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### ABSTRACT

**Background:** Consensus for an operational definition of post-exertion malaise (PEM) and which symptoms best characterize PEM has not been established and may be due to variability within and between studies.

**Purpose:** Determine the magnitude of the effect of maximal and submaximal physical exertion on multiple myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) symptoms that are associated with PEM and explore variability among two studies in which mood, fatigue, and pain symptoms were measured before and after exercise.

**Methods:** Symptoms were measured before, and 48 and 72 hours after exercise in study 1 (ME/CFS = 13; Controls = 11) and before and 24 hours after exercise in study 2 (ME/CFS = 15, Controls = 15). Between-study variability was examined by comparing Hedges *d* effect sizes (95% CI) from studies 1 and 2. Within-patient group variability was examined via inspection of dot density plots.

**Results:** In study 1, large increases in general fatigue ( $\Delta = 1.05$ ), reduced motivation ( $\Delta = 0.93$ ), feelings of fatigue ( $\Delta = 0.90$ ), feelings of confusion ( $\Delta = 0.93$ ), and total mood disturbance ( $\Delta = 0.90$ ) were found at 72 hours. In study 2, a large increase in affective/sensory pain ( $\Delta = 0.79$ ) was found at 24 hours. Dot density plots in both studies revealed substantial variability among people with ME/CFS relative to healthy control participants.

**Conclusions:** PEM symptoms are variable among people with ME/CFS and several gaps in the literature need to be addressed before guidelines for measuring PEM in the clinical or research setting can be established.


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## Introduction

Under controlled laboratory settings, acute exercise is a useful model to study post-exertion malaise (PEM), which has emerged as a cardinal feature of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS; more recently termed Systemic Exertion Intolerance Disease) [1]. Both maximal and submaximal exercise protocols have been used to assess changes across numerous perceptual and physiological outcomes. These studies have documented PEM in a variety of ways including reduced activity levels, abnormal metabolic and cardiorespiratory responses, changes in cognitive function, altered circadian rhythms, and changes in various biological markers such as complement C4a, cytokines, natural killer cells, and markers of oxidative stress [2–8]. Although invaluable in terms of identifying objective indices of PEM and by extension, ME/CFS, their findings have also led to confusion and debate about what constitutes PEM, how it should be defined, and under what circumstances it is induced.

PEM is used as a primary diagnostic criterion for distinguishing ME/CFS cases from other conditions [1], but there are at least three different definitions for the term. For example, the Institute of Medicine/National Academy of Medicine (IOM/NAM) defines PEM as ‘a worsening of a patient’s symptoms and function after exposure to physical or cognitive stressors that were normally tolerated before disease onset’. The Centers for Disease Control and Prevention (CDC) case definition describes PEM as ‘... extreme prolonged exhaustion and sickness following physical and mental activity ... lasting more than 24 hours’ [9]. The Canadian Consensus Criteria (CCC) describes PEM as ‘... debilitating malaise and/or fatigue, generalized pain, deterioration of cognitive functions, and worsening of other symptoms occurring either immediately or a delayed period of time following physical or mental exertion’ [10]. Although these definitions and patient accounts highlight the disabling impact that PEM can have, they also imply that PEM is multidimensional and the experience and time course of PEM may vary from patient to patient.

A commonality between the IOM/NAM, CDC, and CCC definitions is their dependence on measuring patient-reported symptoms in order to characterize PEM. Symptom measurement provides key insight when drawing interpretations about potential biomarkers of dysfunction in central or peripheral pathways that presumably distinguish people with ME/CFS from healthy control participants or other patient groups. However, much of the pathophysiologically focused PEM research has omitted the measurement of symptom changes that would corroborate illness exacerbation. In the absence of a gold standard method for characterizing PEM, information regarding the symptoms that are consistently provoked by physical exertion may help researchers and clinicians narrow down potential biological mechanisms of ME/CFS that should be targeted in future treatment studies.

Data from two acute exercise studies, one using maximal exercise and one using submaximal exercise, involving separate samples of people with ME/CFS were explored to (i) document the magnitude of multiple symptoms associated with PEM at 24, 48, and 72 hours after exercise and (ii) examine potential variability in PEM symptom profiles among people with ME/CFS at 24, 48, and 72 hours after exercise.

## Study 1: maximal exercise

### Methods

The following methods pertain to the symptom data collection portion of an exercise, genetic, and microbiological marker ME/CFS study [3,11]. Participant characteristics, inclusion and exclusion criteria, experimental procedures, questionnaires, and the maximal exercise test are described below in brief and detailed elsewhere [3,11].

### Participants

Thirteen people with ME/CFS and 11 healthy control participants matched for age and self-reported physical activity were recruited from the Madison, Wisconsin metro area and the Marshfield Clinic (Marshfield, WI). This study was approved by the Institutional Review Board of the University of Wisconsin- Madison, and all participants provided written informed consent.

### Inclusion and exclusion criteria

Participants underwent a standard physical examination, battery of blood chemistry tests, and medical history review. Standard diagnostic criteria according to Fukuda et al. [9] were applied including standard laboratory and physical tests for exclusionary blood markers and conditions such as untreated hypothyroidism, sleep disorders, side effects of current medications, relapsing of past medical issues, and severe obesity ( $BMI \geq 45$ ). Participants were also excluded for (1) major depressive disorder with psychotic or melancholic features, (2) alcohol or substance abuse, (3) cardiovascular disease or uncontrolled hypertension, (4) current use of immunomodulatory medications or antibiotics in the past 6 weeks, and (5) any physical limitations that would preclude exercise testing. These criteria were assessed during screening, as well as during the interview portion of the medical history procedure. People with ME/CFS who also met the criteria for fibromyalgia [12] were also included in the study ( $n = 3$ ).

### Procedures

Participants completed four days of testing at the University of Wisconsin-Madison Exercise Psychology Laboratory. Study visit 1 included a clinical interview and screening blood draw to exclude patients with suspected ME/CFS who did not meet the case study criteria [9]. At least one week following the initial study visit, baseline measurement of fatigue, mood, and pain symptoms was assessed followed by a maximal exercise test (study visit 2). Study visits 3 and 4 occurred at 48 and 72 hours after exercise and involved completion of symptom questionnaires.

### Questionnaires

The Fatigue Visual Analog Scale [13], Multidimensional Fatigue Inventory (MFI [14]), McGill Pain Questionnaire – short form (MPQ [15]), and Profile of Mood States (POMS [16]) were administered to participants immediately before and 48 and 72 hours after exercise to monitor postexercise fluctuations in fatigue, mood, and pain symptoms. The participants were instructed to answer each questionnaire item in terms of how they felt at the time that the questionnaire was administered (i.e. ‘right now’).

### Exercise test

Participants performed a maximal exercise test on an electronically braked cycle ergometer (Sensorimedics, Loma Linda, CA). After a three-minute warm-up period at 25 Watts (W), work rate was increased by 5 W every 20 seconds until volitional exhaustion. The exercise ended with a 3-minute active recovery.

### Statistical analyses

Standardized mean difference effect sizes were used to compare the magnitude of symptom changes at 48 and 72 hours after exercise, and 95% confidence intervals were calculated to determine if the effect sizes were statistically significant ( $p < .05$ ). Effect sizes were calculated by dividing the difference between the mean symptom change from baseline to postexercise in the control and ME/CFS groups by the pooled standard deviation of the baseline scores. Effect sizes were converted to Hedges  $d$  ( $\Delta$ ) to adjust for small sample size bias [17]. Confidence intervals (95%) were calculated by adding or subtracting the product of the standard error of the effect size and 1.96 to or from each effect size. Positive effect sizes represent a larger change in the ME/CFS group and negative effect sizes represent a larger change in the control group. Effect size values of .20, .50, and .80 were considered small, medium, and large, respectively [18].

Within-group variability in symptom changes was examined by visual inspection of dot density plots for the patient and control groups at each measurement time point (pre-exercise, 48 hours, and 72 hours).

## Results

### Preliminary results

Participant characteristics are provided in Table 1. Effect sizes and means (standard deviations) for symptoms are presented in Table 2 and Supplemental Table 1, respectively. Coefficients of variation for symptoms are provided in Supplemental Table 2.

### Primary results

Effect sizes for fatigue, mood, and pain outcomes were small-moderate and not statistically significant at 48 hours postexercise. At 72 hours postexercise, large and significant effect sizes were found in the ME/CFS patient group for MFI general ( $\Delta = 1.05$ ; 95% CI: 0.16, 1.94), MFI reduced motivation ( $\Delta = 0.93$ ; 95% CI: 0.05, 1.81), POMS fatigue ( $\Delta = 0.90$ ;

**Table 1.** Study 1 participant characteristics.

	Patients ( $n = 13$ )	Controls ( $n = 11$ )
Age (years)	45.46 (13.79)	44.91 (13.62)
Gender (female/male)	10/3	8/3
BMI ( $\text{kg}/\text{m}^2$ )	24.99 (3.90)	23.17 (4.05)
Duration of illness (years)	11.92 (7.74)	–
Gradual or sudden onset of ME/CFS (Gradual/Sudden/Do not remember)	4/9/0	–
Comorbid fibromyalgia (yes/no)	3/10	–
SF-36 Physical Health	32.23 (7.47)	56.16 (2.95)
SF-36 Mental Health	41.25 (11.32)	53.49 (4.24)

Note: BMI = Body Mass Index; SF-36 = 36 Item Short Form Health Survey.

**Table 2.** Study 1 Hedges' *d* effect sizes and 95% confidence intervals at 48 and 72 hours postexercise.

Symptom	Hedges' <i>d</i> (95% CI) 48 hours postexercise	Hedges' <i>d</i> (95% CI) 72 hours postexercise
Fatigue VAS	0.65 (−0.17, 1.48)	0.58 (−0.24, 1.40)
MFI general	0.68 (−0.18, 1.53)	1.05 (0.16, 1.94) <sup>a</sup>
MFI physical fatigue	−0.10 (−0.94, 0.73)	0.28 (−0.56, 1.11)
MFI reduced activity	0.14 (−0.70, 0.97)	−0.51 (−1.36, 0.34)
MFI reduced motivation	0.69 (−0.17, 1.55)	0.93 (0.05, 1.81) <sup>a</sup>
MFI mental fatigue	−0.28 (−1.12, 0.56)	0.09 (−0.74, 0.93)
POMS tension	0.53 (−0.28, 1.35)	0.48 (−0.34, 1.29)
POMS depression	0.32 (−0.49, 1.13)	0.34 (−0.46, 1.15)
POMS anger	0.26 (−0.55, 1.06)	0.28 (−0.52, 1.09)
POMS vigor	−0.61 (−1.43, 0.21)	−1.03 (−1.89, −0.18) <sup>a</sup>
POMS fatigue	0.54 (−0.28, 1.35)	0.90 (0.06, 1.74) <sup>a</sup>
POMS confusion	0.72 (−0.11, 1.55)	0.93 (0.09, 1.78) <sup>a</sup>
POMS TMD	0.68 (−0.14, 1.51)	0.90 (0.06, 1.75) <sup>a</sup>
MPQ VAS	0.31 (−0.50, 1.11)	−0.01 (−0.81, 0.80)
MPQ total	0.22 (−0.58, 1.03)	−0.18 (−0.99, 0.62)

Note: Hedges' *d* was calculated by subtracting the mean change from pre-exercise to postexercise in the control group from the mean change from pre-exercise to postexercise in the chronic fatigue syndrome group and dividing by the pooled standard deviation at baseline. Positive effect sizes represent a larger change in the ME/CFS group and negative effect sizes represent a larger change in the control group.

MFI = Multidimensional Fatigue Inventory; MPQ = McGill Pain Questionnaire; POMS = Profile of Mood States; TMD = Total Mood Disturbance; VAS = Visual Analog Scale.

<sup>a</sup>Statistically significant effect size ( $p < .05$ ).

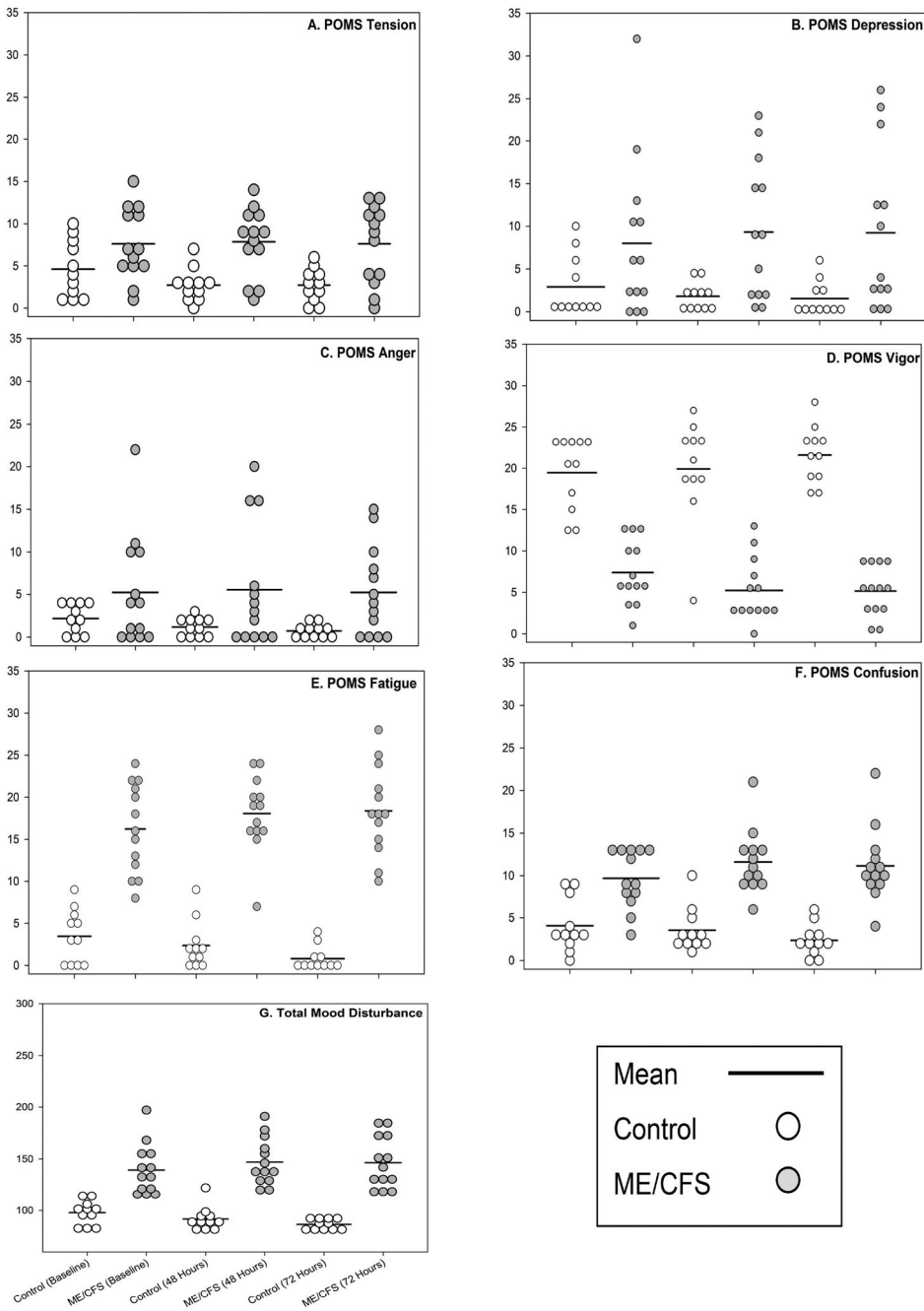
95% CI: 0.06, 1.74), POMS confusion ( $\Delta = 0.93$ ; 95% CI: 0.09, 1.78), and POMS total mood disturbance (TMD) ( $\Delta = 0.90$ ; 95% CI: 0.06, 1.75).

Visual inspection of dot density plots showed substantial variability for reported symptoms within the ME/CFS patient group relative to the control group (Figures 1 and 2; Supplemental Figures 1 and 2).

### Study 1 discussion

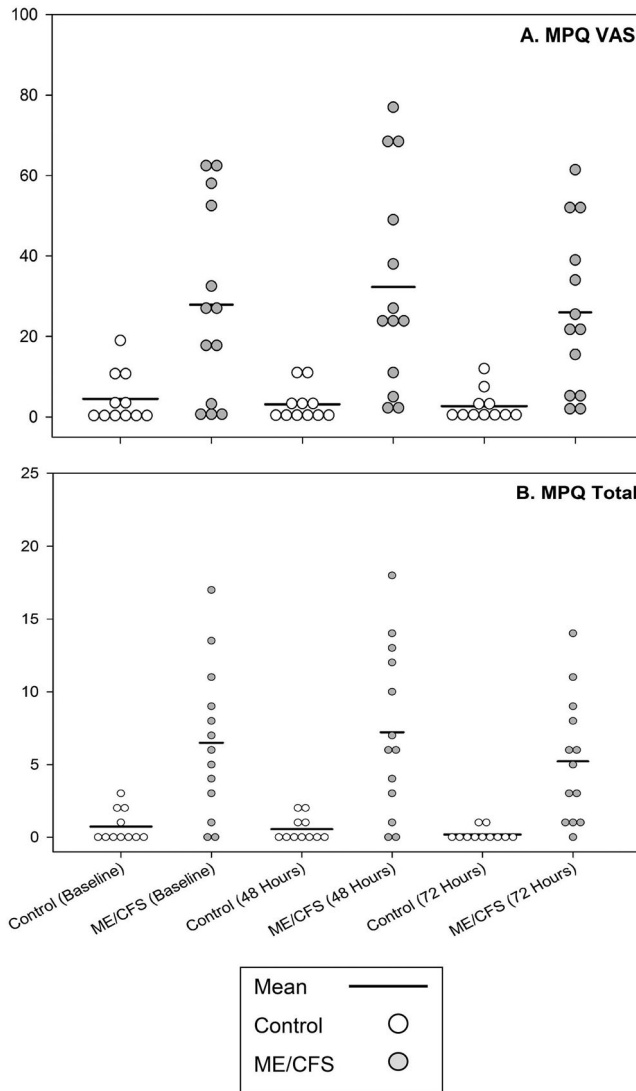
PEM symptom profiles were variable between measurement time points. An examination of effect sizes and 95% confidence intervals indicated that fatigue, mood, and pain symptoms were not significantly different between people with ME/CFS and control participants 48 hours postexercise. However, people with ME/CFS reported large and significant changes in several indices of fatigue and mood at 72 hours postexercise. Maximal exercise studies with symptom measurement periods  $\geq 24$  hours postexercise are seldom reported, but the present findings can be compared to four previous investigations with measurement time points and exercise stimuli that were similar to this study.

Lamanca and colleagues matched people with ME/CFS and control participants for habitual physical activity and measured gene expression levels before and 24 hours after maximal exercise [19]. The investigators also measured fatigue symptoms with the Chalder Fatigue Scale [20] and reported a significant main effect of time for people with ME/CFS but not control participants at 24 hours postexercise. However, when the effect size calculation methods used here were applied to the symptom data reported by Lamanca et al., a moderate effect size for fatigue was found, but the confidence interval overlapped zero ( $\Delta = 0.56$ ; 95% CI: −0.14, 1.26). Thus, it appears that a measurement time period greater than 24 hours postexercise may be needed to capture significant differences between people with ME/CFS and control participants.



**Figure 1.** Study 1 dot density plots of mood symptoms before and after maximal exercise.

Yoshiuchi and colleagues measured physical and psychological symptoms one week before and 11 consecutive days after a maximal exercise challenge [6]. A notable feature of this study is that symptoms were measured at multiple time points per day. Using a multilevel modeling approach to adjust for nesting effects, the authors found



**Figure 2.** Study 1 dot density plots of pain symptoms before and after maximal exercise.

that physical symptoms among people with ME/CFS became worse five days after exercise. The statistical approach used by Yoshiuchi et al. [6] makes direct comparisons with the present study challenging, but one link between the findings of the two studies is that symptoms were not significantly exacerbated until more than two days after the maximal exercise stimulus.

Van Ness and associates used a qualitative approach to assess PEM for up to seven consecutive days among 25 people with ME/CFS and 23 age-matched sedentary control participants. To determine the time course of recovery following a maximal exercise test, participants were asked to provide daily written responses to open-ended questions designed to measure postexercise recovery [21]. A majority of people with ME/CFS ( $n = 15$ ) took at least five days to recover and some reported taking longer than 1 week.

Participants also completed a standardized measure of health-related quality of life [22] at 7 days postexercise, but the absence of data for the pre-exercise time point impeded our ability to calculate and compare effect sizes with the present study.

A fourth maximal exercise study by Togo and associates showed that people with ME/CFS reported significantly higher fatigue, pain, and sleepiness symptoms approximately 24 hours after exercise [23]. This study also found that in spite of patient perceptions of being sleepier following exercise, sleep quality as measured by polysomnography was not significantly different between people with ME/CFS and control participants. Further investigations are needed to confirm whether the sleep-related effects of PEM extend beyond perceptual indices of sleep quality in people with ME/CFS.

In summary, after collectively considering the results of the present study and prior literature, it is apparent that a variety of symptoms aside from fatigue (e.g. pain, mood disturbance, and unrefreshing sleep) play a role in the PEM experience. With respect to diagnosing ME/CFS, the multidimensional nature of the PEM symptom response and within-patient group variability in PEM symptom profiles should be acknowledged and taken into consideration in future research and clinical practice.

## **Study 2: submaximal exercise**

### ***Methods***

The following methods pertain to the symptom data collection portion of a previously published exercise and neuroimaging ME/CFS study [24]. Participant characteristics, inclusion and exclusion criteria, experimental procedures, questionnaires, and the submaximal exercise test are described below in brief and detailed elsewhere [24].

### ***Participants***

Fifteen people with ME/CFS and 15 healthy control participants matched for sex, height, weight, and self-reported physical activity were recruited from the Madison, Wisconsin metro area for a submaximal exercise, gene expression, and neuroimaging study. This study was approved by the Institutional Review Board of the University of Wisconsin-Madison, and all participants provided written informed consent.

### ***Inclusion and exclusion criteria***

Confirmation of diagnosis was obtained by both a letter from each patient's doctor confirming that they met both CDC criteria and CCC and completion of the DePaul Symptom Questionnaire at study entry [25]. The DePaul Symptom Questionnaire contains diagnostic algorithms that are based on items meant to represent the case definition criteria of ME/CFS and was specifically developed to assess both CDC criteria and CCC [26]. It has also demonstrated good test-retest reliability [27]. People with ME/CFS who met the criteria for fibromyalgia [28] were also included in the study ( $n = 13$ ). Participants were excluded for (1) active medical conditions that accounted for the symptoms of chronic fatigue; (2) current use of immunomodulatory medications or antibiotics in the past 6 weeks; (3) self-report or physician-confirmed diagnosis of present psychosis, major depression with psychotic or melancholic features, bipolar disorders, anorexia or bulimia nervosa, and alcohol or substance abuse within the past 2 years of the onset illness; (4) fatigue sufficient to



impair functioning or preclude exercise testing; and (5) cardiovascular contraindications to submaximal exercise.

### **Procedures**

Participants completed three days of testing at the University of Wisconsin-Madison Exercise Psychology Laboratory. Study visit 1 involved baseline data collection and included a detailed symptom and illness assessment. Study visit 2 occurred one week following baseline data collection. During this study visit, participants completed fatigue, mood, pain, and physical symptom questionnaires followed by a submaximal bout of exercise. Participants returned to the laboratory 24 hours postexercise to complete the study questionnaires (visit 3).

### **Exercise test**

Participants performed a submaximal exercise test on an electronically braked cycle ergometer (Sensorimedics, Loma Linda, CA). Exercise began at 20 Watts and the intensity of exercise was gradually increased until the participants reached their target heart rate (70% HR<sub>peak</sub>). Once the target HR was reached (~4 minutes), the participants completed 25 minutes of steady-state exercise at the target intensity. Exercise intensity was maintained by making minor Watt adjustments throughout the 25-minute session. The exercise ended with a 3-minute active recovery.

### **Questionnaires**

The POMS, MPQ, and a VAS-adapted version of the CDC symptom inventory (CDC VAS) [29] were administered immediately before exercise and 24 hours after exercise. Participants were instructed to answer each questionnaire item in terms of how they felt at the time that the questionnaire was administered (i.e. 'right now').

### **Statistical analyses**

Statistical analyses were identical to that of study 1 to facilitate between-study comparisons.

## **Results**

### **Preliminary results**

Participant characteristics are presented in Table 3. Effect sizes and means (standard deviations) for symptoms are presented in Table 4 and Supplemental Table 3, respectively. Coefficients of variation for symptoms are presented in Supplemental Table 4.

### **Primary results**

At 24 hours postexercise, the standardized mean difference for the MPQ total score was large and significant for participants with ME/CFS ( $\Delta = 0.79$ ; 95% CI: 0.05, 1.54). Effect size confidence intervals overlapped zero for all remaining questionnaire subscale scores.

Visual inspection of dot density plots showed substantial variability for reported symptoms within the ME/CFS patient group relative to the control group (Figures 3 and 4; Supplemental Figure 3).

**Table 3.** Study 2 participant characteristics.

	Patients (n = 15)	Controls (n = 15)
Age (years)	42.67 (11.11)	43.20 (10.45)
Gender (female/male)	15/0	15/0
BMI (kg/m <sup>2</sup> )	25.15 (4.51)	24.98 (3.14)
Duration of illness (years)	13.5 (7.4) <sup>a</sup>	–
Gradual or sudden onset of ME/CFS (gradual/sudden/do not remember)	2/11/2	–
Comorbid fibromyalgia (yes/no)	13/2	–
SF-36 physical health	27.58 (10.57)	55.30 (4.47)
SF-36 mental health	46.54 (9.05)	54.11 (6.38)

Note: BMI = Body Mass Index; SF-36 = 36 Item Short Form Health Survey.

<sup>a</sup>n = 14.

**Table 4.** Study 2 Hedges' *d* effect sizes and 95% confidence intervals at 24 hours postexercise.

Symptom	Hedges' <i>d</i> (95% CI)
POMS tension	0.44 (–0.29, 1.16)
POMS depression	0.22 (–0.50, 0.94)
POMS anger	0.29 (–0.43, 1.01)
POMS fatigue	0.47 (–0.25, 1.20)
POMS vigor	–0.08 (–0.79, 0.64)
POMS confusion	0.46 (–0.26, 1.19)
POMS TMD	0.41 (–0.31, 1.14)
MPQ VAS	0.63 (–0.10, 1.36)
MPQ total	0.79 (0.05, 1.54) <sup>a</sup>
CDC fatigue	0.60 (–0.13, 1.33)
CDC muscle pain	0.59 (–0.14, 1.32)
CDC joint pain	0.27 (–0.45, 0.99)
CDC fever	0.09 (–0.63, 0.80)
CDC chills	0.31 (–0.41, 1.03)
CDC lymph nodes	0.41 (–0.31, 1.13)
CDC sore throat	0.51 (–0.22, 1.24)
CDC headache	0.58 (–0.15, 1.31)
CDC memory problems	0.46 (–0.27, 1.18)
CDC difficulty concentrating	0.68 (–0.05, 1.42)

Note: Hedges' *d* was calculated by subtracting the mean change from pre-exercise to postexercise in the control group from the mean change from pre-exercise to postexercise in the chronic fatigue syndrome group and dividing by the pooled standard deviation at baseline. Positive effect sizes represent a larger change in the ME/CFS group and negative effect sizes represent a larger change in the control group.

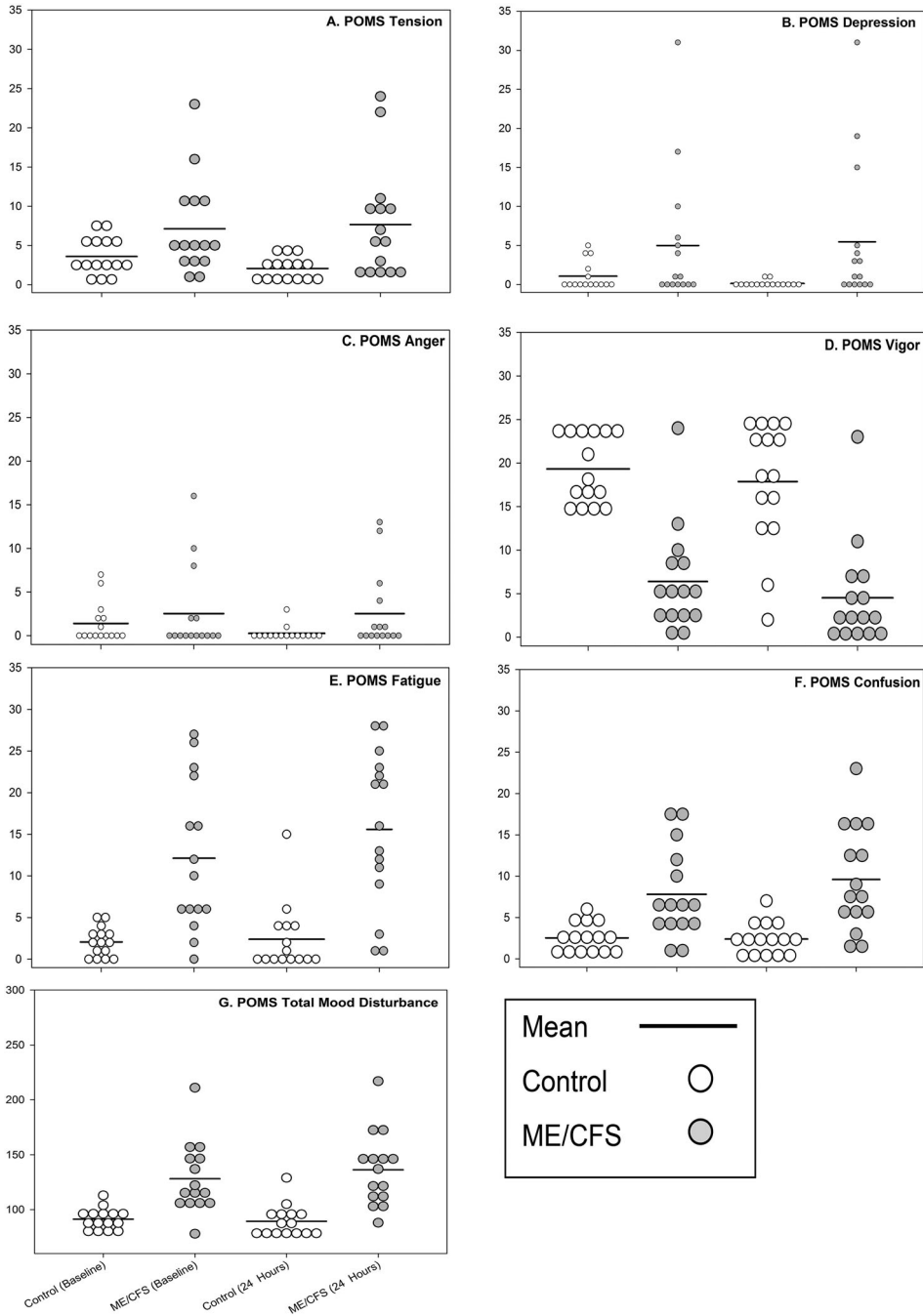
CDC = Centers for Disease Control and Prevention Symptom Inventory; MPQ = McGill Pain Questionnaire; POMS = Profile of Mood States; TMD = Total Mood Disturbance; VAS = Visual Analog Scale.

<sup>a</sup>Statistically significant effect size ( $p < .05$ ).

## Study 2 discussion

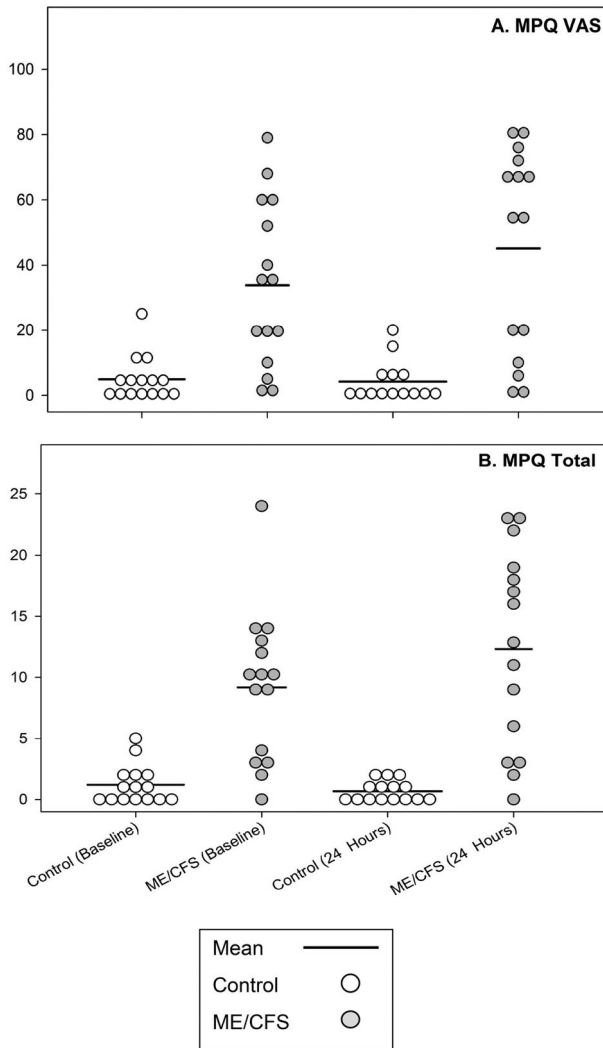
The primary finding in this study was that a large ( $\Delta = 0.79$ ) and significant ( $p < .05$ ) post-exercise increase in pain was detected for participants with ME/CFS. Our findings are consistent with two previous reports that measured pain symptoms in people with ME/CFS before and 24 hours after submaximal exercise [2,30]. Van Oosterwijck and colleagues reported that submaximal exercise had a large and significant effect on pain symptoms ( $\Delta = 1.29$ ; 95% CI: 0.64, 1.94) in people with ME/CFS and comorbid fibromyalgia ( $n = 22$ ) [30]. Furthermore, submaximal exercise has similar effects on pain symptoms in ME/CFS patients with ( $\Delta = 1.26$ ; 95% CI: 0.82, 1.69) and without ( $\Delta = 1.46$ ; 95% CI: 0.83, 2.09) comorbid fibromyalgia [2]. Therefore, it appears that pain symptoms are a key component of PEM.

One empirical question that has not been directly tested is whether different types of pain symptoms have different time courses following exercise. For instance, it is possible



**Figure 3.** Study 2 dot density plots of mood symptoms before and after submaximal exercise.

that the time course of PEM-related joint pain is shorter than other specific domains of pain (e.g. sensory, affective, and whole body). Peterson et al. showed a large and significant ( $\Delta = 1.15$ ; 95% CI: 0.20, 2.09) increase in joint pain measured immediately after 30 minutes of light-intensity walking (1 mph) [31]; however, in the present study, a small,



**Figure 4.** Study 2 dot density plots of pain symptoms before and after submaximal exercise.

nonsignificant effect was found for the CDC VAS joint pain item at 24 hours postexercise ( $\Delta = 0.27$ ; 95% CI:  $-0.45, 0.99$ ).

***Fatigue symptom changes were nonsignificantly different between groups***

One unexpected finding was that between-group differences in fatigue symptoms were nonsignificant at 24 hours postexercise, which is inconsistent with at least two other studies that measured fatigue-related responses to submaximal exercise. Light and colleagues found that symptoms of mental ( $\Delta = 0.88$ ; 95% CI: 0.28, 1.47) and physical fatigue ( $\Delta = 1.61$ ; 95% CI: 0.97, 2.25) were significantly higher for people with ME/CFS than control participants at 24 hours postexercise. Furthermore, a second study found that the reduced activity and mental fatigue subscale scores of the MFI were significantly higher for people with ME/CFS following exercise [32]. It should be noted that the authors

analyzed postexercise symptoms as collapsed scores across a seven-day period; thus, the specific time point at which fatigue symptoms showed the largest between-group differences is not clear.

## General discussion

The results of studies 1 and 2 raise important questions relevant to the study and understanding of PEM. Central to each question is the considerable amount of symptom variability both between and within studies. Here, using relatively conservative statistical methods for evaluating significant findings, it was shown that the specific symptoms that were exacerbated by exercise were not consistent between the two exercise challenge studies. Furthermore, the substantial degree of within-patient group variability in symptoms that were consistently measured in both studies (Figures 1–4) and those that were unique to each study (Supplemental Figures 1–3) suggests that the experience of PEM among participants with ME/CFS may be subject to individual differences. When applicable, the results of studies 1 and 2 are integrated in the following discussion of critical gaps in the literature.

### *Which symptoms change the most after physical exertion?*

Between studies 1 and 2, the largest significant change in symptom severity was found for general fatigue on the MFI ( $\Delta = 1.05$ ); however, large and significant symptom changes were also found for reduced motivation ( $\Delta = 0.93$ ), feelings of confusion ( $\Delta = 0.93$ ), feelings of fatigue (VAS;  $\Delta = 0.90$ ), and TMD ( $\Delta = 0.90$ ) in study 1 and sensory/affective pain ( $\Delta = 0.79$ ) in study 2. The findings suggest that PEM is a complex, multidimensional composite of fatigue, motivation, mood, and pain symptoms and more research is needed to develop a PEM definition that incorporates the variety of symptoms that change with exercise. Additionally, studies of interactions between central (e.g. brain function) and peripheral (e.g. autonomic and immune) mechanisms that are linked to fatigue, motivation, mood, and pain are warranted.

### *How should PEM be defined?*

Despite reliance on the presence of PEM for diagnosing ME/CFS, a consistent definition for PEM has yet to be established. More recent consensus statements endorse the use of the term post-exertional neuroimmune exhaustion [33]. In addition to findings from studies reporting cardiorespiratory (e.g. oxygen consumption) and performance-based (e.g. workload) outcomes utilizing the repeated-exercise model [34], consideration should be given to (i) the substantial amount of symptom variability that appears both before and after physical exertion and (ii) symptoms in addition to fatigue that are influenced by exertion (e.g. mood, motivation, and pain). Large, independently conducted studies that measure the host of psychological and physical symptoms that appear to be exacerbated by exercise are needed to improve the conceptualization of PEM.

A preliminary step to defining PEM may be to define exertion *per se*. In terms of physical exertion, the specific intensity threshold that reliably exacerbates symptoms has not been experimentally established. Although symptoms were exacerbated in both studies, it was found that maximal exercise induced different symptom responses compared to

submaximal exercise. Presumably, a study that compares various exercise intensities to a seated rest control condition would enable investigators to test whether PEM occurs in a dose-dependent fashion and confirm whether different intensities elicit different types and magnitudes of symptom changes.

An additional issue to consider is how various modes of exercise influence the PEM symptom response. A majority of studies have used either cycling or treadmill exercise to elicit PEM, but the potential effect of other exercise modes (e.g. swimming, weight lifting, and yoga) is unknown and no studies have been conducted that directly compare two or more modes of exercise. The conceptualization of PEM as a diagnostic criterion for ME/CFS could be altered if symptoms are only exacerbated by certain modes of exercise. This information would help clinicians make evidence-based suggestions about which activities are less likely to induce PEM and are thereby safer for people with ME/CFS.

### ***What is the effect of mental exertion on PEM?***

In light of recent evidence that mental exertion elicits PEM [35] and the inclusion of cognitive/mental exertion as a precipitating event in all three PEM definitions provided by the IOM/NAM, CDC, and CCC, no studies have directly compared the effect of physical exertion to cognitive/mental exertion. Of particular interest is whether physical and mental exertion are equally effective in distinguishing people with ME/CFS from healthy control participants as well as patients with other types of chronic, multi-symptom illnesses with no definitive etiology or pathophysiology (e.g. fibromyalgia and Gulf War Illness).

Another important consideration is how potential interactions between mental and physical exertion influence PEM. A recent systematic review has provided evidence that mental fatigue induced by the performance of a cognitive task decreases exercise performance and increases perceived exertion in healthy adults [36]. Whether these findings extend to people with ME/CFS is unknown, but they imply that pre-exercise levels of mental fatigue should be taken into account in PEM research.

### ***How should PEM symptoms be measured?***

Validation of a psychometric instrument that is specifically designed to measure PEM may also be warranted. In addition to the types of symptoms that are measured, close attention should be given to the questionnaire instructions to prevent baseline ceiling effects, which make measuring subsequent symptom increases difficult. For instance, significant changes in fatigue following exercise may appear to be marginal if a participant issues a pre-exercise rating that is close to the maximum scale value. Therefore, the sensitivity of a questionnaire to detect changes in symptom severity could be augmented by asking participants to rate their experience of a given symptom 'relative to a bad day'. An alternative solution when measuring postexercise symptoms may be to ask people with ME/CFS to rate their responses 'relative to how you felt prior to physical exercise'.

### ***What is the time course of the PEM response?***

The understanding of the PEM time course is limited in the current literature. For instance, a recent quantitative review by Loy and colleagues reported that, on average, PEM onset

occurs within four hours of exercise and lasts up to 92 hours after exercise. However, no single study included in the analysis measured symptoms longer than 92 hours, which limited the authors' ability to determine if PEM extended past that time period [37]. Furthermore, the scope of the meta-analysis by Loy and colleagues was focused on fatigue symptoms; thus, the time course of other symptom types (e.g. pain and mood disturbance) that are exacerbated by exercise remains unknown. Thus, longitudinal studies with consecutive daily measurements that exceed 92 hours and capture multiple symptom types are needed to determine the time frame for (i) the initial onset of PEM, (ii) the fluctuation of PEM severity following initial onset, and (iii) return to baseline.

Studies of PEM symptom heterogeneity may also require an extended baseline assessment to determine the magnitude of symptom variability prior to exercise. For instance, Parkitny et al. measured self-reported fatigue and pro- and anti-inflammatory immune markers over 25 consecutive days in a sample of Veterans diagnosed with Gulf War Illness [38]. Although the study by Parkitny and colleagues did not involve an exercise challenge, a similar design incorporating two weeks of daily symptom measurements both before and after exercise could be used to determine whether symptom variability is specific to the PEM experience or if it is also present prior to exercise. Because activities associated with participation in a study (e.g. travel to and from the laboratory) may exacerbate ME/CFS symptoms [39], the design of a study of this magnitude should incorporate technological strategies for reducing participant burden such as measuring symptoms via personal handheld devices at home [40].

A third issue that limits the ability to determine the time course of PEM is the dearth of evidence from experimental studies that randomly assign people with ME/CFS to an exercise or control condition. A majority of the PEM literature comprises studies with case-control designs, which do not provide Level 1 evidence to suggest that symptom exacerbations are *caused* by exercise. Despite compelling results from case-control exercise challenge studies and surveys from patient experiences of PEM symptoms, the extent to which symptoms are exacerbated by physical exercise *per se* is open to interpretation until high-quality evidence from randomized controlled studies focused on patient-only samples is generated.

### ***How does ME/CFS illness duration influence PEM?***

Illness duration was relatively similar between studies 1 and 2 of the present report, but data from pathophysiology work focused on cytokines [41] and gut microbiota [42] points to illness duration as another factor that should be taken into account in PEM research. For instance, within-patient group variability in the PEM symptom response could be partially explained by complications arising in people with ME/CFS with a longer illness duration (e.g. physiological deconditioning) that cause them to perceive exercise as more fatiguing or painful than people with ME/CFS with a more recent diagnosis.

### ***Is there a clear pathophysiological marker of PEM?***

Three biologically plausible models have emerged at the forefront of central and/or peripheral pathophysiological explanations for ME/CFS [43]. However, with the exception of a few notable studies [2], corresponding symptom changes following exercise are rarely

measured in mechanistic investigations. For instance, a recent meta-analysis of the effect of exercise on self-reported fatigue among people with ME/CFS was limited to seven studies [37]. This finding is somewhat surprising when considering that the diagnosis of ME/CFS is largely dependent on patient-reported symptoms. The development of objective biological markers to confirm patient reports is critical, but the measurement of corresponding symptom changes should be included to aid the interpretation of biological data.

### ***Expectations and demand characteristics***

One methodological issue that has received little attention in the PEM literature is the impact of patient expectations on measurement outcomes. The relationship between expectations and placebo/nocebo effects is well documented [44]; however, partitioning placebo/nocebo effects from true effects remains a difficult barrier in exercise studies that measure psychological outcomes because of the inability to blind participants to receiving exercise and the absence of a valid exercise placebo. A partial solution is to measure pre-existing expectations, which can influence exercise behavior. In a study of 49 people with ME/CFS, Heins et al. found that, independent of gender, age, BMI, and present level of fatigue, anticipated fatigue was inversely related to duration of stair climbing ( $r = 0.30$ ;  $p < .001$ ) [45].

Investigators should also consider the potential for demand characteristics, the totality of cues responsible for communicating the experimental hypothesis [46], to influence participant expectations and bias responses to subjective measurement tools. In order to reduce bias, neutral language should be used in informed consent documents and informal discussions of the study purpose between the test administrator and participants. For instance, ratings of fatigue may be artificially inflated if a participant is told that the purpose of an experiment is to 'measure postexercise *increases* in fatigue' compared to a situation in which s/he is told that the purpose is to 'measure postexercise *changes* in fatigue'. Methods for reducing demand characteristics when measuring psychological responses to exercise have recently been published [47].

### ***Limitations and future research***

Several methodological differences between studies 1 and 2 should be addressed as potential limitations. Most notable are the characteristics of the exercise stimuli that were used to elicit PEM; two different exercise intensities were used in studies 1 and 2, which may explain why PEM symptom responses were inconsistent between the studies.

A second methodological feature that limits comparisons between studies 1 and 2 is the measurement of PEM symptoms at varying time points. Postexercise symptom measurements took place at 48 and 72 hours in study 1 and at 24 hours in study 2. It is possible that different types of symptoms have different time courses and more studies with 24, 48, and 72 hours postexercise measurement points and beyond are needed to explore the time courses of individual symptom types.

A third inconsistency between studies was the inclusion of male participants in study 1 but not in study 2. A sensitivity analysis with males excluded from the effect size calculation showed that all study 1 findings at 72 hours remained significant. However,



POMS Depression ( $\Delta = 1.02$ ; 95% CI: 0.03, 2) and POMS TMD ( $\Delta = 1.5$ ; 95% CI: 0.45, 2.55) scores became significant at 48 hours postexercise when data from male participants were excluded from the effect size calculation. These findings suggest that females with ME/CFS may be more susceptible to mood-related PEM symptoms than males with ME/CFS. The influence of gender on PEM symptom variability should be investigated in larger samples of people with ME/CFS that are adequately powered to detect statistically significant differences between males and females.

Another between-study difference lies in the criteria that were used to diagnose participants as ME/CFS positive. Study 2 used both CDC criteria [9] and CCC [10] and study 1 ME/CFS diagnosis was solely based on CDC criteria. A recent narrative review by Nacul and associates has recommended that researchers restrict their ME/CFS samples only to people who meet multiple case definitions [48], although there is some evidence from a quantitative review that the PEM response is not moderated by case definition criteria [37].

Finally, a much larger percentage of the ME/CFS sample in study 2 had comorbid fibromyalgia, which may explain why pain symptoms were significantly increased in study 2 but not in study 1. Fibromyalgia is a prevalent comorbidity in ME/CFS and it is challenging to elicit the characteristics and severity of pain attributable solely to ME/CFS [49]. Moreover, the 1990 American College of Rheumatology criteria were used in study 1 [12] and the 2010 American College of Rheumatology criteria were used in study 2 [28]. The more recent 2010 criteria have been suggested to greatly increase the overlap between ME/CFS and fibromyalgia [49], which could partially explain the discrepancy in the number of people with ME/CFS with comorbid fibromyalgia between studies. The potential impact of using earlier [12,28] or more recent [50] criteria to diagnose fibromyalgia comorbidity is beyond the scope of this report, but this is another important consideration in future PEM research.

## Conclusion

Results from studies 1 and 2 showed substantial variability in the PEM symptom response both between studies and among two samples of people with ME/CFS, and suggest that research focused on determining the type, severity, duration, and pattern of symptom responses is needed. Before guidelines for measuring PEM in the clinical or research setting can be established, several key gaps in the literature need to be addressed, as discussed. Given that PEM research involves subjecting people with ME/CFS to physical stress that exacerbates their illness, ethical considerations are also necessary. These include ensuring **that** (i) participants are exposed to minimum amounts of stress (e.g. exercise) necessary to answer the research question, (ii) accommodations be made to protect the safety of the participants during and following the exercise stimulus, and (iii) study designs take into account disease severity. Achieving a greater understanding of PEM is important toward determining the pathophysiology of ME/CFS. Therefore, this research requires careful attention from scientific, clinician, and patient safety perspectives.

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