, leading to circadian misalignment, which has been implicated in metabolic dysregulation, including impaired lipid homeostasis and increased cardiometabolic risk [48,49]. In addition to metabolic effects, circadian disruption has been associated with endothelial dysfunction and low-grade inflammation [50]. VCAM-1 is a marker of endothelial activation upregulated by inflammatory and oxidative stress pathways, thus, the observed association may reflect downstream vascular consequences of circadian misalignment [51], although causality cannot be inferred from the present data.

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The associations found with circulating serotonin levels should be interpreted with caution given the limited sample size. Also, while circadian and sleep-related mechanisms may influence serotonergic regulation, evidence in humans remains limited and the underlying pathways are not yet fully established [52].

Thus, it is possible that altered light exposure contributes to symptom severity through mechanisms such as circadian misalignment, altered melatonin secretion, and autonomic dysfunction in ME/CFS patients.

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Anyhow, these findings together support the hypothesis that environmental light exposure may influence multiple physiological domains relevant to ME/CFS, including autonomic, metabolic, and affective regulation. Intervention studies in other clinical populations further support the relevance of light timing. In cancer-related fatigue, condition frequently associated with sleep disruption, morning bright light exposure has been shown to improve sleep quality and related symptoms [53]. Likewise, systematic evidence from meta-analysis data suggests that light exposure and light-based interventions are associated with small-to-moderate improvements in subjective wellbeing in general populations [54]. In neurological disorders such as traumatic brain injury and stroke, dynamic light interventions have demonstrated improvements in sleep and psychomotor performance, supporting the feasibility of home-based light approaches for fatigue-related symptoms [55].

This suggests that personalized chronotherapy interventions such as structured light therapy, increased daytime outdoor exposure, or reduction of evening and nighttime light may offer low-cost and non-invasive approaches with potential clinical benefit in individuals with ME/CFS. However, a randomized controlled crossover study involving 36 ME/CFS patients found that bright light therapy (+10.000 lux) administered 30 min each morning at home over two weeks was not significantly effective for fatigue (assessed by Chalder Fatigue Questionnaire (CFQ), although improvement of fatigue scores was observed immediately after two weeks of BLT and also light seemed to have beneficial effects on attention in patients with ME/CFS [56].

Thus, environmental light exposure is a potentially modifiable behavioral factor with low cost and non-invasive characteristics, that may improve sleep quality [57–59], circadian alignment [60], and mood-related outcomes [61], although these findings are not specific to ME/CFS and should be interpreted cautiously. The present findings suggest that the impact of

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light extends beyond simple measures of intensity or timing, encompassing also the stability, amplitude, and fragmentation of the circadian light–dark rhythm. This is especially important, since vision-related symptoms are frequent in ME/CFS and sensory hypersensitivity, including increased sensitivity to light stimuli, has also been frequently reported in ME/CFS [62]. Thus, high light intensity should not generally be recommended in ME/CFS, unless well tolerated.

Potential interventions in ME/CFS may need to consider not only daytime light exposure, but also the temporal organization of light across the 24-hour cycle, including the minimization of irregular exposure patterns and nocturnal light. This is particularly relevant given the sensory hypersensitivity and symptom exacerbation that may occur in response to environmental stimuli in ME/CFS. Accordingly, light-based strategies should aim to reinforce stable circadian light–dark patterns by promoting consistent daytime light exposure while reducing, and ideally avoiding, light exposure during the biological night. Such an approach may help mitigate the potential adverse effects associated with disrupted light–dark rhythms and could be considered as a general, low-risk behavioral recommendation in the management of ME/CFS.

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Strengths and limitations

Despite several strengths, including the recording of actigraphy-derived measurements, dimensionality reduction via principal component analysis, and the assessment of interaction effects, this study has several limitations that should be acknowledged.

First, the observational cross-sectional cohort design precludes causal inference. Although associations between light exposure patterns and clinical outcomes were identified, the directionality of these relationships remains unclear. Moreover, reverse causation cannot be excluded, as individuals with more severe symptoms may adopt behaviors that reduce or shift light

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exposure, such as spending more time indoors or utilizing artificial light during nighttime awakenings. In this context, circadian misalignment may represent a downstream consequence that further contributes to fatigue, sleep disruption, dysautonomia, and endothelial dysfunction. Future prospective longitudinal studies are therefore required to clarify precise temporal and causal relationships.

Second, although actigraphy provides objective and ecologically valid estimates of environmental light exposure in real-world settings, the recording period may not fully reflect habitual long-term exposure patterns. Importantly, wrist-worn light sensors do not accurately reflect retinal light exposure, as factors such as sleeve coverage and arm positioning relative to light sources may introduce measurement error. In addition, standard photopic illuminance (lux) lacks spectral sensitivity and does not capture circadian-effective metrics such as melanopic illuminance, which more directly influence the human circadian system via non-visual retinal pathways. While any resulting measurement error is likely non-differential between groups, future studies should incorporate eye-level wearable sensors or spectral light measurements to more precisely quantify biologically relevant light exposure in ME/CFS patients.

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Third, while the sample size was sufficient to detect moderate effects, the study may have been underpowered to identify smaller interaction effects or subtle subgroup differences, including those related to chronotype and comorbidities. In addition, the tertiary care setting may limit the generalizability of the findings to the broader ME/CFS population, particularly those with severe or bedbound disease.

Fourth, polypharmacy and concomitant use of psychotropic or hypnotic medications in the ME/CFS cohort, may affect activity and may potentially introducing residual confounding. This highlights the need for more detailed stratification in future prospective longitudinal studies.

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Lastly, although PCA allowed the reduction of complex light exposure variables into a smaller set of interpretable components, these data-driven patterns are inherently sample-dependent and require replication in independent cohorts to confirm their robustness and generalizability. Accordingly, the stratified analysis based on median splits of the four light exposure profiles should be interpreted with caution as exploratory and hypothesis-generating, providing a conceptual framework for future research and complementing our primary continuous regression analyses.

Conclusions and recommendations for further research

To the best of our knowledge, this is the exploratory first study to provide evidence that environmental light exposure patterns are associated with illness severity and well-being in ME/CFS, particularly for fatigue, anxiety/depression, dysautonomia, sleep disturbances, and health-related quality of life. Profiles characterized by stable daytime light exposure and reduced evening or nocturnal light exposure were generally associated with more favorable clinical outcomes measures among the participants. This study contributes to our understanding of the role of the light exposure patterns in ME/CFS severity.

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Overall, these findings extend previous analyses based on continuous light exposure metrics by suggesting that the temporal organization of light exposure, rather than intensity alone, may have clinically relevant associations in ME/CFS. This supports the notion that not only the quantity but also the timing and stability of light exposure are critical determinants of symptom expression in ME/CFS.

From a clinical perspective, these findings highlight environmental light exposure as a potentially modifiable, non-invasive factor that may contribute to symptom management in ME/CFS. Behavioral strategies aimed at increasing daytime light exposure, if possible, while minimizing evening and

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nighttime light exposure and improving light timing may help support circadian alignment and improve sleep-wake cycle regulation in ME/CFS.

Emerging studies have increasingly used wearable-based approaches to assess sleep–wake patterns and rest-activity rhythms, underscoring the value of continuous, ecologically valid monitoring to capture behavioral heterogeneity and circadian disruption in everyday life. Within this context, actigraphy remains a well-established and widely used method for the longitudinal assessment of rest-activity rhythms in clinical populations [63]. In parallel, advances in biomedical sensing and digital health technologies reflect a broader shift toward more sensitive, objective, and personalized approaches to physiological monitoring [64]. These developments provide general methodological context for the increasing use of wearable and biosensor-based tools in the post-acute infection syndromes such as ME/CFS and Long COVID.

Thus, although promising, more evidence is needed to clarify the directionality and clinical relevance of these associations, and to determine whether targeted modulation of light exposure may lead to meaningful improvements of health status in ME/CFS. In this context, longitudinal study design and light assessment should consider not only photopic intensity (lux), but also circadian-effective metrics such as melanopic illuminance, spectral composition, and seasonal variation, all of which may critically influence circadian responses. Further research should also explore the potential neurobiological mechanisms linking light exposure, circadian regulation, and clinical characteristics including comorbidities in ME/CFS, and in other post-acute infection syndromes such as Long COVID.

Highlights

- Environmental light exposure is associated with symptom severity in ME/CFS.

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- Greater evening/nighttime light exposure and reduced rhythm stability are linked to metabolic disruption and cardiovascular risk in ME/CFS.
- Association between light exposure, health outcomes measures and biochemical parameters are evident in ME/CFS but not in healthy controls.
- Data-driven light exposure profiles might identify clinically relevant behavioral patterns.
- Light exposure may represent a modifiable, non-invasive target for symptom management in ME/CFS patients.

Abbreviations

A_Acos: amplitude of the 24-hours rhythm

BMI: Body mass index

COMPASS-31: 31-item composite autonomic symptom scale

DST: Distal skin temperature

ET-1: Endothelin-1

EUROMENE: European network on ME/CFS

FIS-40: 40-item fatigue impact scale

HADS: Hospital anxiety and depression scale

HDL: High density lipoproteins

ICAM-1: Intercellular adhesion molecule-1 ICC:

International consensus criteria for ME/CFS

ipRGC: Intrinsically photosensitive retinal ganglion

cells

IS: Interdaily stability of the 24-hour rhythm

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IV: Intradaily variability of the 24-hour rhythm

L_2-6: Mean light intensity from 02:00 to 06:00 hours

L_8-12: Mean light intensity from 08:00 to 12:00 hours

L_12-16: Mean light intensity from 12:00 to 16:00 hours

L_16-20: Mean light intensity from 16:00 to 20:00 hours

L_20-24: Mean light intensity from 20:00 to 24:00 hours

L_mean: Mean light values in 24 hours

L10_temperature: Mean value of the 10 consecutive hours of lowest value of wrist temperature

L5: Mean value of the 5 consecutive hours of lowest activity or light exposure

LAN: Light at night

LDL: Low density lipoproteins

LSD: Last significant difference

M10: Mean value of the 10 consecutive hours of highest activity or light exposure

M5_temperature: Mean value of the 5 consecutive hours of highest value of wrist temperature

ME/CFS: Myalgic encephalomyelitis/chronic fatigue syndrome

OLS: Ordinary least squares

PCA: Principal component analysis

PSQI: Pittsburg sleep quality index

SF-36: 36-item short-form health survey

TG: Triglycerides

TSP-1: Thrombospondin-1

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VCAM-1: Vascular cell adhesion molecule-1

VIF: Variance inflation factor

Supplementary material

Tables S1 and S2

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Author contributions

Conceptualization and design, T.C., J.A.-M. and J.C.-M.; methodology, T.C., J.C.D.,
R.S.-S., J.A.-M. and J.C.-M.; formal analysis and investigation, T.C., R.S.-S, J.C.D. and J.C.-M.; writing original draft preparation, T.C. and J.C.-M.; writing-review and editing of final manuscript, T.C., J.C.D., R.S.-S. and J.C.-M.; funding acquisition, T.C., J.C.-M.
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Data availability

The raw data supporting the findings of this study are available in the CORA repository (https://doi.org/10.34810/DATA2950). Publicly shared datasets have been de-identified and processed to comply with institutional confidentiality requirements. Access to additional or more detailed data may be granted by the corresponding author upon reasonable request and in accordance with ethical and data protection regulations.

Declarations

Ethical approval and consent to participate

This study protocol has been revised and approved by the local Ethics Committee of Vall d’Hebron University Hospital, Barcelona, Spain (approval code: PR/AG-201/2016 on 19 September 2019). Written informed consent for the publication of anonymized data was obtained from all the participants. Meanwhile, the ethical principles for medical research involving human participants as stipulated in the 2024 Declaration of Helsinki have been complied with.

Competing interests

The authors declare that they have no conflict of interest.

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LEGENDS FOR FIGURES

Figure 1. Rhythmic profiles of light intensity (A), physical activity (B), and skin temperature (C) in individuals with ME/CFS (red lines) and healthy controls (black lines). Maximum and lowest values are indicated as horizontal lines. Asterisks indicate significant differences between groups ($p < 0.001$). The horizontal bar above the plots represents the nocturnal period (02:00–06:00 hours).

Figure 2. Principal component analysis (PCA) of light exposure variables. (A) Variable loadings for the first two principal components (named Light1 and Light2), representing the contribution of each light exposure variable to each component. The distribution of Light1 and Light2 values is shown for ME/CFS as empty circles (B) and for healthy controls as filled circles (C). In panels B and C, the axes intersect at the median value of each component, generating four light exposure patterns according to whether values were above or below the median of each component: high nocturnal light, healthy light pattern,

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adverse light pattern, and low diurnal light. The percentage of participants in each group is indicated.

Figure 3: Estimated marginal means ± standard error of outcome measures according to light exposure pattern (x-axis) and participant group (black bars: ME/CFS; white bars: healthy controls). All models were adjusted for age, sex, body mass index, season and amplitude of the activity rhythm. Statistically significant post-hoc differences ($p < 0.05$) within the ME/CFS group are indicated as follows: (a) healthy vs. nocturnal light, (b) healthy vs. adverse light, and (c) healthy vs. low diurnal light. No significant differences between the light exposure patterns were found in healthy controls.

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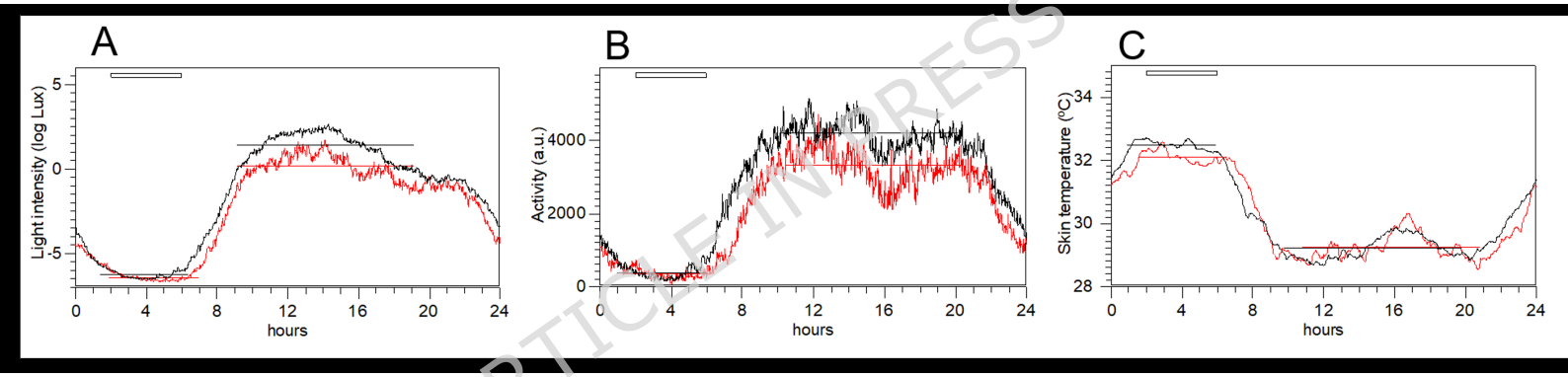

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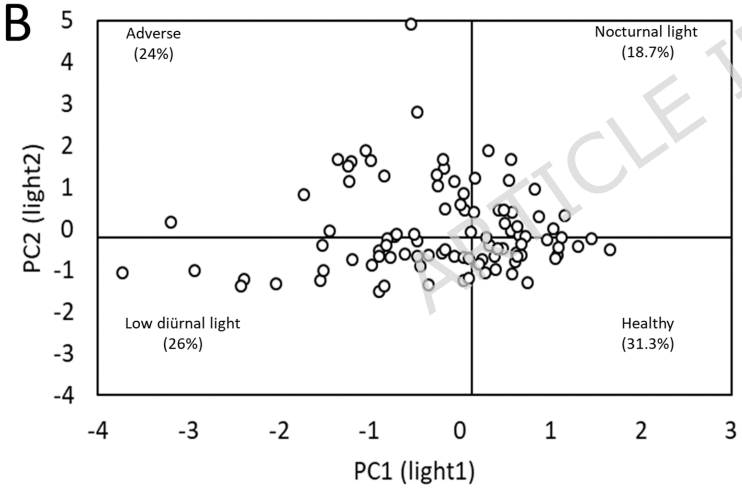
A

Rotated Component Matrix (PCA analysis)

	Component 1	Component 2
	Light 1 (61.78% of variance)	Light 2 (16.13% of variance)
L_mean	0.82	0.526
L_A_cos	0.928	-0.197
L_IV	-0.768	-0.193
L_PV	0.891	-0.1
L_2_6	-0.135	0.916
L_8_12	0.749	0.11
L_16_20	0.855	0.313
L_20_24	0.535	0.612
L_12_16	0.887	0.163

B



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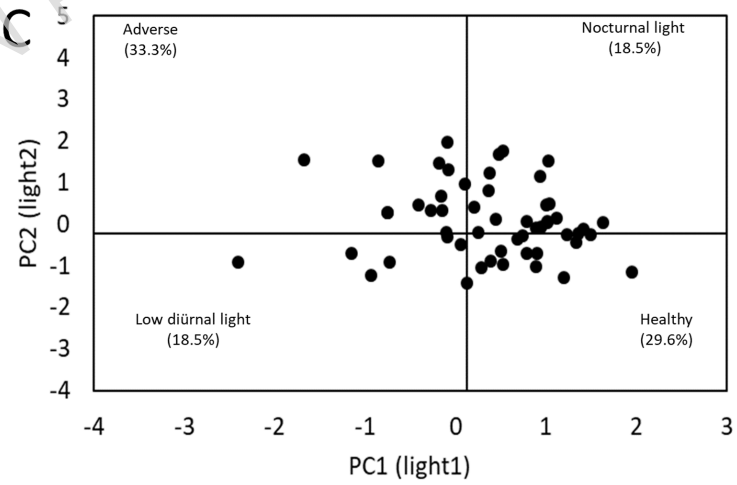

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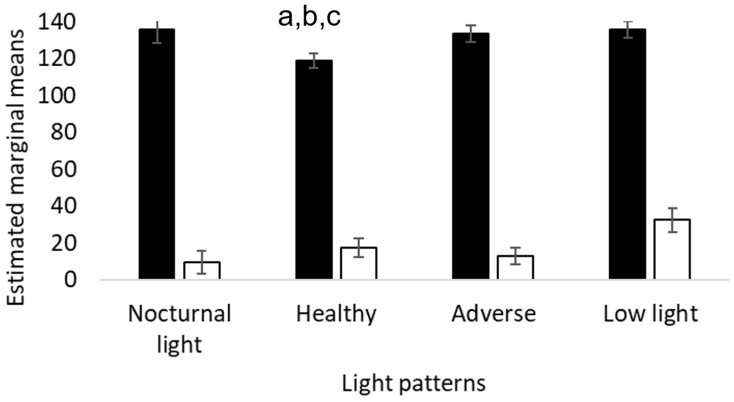

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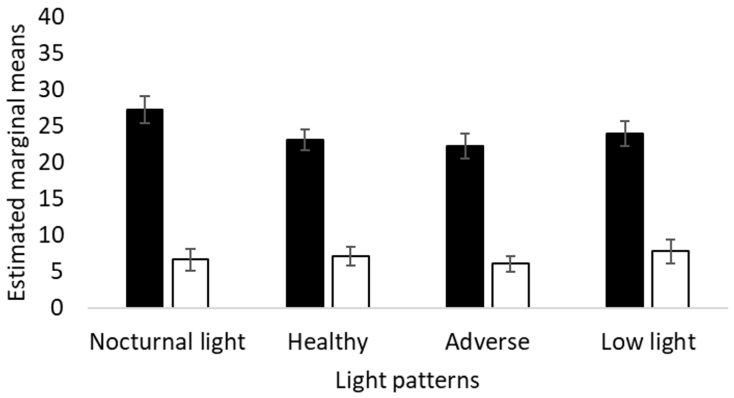

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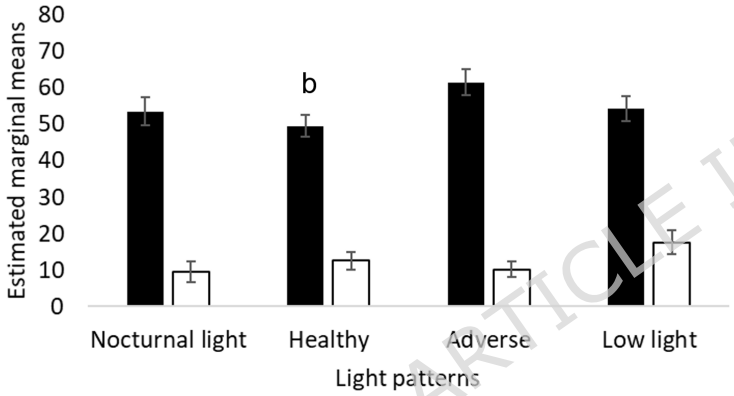

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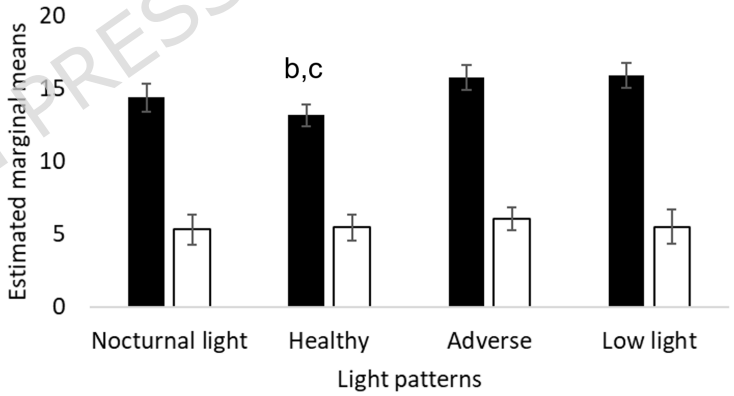

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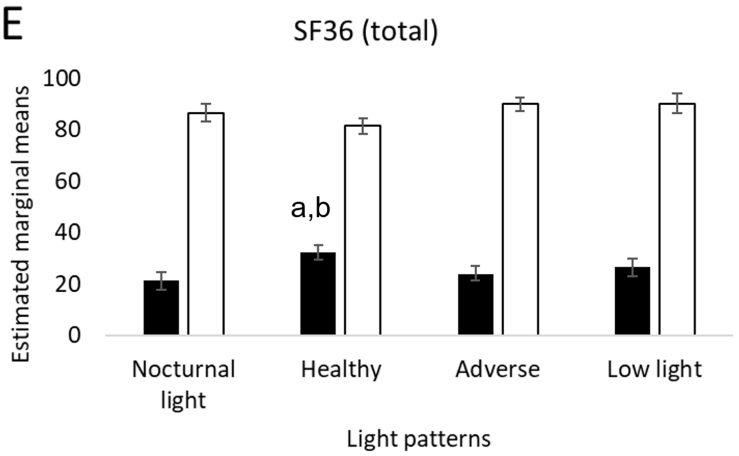

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Table 1. Demographic and clinical characteristics of the study participants

Variables	ME/CFS (n = 100)	Healthy (n = 56)	*P*-value
Age, years	49.5 ± 1.0	42.9 ± 1.8	**0.001**
Female, n (%)	80 (80)	45 (80)	n.s.
BMI, kg/m^2	27.0 ± 0.5	24.4 ± 0.6	**0.002**
Measures [a]			
FIS-40			
Global score (0-160)	130.5 ± 2.1	17.5 ± 2.7	**< 0.001**
Physical	61.7 ± 1.2	8.4 ± 1.4	**< 0.001**
Cognitive	33.9 ± 0.5	5.4 ± 0.8	**< 0.001**
Psychosocial	34.7 ± 0.5	4.3 ± 0.7	**< 0.001**
PSQI			
Global score (0-21)	14.9 ± 0.4	5.6 ± 0.4	**< 0.001**
Subjective sleep quality	2.2 ± 0.1	0.7 ± 0.1	**< 0.001**
Sleep latency	2.4 ± 0.1	1.3 ± 0.1	**< 0.001**
Sleep duration	1.9 ± 0.1	1.2 ± 0.1	**< 0.001**
Habitual sleep efficiency	2.1 ± 0.2	0.6 ± 0.1	**< 0.001**
Sleep disturbances	2.2 ± 0.1	1.0 ± 0.1	**< 0.001**
Use of sleeping medication	2.0 ± 0.1	0.3 ± 0.1	**< 0.001**
Daytime dysfunction	2.3 ± 0.1	0.6 ± 0.1	**< 0.001**
HADS			
Global score (0-42)	24.1 ± 0.8	6.6 ± 0.6	**< 0.001**
Anxiety	12.4 ± 0.4	5.0 ± 0.4	**< 0.001**
Depression	11.7 ± 0.5	1.9 ± 0.3	**< 0.001**
COMPASS-31			
Global score (0-100)	54.7 ± 1.7	12.0 ± 1.3	**< 0.001**
Orthostatic intolerance	23.4 ± 0.9	5.4 ± 0.8	**< 0.001**
Vasomotor	1.7 ± 0.2	0.1 ± 0.1	**< 0.001**
Secretomotor	9.6 ± 0.3	1.2 ± 0.3	**< 0.001**
Gastrointestinal	12.1 ± 0.5	4.2 ± 0.5	**< 0.001**
Bladder	4.3 ± 0.3	0.6 ± 0.1	**< 0.001**
Pupillomotor	3.6 ± 0.1	1.0 ± 0.1	**< 0.001**
SF-36			
Global score (0-100)	26.3 ± 1.4	86.8 ± 1.5	**< 0.0001**
Physical functioning	33.0 ± 2.3	97.1 ± 0.7	**< 0.0001**
Physical role functioning	1.8 ± 0.8	92.8 ± 2.7	**< 0.0001**

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Bodily pain	22.2 ± 2.3	85.7 ± 2.5	**< 0.0001**
General health perception	23.6 ± 1.5	86.1 ± 1.6	**< 0.0001**
Vitality	15.6 ± 1.7	71.0 ± 2.4	**< 0.0001**
Social role functioning	33.1 ± 2.5	93.7 ± 1.9	**< 0.0001**
Emotional role functioning	38.4 ± 4.6	90.1 ± 3.3	**< 0.0001**
Mental health	43.4 ± 2.3	75.6 ± 2.2	**< 0.0001**
Physical health component	36.1 ± 3.7	76.4 ± 2.2	**< 0.0001**
Mental health component	7.8 ± 3.1	69.3 ± 2.6	**< 0.0001**
Motor activity			
A_m (a.u.)	2141.6 ± 81.8	2871.8 ± 124.5	**< 0.001**
A_Acos (a.u.)	1817.0 ± 72.3	2213.6 ± 127.2	**0.004**
A_IV	0.4 ± 0.1	0.4 ± 0.1	**0.002**
A_IS (%)	32.8 ± 0.8	30.5 ± 0.9	0.056
A_M10 (a.u.)	3532.8 ± 131.6	4530.4 ± 224.6	**< 0.001**
A_L5 (a.u.)	185.9 ± 18.6	227.2 ± 32.4	0.236
Wrist temperature			
T_m (ºC)	30.3 ± 0.1	30.3 ± 0.1	0.978
T_Acos (ºC)	1.8 ± 0.1	1.8 ± 0.1	0.996
T_IV	0.006 ± 0.0005	0.004 ± 0.0003	**0.008**
T_IS (%)	40.2 ± 1.8	40.6 ± 1.8	0.905
T_M5 (ºC)	32.5 ± 0.1	32.7 ± 0.1	0.361
T_L10 (ºC)	28.9 ± 0.1	29.0 ± 0.2	0.776
Light			
L_mean (log lux)	-2.3 ± 0.1	-1.5 ± 0.1	**< 0.001**
L_A_cos (log lux)	3.8 ± 0.1	4.3 ± 0.1	**0.003**
L_IV	0.1 ± 0.01	0.08 ± 0.01	**0.021**
L_IS (%)	58.1 ± 1.4	61.2 ± 1.8	0.177
L_M10 (log lux)	1.7 ± 0.1	2.5 ± 0.2	**< 0.001**
L_L5 (log lux)	-6.4 ± 0.1	-6.4 ± 0.1	0.893
L_2_6 (log lux)	-6.3 ± 0.1	-6.3 ± 0.1	0.861
L_8_12 (log lux)	-1.00 ± 0.2	0.6 ± 0.2	**< 0.001**
L_12-16 (log lux)	0.8 ± 0.2	2.2 ± 0.2	**0.001**
L_16_20 (log lux)	-0.4 ± 0.2	0.4 ± 0.2	**0.013**
L_20_24 (log lux)	-1.7 ± 0.2	-1.3 ± 0.2	0.181
Biochemical parameters			
ET-1, pg/mL	1.5 ± 0.1	1.2 ± 0.1	**0.015**
TSP-1, ng/mL	53.1 ± 3.2	86.4 ± 6.5	**< 0.001**

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VCAM-1, ng/mL	703.1 ± 23.0	508.9 ± 15.2	**< 0.001**
ICAM-1, ng/mL	283.8 ± 8.7	285.1 ± 15.7	0.936
Total Chol, mg/dL	220.2 ± 5.2	201.5 ± 5.9	**0.022**
cHDL, mg/dL	62.5 ± 1.8	68.7 ± 2.7	0.053
cLDL, mg/dL	136.3 ± 4.5	119.6 ± 5.0	**0.018**
Triglycerides, mg/dL	110.2 ± 7.9	72.0 ± 4.9	**< 0.001**
Total Chol/cHDL	3.6 ± 0.1	3.1 ± 0.1	**0.001**
cLDL/cHDL	2.3 ± 0.1	1.8 ± 0.1	**0.005**
Total Chol-cHDL, mg/dL	157.6 ± 4.8	133.9 ± 5.4	**0.002**
Triglycerides/cHDL	1.9 ± 0.2	1.2 ± 0.1	**0.002**
Cortisol, µg/dL	14.3 ± 0.8	12.8 ± 1.0	0.231
Serotonin, ng/mL	115.4 ± 18.4	113.0 ± 7.5	0.903

Data are displayed as mean ± standard error (SD) or number of participants (percentages), unless otherwise indicated. *P*-values were calculated by Mann-Whitney *U*-tests for continuous variables and from Fisher's exact test for categorical variables. Bold values denote statistical significance at $p \leq 0.05$ between cohorts. [a] Baseline self-reported outcome measures of symptoms (global and domain scores), as explained in the *Methods* section. n.s. not significant.

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Table 2. Unstandardized Beta coefficients and adjusted coefficient of determination from linear regression models between light components and outcomes measures and biochemical parameters for all study participants (n = 156)

Measures	Group (B, *p*)	Light1 (B,	Light2 (B,	Group×Light1 (B, *p*)	Group×Light2 (B, *p*)	Adjusted R^2	Model significance
Total FIS-40	**110.76 (0.001)**	-1.69 (0.54)	**-6.35 (0.02)**	0.38 (0.83)	**5.10 (0.04)**	0.875	0.001
Cognitive	**27.88 (0.001)**	-0.30 (0.68)	**-1.84 (0.01)**	-0.03 (0.95)	1.24 (0.06)	0.862	0.001
Psychosocial	**52.35 (0.001)**	-0.52 (0.74)	**-3.86 (0.01)**	0.28 (0.78)	**3.06 (0.03)**	0.834	0.001
Physical	**29.57 (0.001)**	-1.07 (0.15)	-00.75 (0.30)	0.44 (0.35)	0.75 (0.25)	0.880	0.001
Total HADS	**17.48 (0.001)**	0.00 (1.00)	-0.84 (0.37)	0.77 (0.19)	0.27 (0.75)	0.586	0.001
Anxiety	**7.55 (0.001)**	0.04 (0.94)	-0.41 (0.43)	**0.72 (0.03)**	0.16 (0.74)	0.470	0.001
Depression	**9.62 (0.001)**	-0.07 (0.89)	-0.51 (0.36)	0.07 (0.85)	0.15 (0.77)	0.566	0.001
Total COMPASS-31	**44.21 (0.001)**	-0.66 (0.72)	-1.76 (0.34)	0.75 (0.51)	**4.02 (0.01)**	0.712	0.001

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Orthostatic intolerance	**18.63 (0.001)**	-1.09 (0.31)	-1.03 (0.33)	-0.06 (0.94)	1.65 (0.08)	0.564	0.001
Vasomotor	**1.79 (0.001)**	0.31 (0.06)	0.09 (0.57)	-0.20 (0.06)	0.22 (0.13)	0.309	0.001
Secretomotor	**8.22 (0.001)**	-0.28 (0.46)	-0.11 (0.77)	0.45 (0.06)	0.34 (0.31)	0.685	0.001
Gastrointestinal	**8.56 (0.001)**	0.35 (0.52)	-0.43 (0.43)	-0.10 (0.78)	**1.20 (0.01)**	0.524	0.001
Bladder	**3.98 (0.001)**	0.09 (0.80)	-0.27 (0.43)	0.26 (0.24)	0.45 (0.15)	0.329	0.001
Pupillomotor	**2.54 (0.001)**	-0.03 (0.82)	-0.22 (0.11)	0.16 (0.08)	**0.31 (0.01)**	0.611	0.001
Total SF-36	**-60.92 (0.001)**	-0.37 (0.84)	3.18 (0.08)	0.15 (0.90)	**-4.13 (0.01)**	0.824	0.001
Physical functioning	**-62.17 (0.001)**	-1.61 (0.49)	**5.97 (0.01)**	2.37 (0.11)	**-9.28 (0.00)**	0.774	0.001
Physical role functioning	**-89.31 (0.001)**	0.92 (0.63)	1.60 (0.40)	-0.03 (0.98)	-0.51 (0.77)	0.905	0.001
Bodily pain	**-66.20 (0.001)**	-2.54 (0.36)	3.37 (0.22)	1.84 (0.30)	**-5.68 (0.02)**	0.699	0.001
General health perception	**-62.80 (0.001)**	-0.17 (0.92)	**4.30 (0.02)**	-0.46 (0.69)	**-4.24 (0.01)**	0.832	0.001
Vitality	**-55.28 (0.001)**	-1.49 (0.50)	-0.23 (0.92)	0.48 (0.73)	-1.99 (0.31)	0.732	0.001

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Social role functioning	**-61.34 (0.001)**	-2.11 (0.47)	2.99 (0.31)	2.47 (0.19)	-2.48 (0.34)	0.647	0.001
Emotional role functioning	**-53.26 (0.001)**	1.71 (0.75)	3.81 (0.48)	-4.95 (0.15)	-5.43 (0.26)	0.267	0.001
Mental health	**-31.91 (0.001)**	2.79 (0.33)	2.67 (0.35)	-3.09 (0.09)	-1.72 (0.50)	0.332	0.001
Overall PSQI	**9.00 (0.001)**	0.05 (0.92)	0.20 (0.70)	-0.05 (0.87)	0.29 (0.52)	0.587	0.001
Sleep quality	**1.38 (0.001)**	-0.09 (0.40)	0.10 (0.38)	0.02 (0.81)	-0.05 (0.64)	0.397	0.001
Sleep latency	**1.02 (0.001)**	0.10 (0.43)	0.04 (0.76)	-0.05 (0.48)	0.09 (0.40)	0.299	0.001
Sleep duration	**0.66 (0.001)**	0.04 (0.71)	0.06 (0.61)	-0.11 (0.13)	0.01 (0.91)	0.094	0.001
Sleep efficiency	**1.48 (0.001)**	0.19 (0.20)	-0.06 (0.68)	**-0.19 (0.05)**	0.01 (0.97)	0.289	0.001
Sleep disturbances	**1.17 (0.001)**	-0.06 (0.39)	0.01 (0.85)	0.04 (0.35)	0.06 (0.35)	0.515	0.001
Sleeping medication	**1.62 (0.001)**	-0.09 (0.56)	-0.11 (0.50)	0.14 (0.15)	0.22 (0.12)	0.346	0.001
Daytime dysfunction	**1.60 (0.001)**	-0.05 (0.61)	0.09 (0.39)	**0.19 (0.01)**	-0.07 (0.46)	0.560	0.001
Biochemical parameters							

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ET-1	**0.36 (0.050)**	-0.06 (0.59)	0.12 (0.29)	0.05 (0.45)	0.02 (0.83)	0.013	n.s.
TSP-1	**-32.27 (0.001)**	**9.04 (0.05)**	**14.16 (0.01)**	-3.87 (0.15)	**-9.64 (0.03)**	0.326	0.001
VCAM-1	**204.43 (0.001)**	5.44 (0.82)	30.76 (0.24)	-10.90 (0.43)	22.85 (0.31)	0.258	0.001
ICAM-1	-17.57 (0.430)	-0.06 (1.00)	17.29 (0.22)	3.22 (0.66)	-15.31 (0.21)	0.032	n.s.
Total Chol	-4.71 (0.240)	-0.52 (0.83)	-0.66 (0.79)	1.14 (0.40)	-1.61 (0.46)	0.101	n.s.
cHDL	5.59 (0.520)	-8.02 (0.13)	7.08 (0.20)	2.71 (0.36)	-2.70 (0.57)	0.089	n.s.
cLDL	**39.34 (0.001)**	6.80 (0.38)	4.11 (0.62)	-5.49 (0.22)	**14.66 (0.05)**	0.235	0.001
Triglycerides	0.33 (0.130)	-0.09 (0.46)	0.16 (0.22)	-0.02 (0.82)	0.04 (0.71)	0.162	<0.01
Total Chol/cHDL	12.23 (0.190)	-6.40 (0.25)	7.41 (0.20)	1.76 (0.57)	-1.18 (0.81)	0.140	<0.05
cLDL/cHDL	**0.81 (0.010)**	0.14 (0.40)	0.05 (0.76)	-0.14 (0.14)	**0.39 (0.01)**	0.243	0.001
Total Chol-cHDL	**3.74 (0.040)**	1.39 (0.17)	0.25 (0.82)	-0.89 (0.13)	1.01 (0.29)	0.008	n.s.

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Triglycerides/cHDL	-3.46 (0.890)	6.37 (0.62)	7.26 (0.64)	0.12 (0.99)	**-33.31 (0.01)**	0.160	<0.05
Cortisol	**3.85 (0.027)**	1.41 (0.18)	0.22 (0.84)	-0.91 (0.12)	1.03 (0.28)	0.008	n.s.
Serotonin	-3.22 (0.890)	5.39 (0.68)	7.42 (0.63)	0.77 (0.99)	**-32.90 (0.01)**	0.161	<0.05

Correlations between variables were assessed using the Pearson correlation coefficient and models were estimated using the ordinary least squares (OLS). All analyses were adjusted for age, sex, body mass index (BMI), season, and amplitude of the activity rhythm. Independent variables: Group (ME/CFS vs. healthy controls), Light1 and Light2 are the two components derived from principal component analysis (PCA), GroupxLight1 and GroupxLight2 correspond to the interactions between the group and each component. Adjusted R^2 and the model significance are also included. n.s. indicates the model was not significant.

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