CDC ME/CFS SEC Call

"Exercise Testing in the MCAM Study"

Dane B. Cook, PhD

May 13, 2021

3:00 PM ET

AGENDA

- Welcome—Christine Pearson
- CDC Program Overview—Dr. Beth Unger
- Guest Speaker—Dr. Dane B. Cook
- Questions and Answers

Federal Relay
Event ID: 4780203
For closed captioning, please visit
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The findings and conclusions in these presentations are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Disclosure

Dr. Dane Cook received funding from CDC for the analysis of the MCAM study.

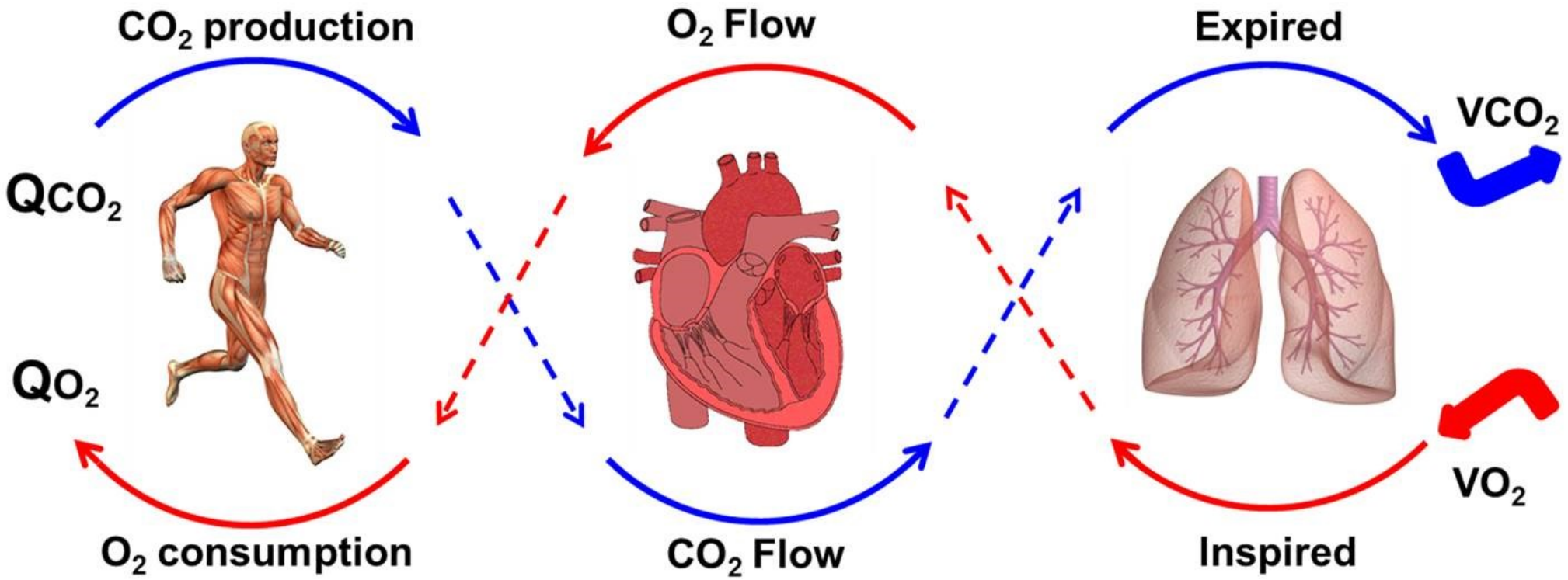
Exercise Testing in the MCAM Study

Dane B. Cook, PhD

University of Wisconsin-Madison

Rationale for Cardiopulmonary Exercise Testing (CPET)

Determine the Integrative response to physical effort

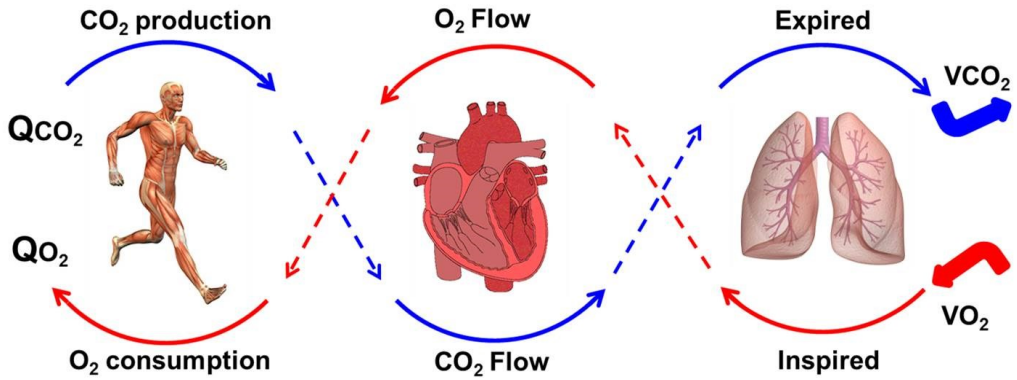


CPET Measures & Indications

DIRECT MEASURES	INDIRECT MEASURES	INDICATIONS/EVALUATION
Oxygen Consumption ($\dot{V}O_2$)	$\dot{V}E/\dot{V}O_2$ & $\dot{V}E/\dot{V}CO_2$	Exercise Tolerance
Carbon Doxide Production ($\dot{V}CO_2$)	Oxygen Pulse ($\dot{V}O_2$/HR)	Heart and Lung Disease/Symptoms
Ventilation [$\dot{V}E$: (B*f* & T_v)]	$\dot{V}O_2$/WR	Impairment/Disability
Heart Rate (HR)		Safety/Prescription for Rehabilitation
Work Rate (WR)		
Oxygen Saturation		

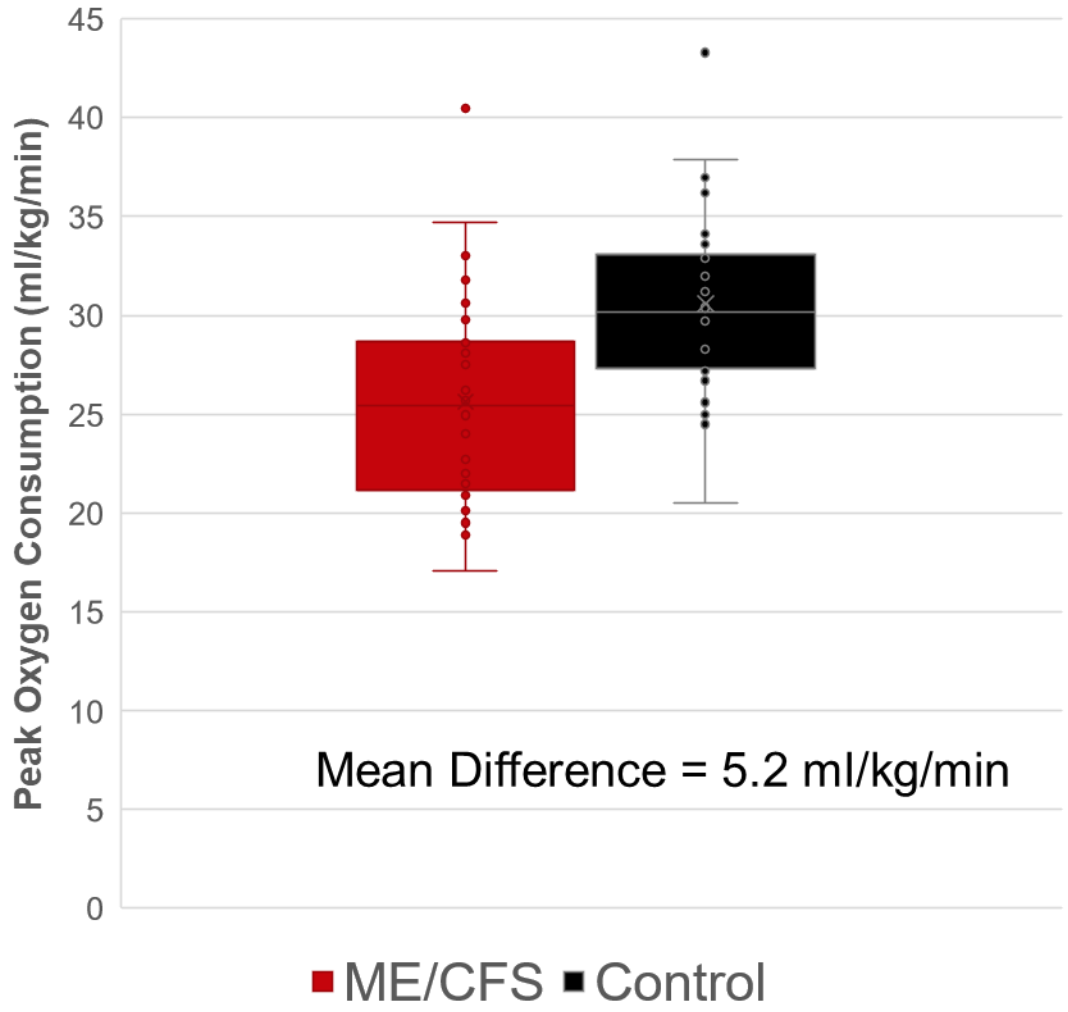
Exercise Testing in ME/CFS

- **Valuable method and clinical tool:**
  - Test cardiopulmonary system
  - Determine exercise tolerance
  - Guide exercise prescription
  - Challenge physiological systems



Phenomenon or Epi-phenomenon

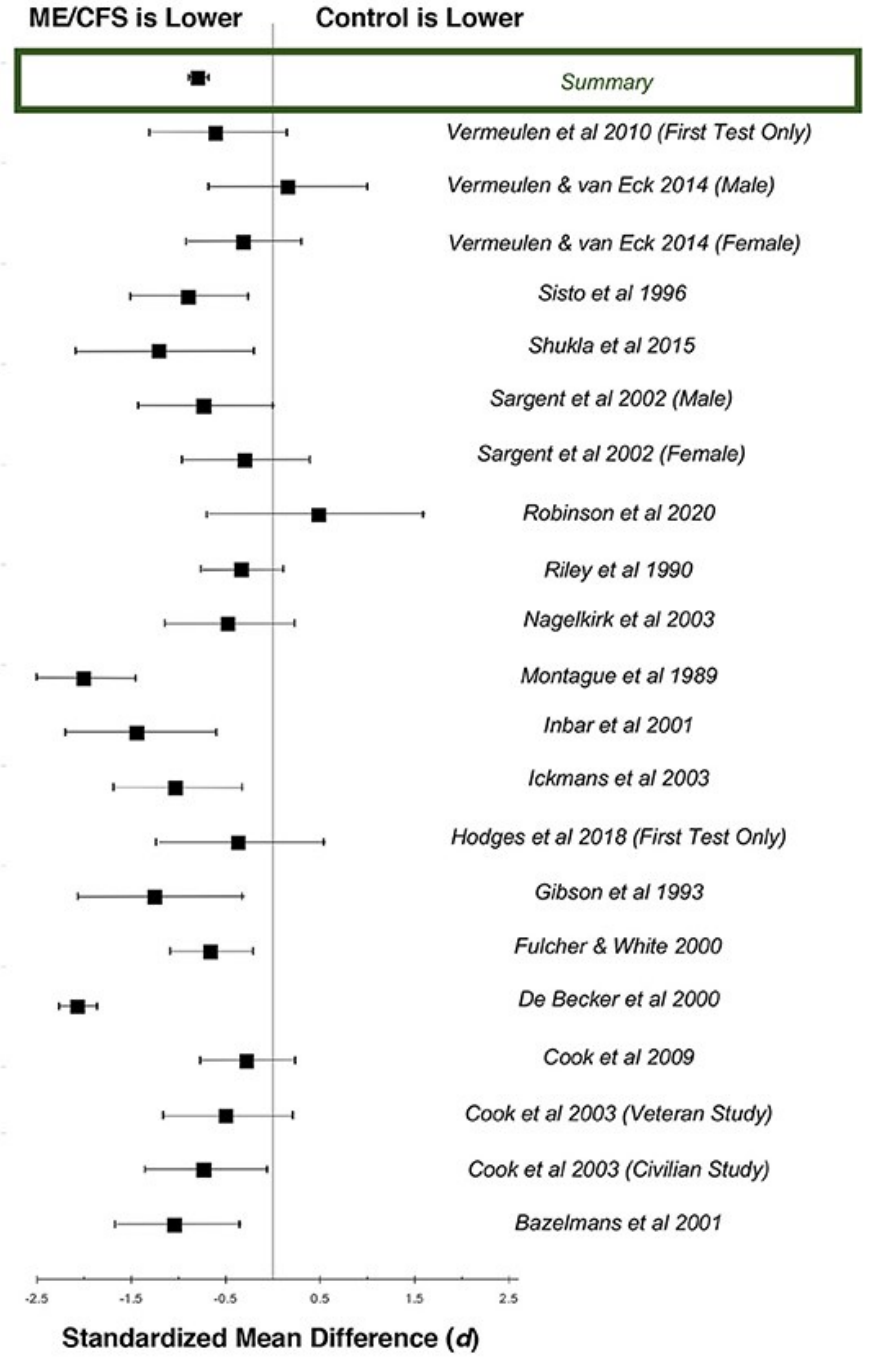
- Critical for interpretation
- Recent meta-analysis found clinically meaningful differences in peak oxygen capacity
- We know little beyond threshold and peak responses



Franklin et al. 2019; Int J Sports Med

Chronotropic incompetence

- Cardiac responses to exercise have been the focus of several studies
- Meta-analysis showed large effect size differences between ME/CFS and controls at peak exercise
  - *Effect size d* = 1.37
  - Controls = 94% age-predicted
  - ME/CFS = 82.2% age-predicted



Davenport et al., 2019. Chronotropic intolerance: an overlooked determinant of symptoms and activity limitation in myalgic encephalomyelitis/chronic fatigue syndrome?. Frontiers in Pediatrics, 7, p.82.

Purpose

1. Characterize

- Exercise capacity of the MCAM cohort

2. Conduct

- Comprehensive assessment of the cardiopulmonary, metabolic, and perceptual responses to exercise in ME/CFS

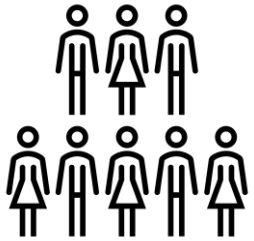
3. Determine

- The role of aerobic fitness

Methods

Procedures

Participants



ME/CFS

(n=179; 65% Female)

Controls

(n=169; 68% Female)

Testing

20–24°C

40–60% relative humidity

No smoking 2 hrs

No caffeine or food 4 hrs

No exercise 24 hrs

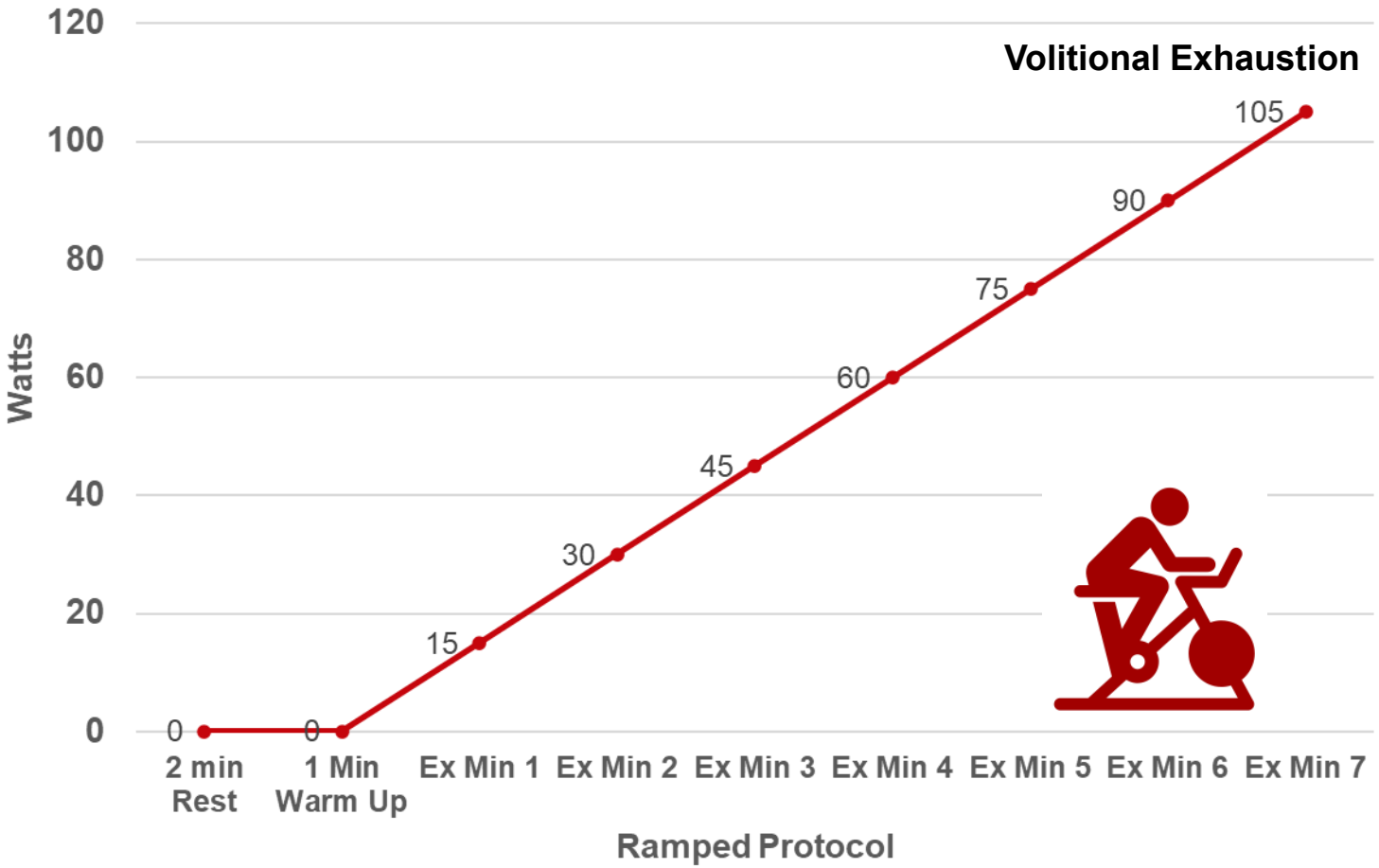
<u>12-lead ECG</u>

Exercise Safety

Resting HR

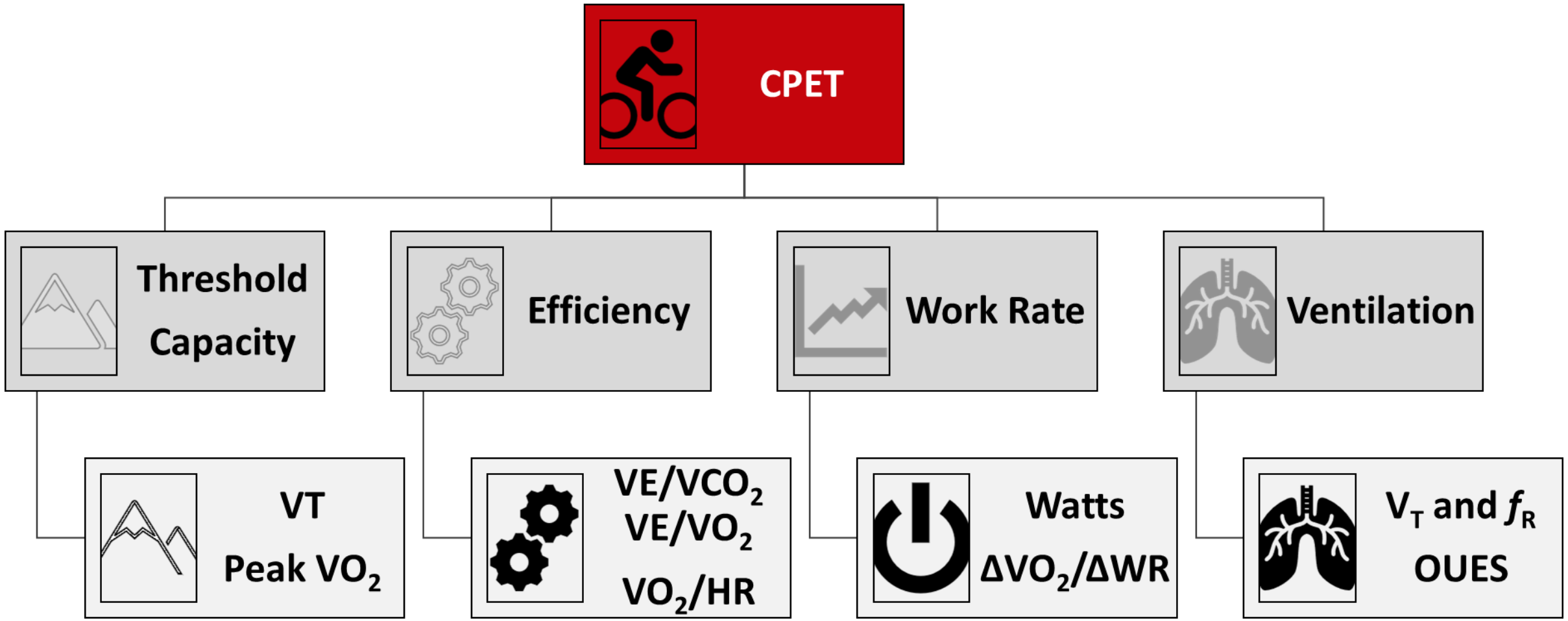
Exercise Testing (Ramped Cycle Ergometry)

Sample Max Test



- Metabolic measurement
  - Oxygen consumption ($\dot{V}O_2$)
  - Carbon dioxide production ($\dot{V}CO_2$)
  - Ventilation ($\dot{V}E$)
  - Heart rate (HR)
  - Work rate (Watts)

Metabolic Exercise Testing Analyses



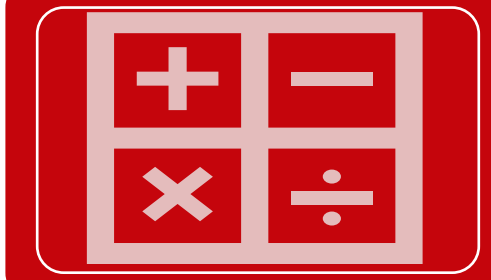
Data Processing (Independent & blind to clinical status)

Protocol check

- Systems Calibrated
- Obvious data artifacts

Peak Criteria check

- RER ≥ 1.1
- Reaching ≥ 85% age-predicted peak HR
- RPE ≥ 17



Calculation of Relative Exercise Intensities (0-100%)

- 20-sec intervlas (backward from peak VO2 timepoint)
- Linear model to determine the relative percent of peak VO2 for each variable

Results

Entire Sample and Fitness-Matched Subset

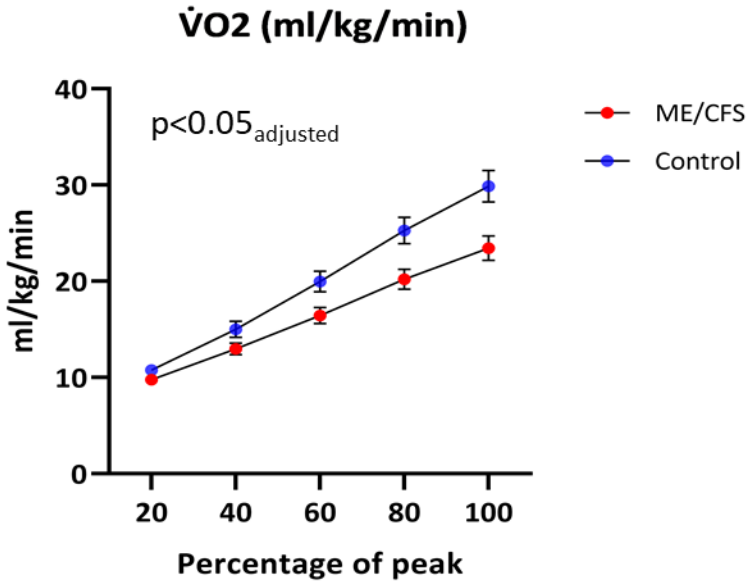
Demographic Data

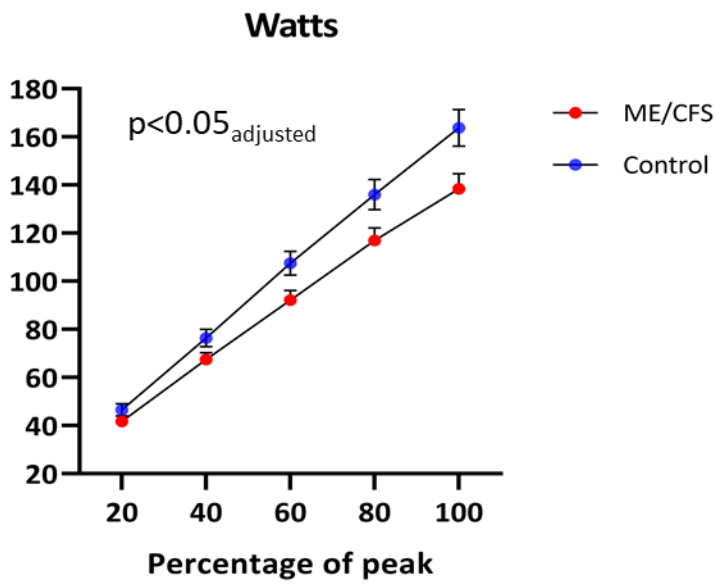
	Entire Sample			Fitness –Matched		
	ME/CFS (n=179)	**Controls (n=169)**	**ES (CI)**	**ME/CFS (n=99)**	**Controls (n=99)**	**ES (CI)**
% Female	65	68	na	61	70	na
Age (yrs)	**49.4 (13.2)**	**42.5 (14.0)**	**0.51** (.29 – .72)**	47.3 (13.2)	47.1 (12.7)	0.02 (-0.38 – 0.41)
Height (m)	1.7 (0.1)	1.7 (0.09)	0.0 (-0.21 – 0.21)	1.7 (0.09)	1.7 (0.08)	0.35 (-.05 – 0.75)
Weight (kgs)	78.5 (18.7)	73.0 (16.0)	0.32** (0.10 – 0.53)	77.4 (16.5)	76.0 (16.6)	0.08 (-.31 – 0.48)
BMI (kg/m^2)	27.3 (6.9)	26.0 (5.1)	0.21** (0.00 – 0.42)	26.7 (5.6)	27.2 (5.2)	-.09 (-0.49 – 0.30)

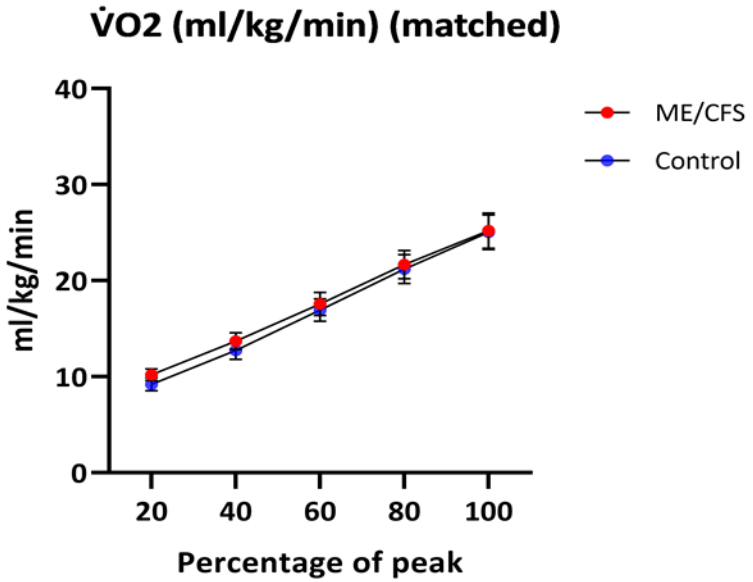
Ventilatory and cardiac performance during exercise

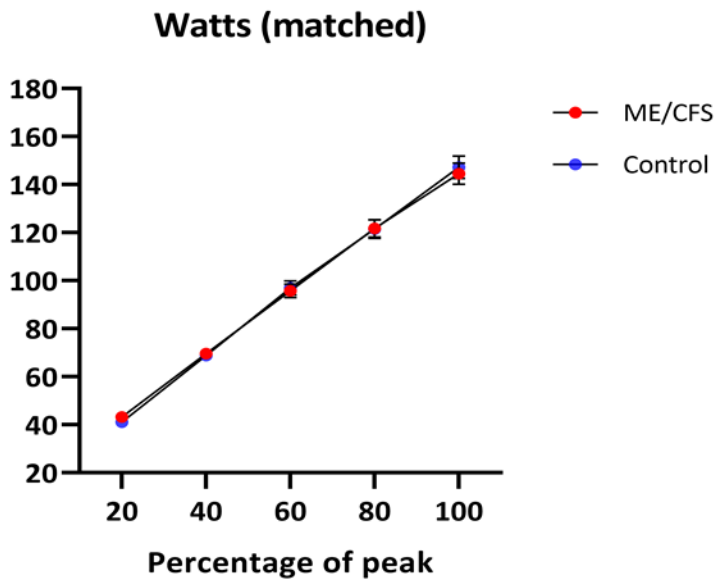
Ventilatory & Cardiac Performance	Entire Sample			Fitness –Matched		
	ME/CFS (n=179)	Controls (n=169)	ES (CI)	ME/CFS (n=99)	Controls (n=99)	ES (CI)
$\dot{V}E/\dot{V}CO_{2nadir}$	27.8 (5.9)	25.3 (3.1)	0.51** (0.29 – 0.72)	**27.1 (5.4)**	**25.4 (3.1)**	**0.39** (0.10 – 0.67)**
OUES	1.87 (0.67)	2.16 (0.78)	-0.42** (-0.63 – -0.21)	1.98 (0.67)	1.91 (0.74)	0.09 (-0.19 – 0.36)
$OUES_{BSA}$	0.97 (0.30)	1.18 (0.39)	-0.61** (-0.82 – -0.39)	1.03 (0.31)	1.02 (0.35)	0.04 (-0.24 – 0.32)
% $HRR_{adjusted}$	83.5 (15.7)	89.8 (12.1)	-0.44** (-0.66 – -0.23)	**83.7 (14.7)**	**88.3 (13.6)**	**-0.30** (-0.58 – -0.02)**
% Predicted Max HR	90.0 (9.8)	93.3 (7.8)	-0.39** (-0.60 – -0.18)	90.0 (9.1)	92.3 (8.7)	-0.22 (-0.50 – 0.06)

Dynamic Exercise Responses—Fitness

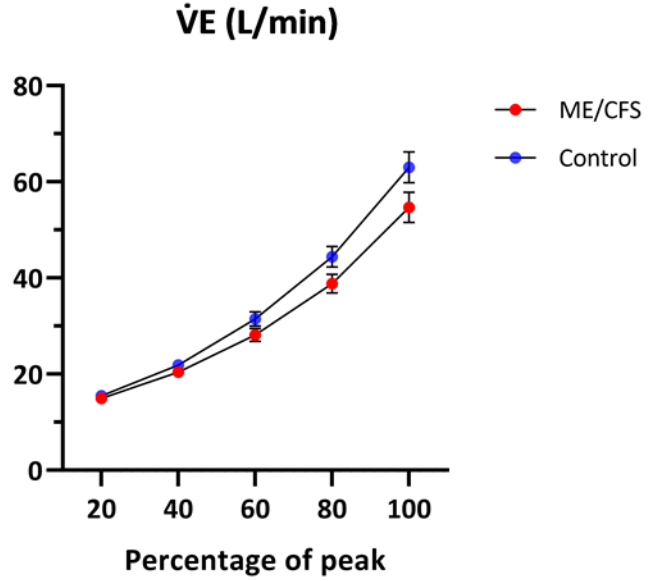


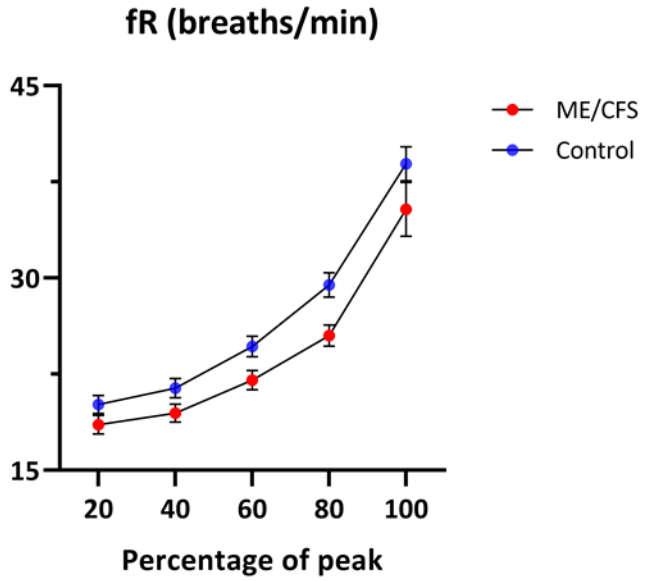


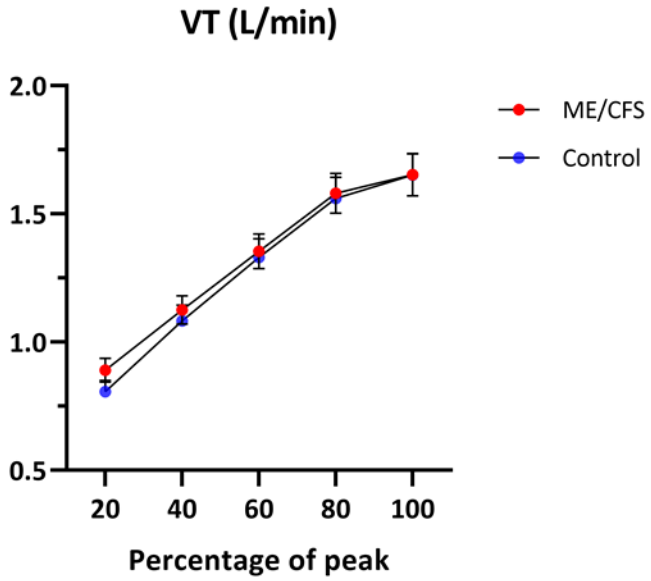


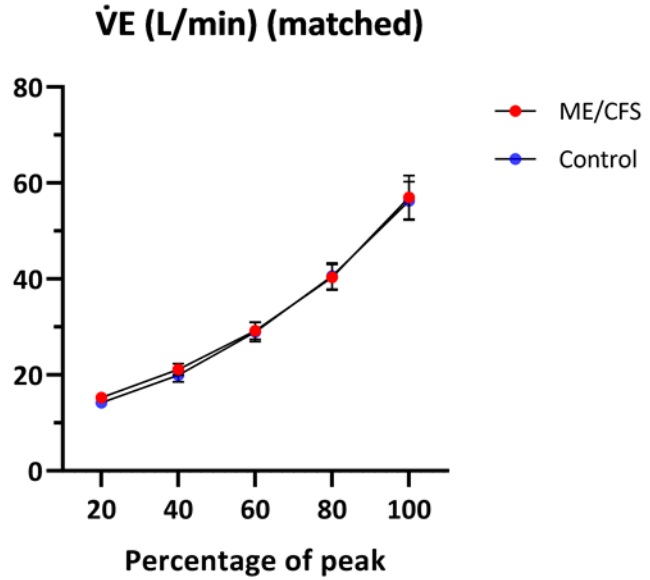


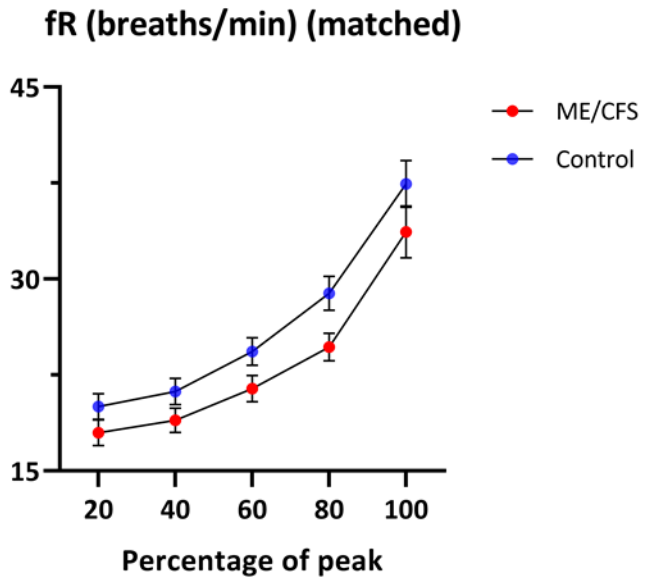
Dynamic Exercise Responses #1

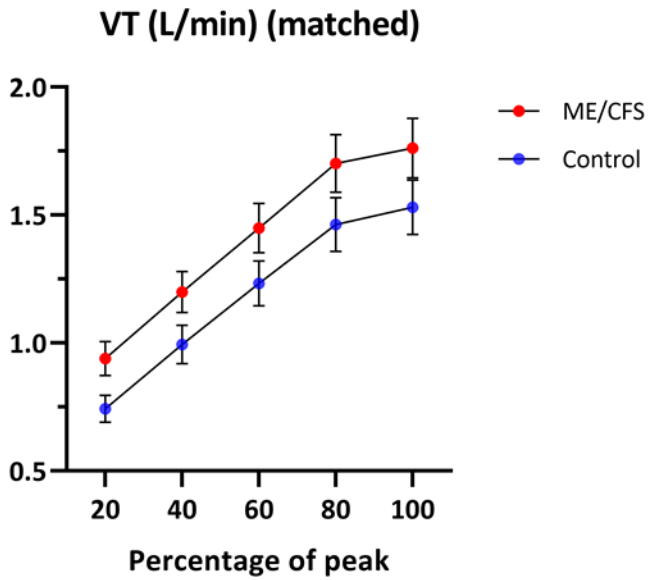




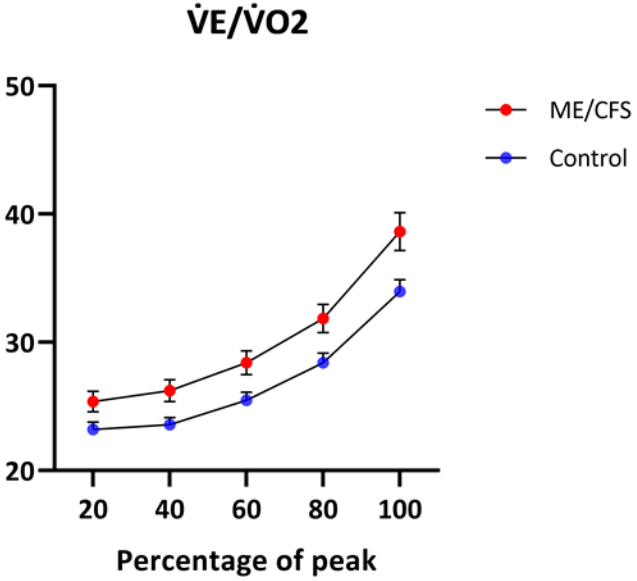


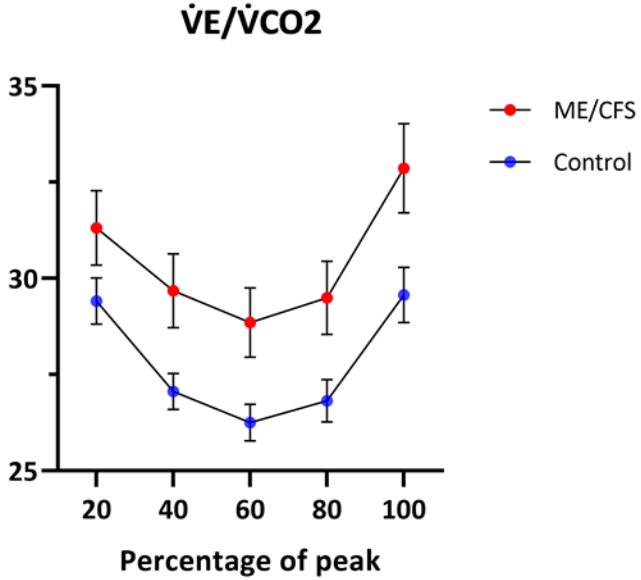


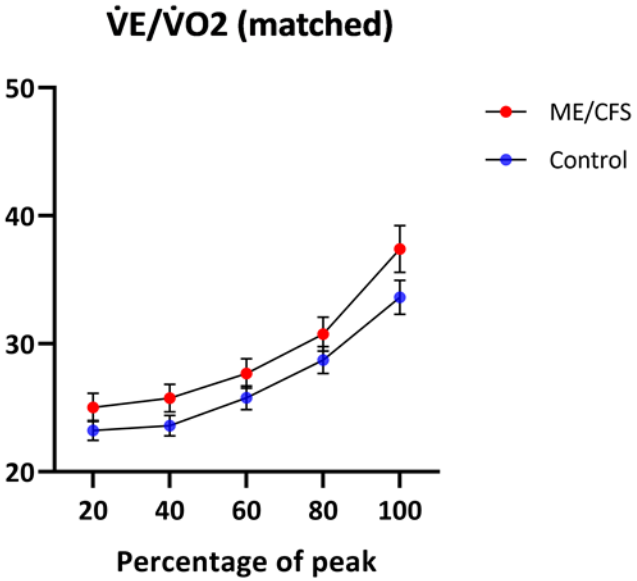


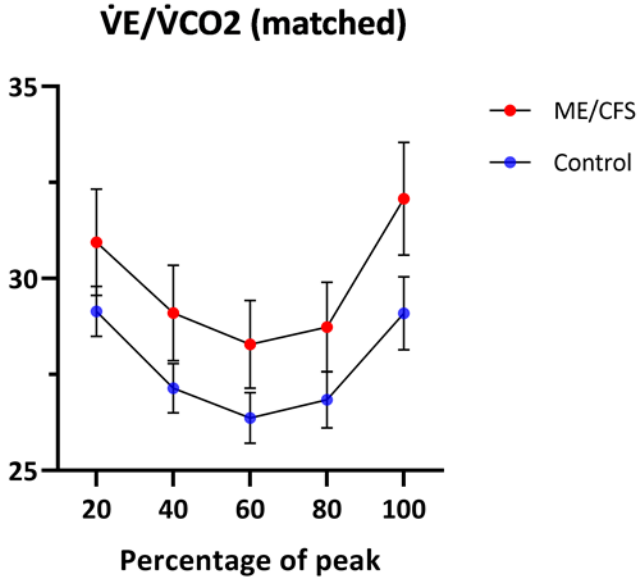


Dynamic Exercise Responses #2









Discussion

Summary & Conclusions

Entire Sample

- ↓ reduced oxygen uptake
- ↓ cardiac performance
- Inefficient pulmonary ventilation (↑ VE/VCO2 & VE/VO2)
- ↑ perception of effort

Fitness-Matched Sample

- Inefficient pulmonary ventilation:
  - ↑ VE/VCO2 & VE/VO2; ↓ breathing frequency & ↑ volume)
  - ↑ perception of effort

Summary & Conclusions #2

Gas Exchange

- VE/VCO2 = poor perfusion
- VE/VO2 = poor extraction from skeletal

Unique breathing pattern

- Improve alveolar ventilation (make-up for dead-space)
- Respiratory muscle fatigue and subsequent metaboreflex (vasoconstriction of exercising muscle) – aka Robin Hood for the lungs

Summary & Conclusions #3

Little evidence for overt chronotropic incompetence

- Fitness matching appears critical

Future Directions

- Relationships between cardiopulmonary inefficiencies
  - Symptoms
  - Cognition
  - Sleep

Take Home Message

We observed clinically relevant indications of a compromised cardiopulmonary response in ME/CFS

- Inefficient exercise ventilation even when accounting for fitness

ME/CFS is not a disease of low aerobic fitness

- False narrative
  - Damaging to ME/CFS community & research
  - Understanding how the cardiopulmonary system interacts with the disease is important

Acknowledgements

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- MCAM Study Participants
- Pain and Fatigue Study Center, NY
- Center for Neuro-Immune Disorders, FL
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  - Open Medicine Clinic, CA
  - Sierra Internal Medicine Associates, NV
  - Fatigue Consultation Clinic, UT
  - Hunter-Hopkins Center, NC
  - Richard Podell Clinic, NJ
- CDC Chronic Viral Diseases Branch, ME/CFS Program

Questions and Answers

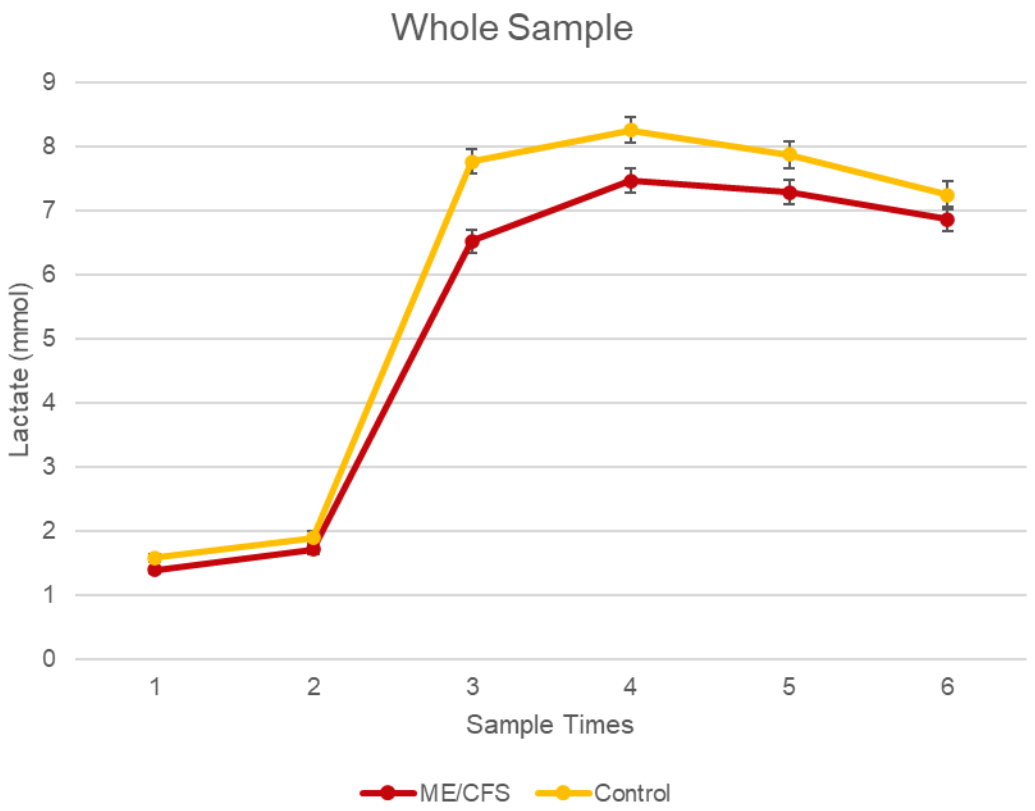
To ask a question within the Zoom webinar platform during the meeting, please:

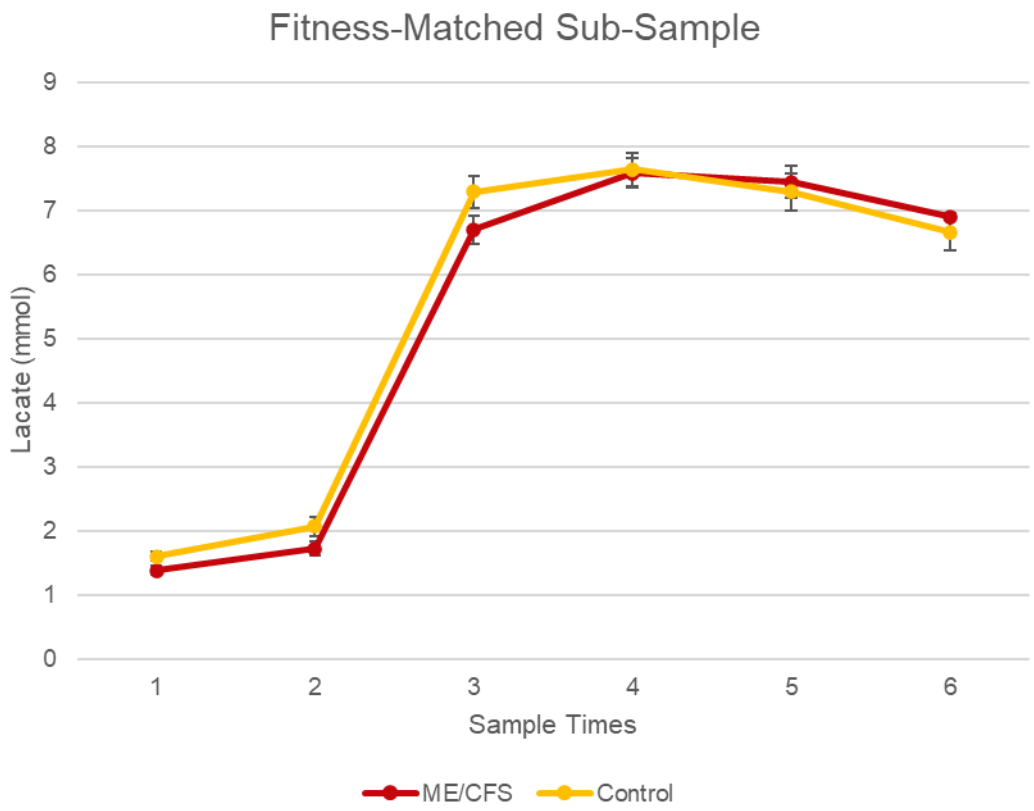
- Click on the “Q&A” button.
- Type your question in the “Q&A” box.
- Submit your question.

If you have additional questions following the call, please email MECFSSEC@cdc.gov.

Extras

Dynamic Exercise Responses View Two

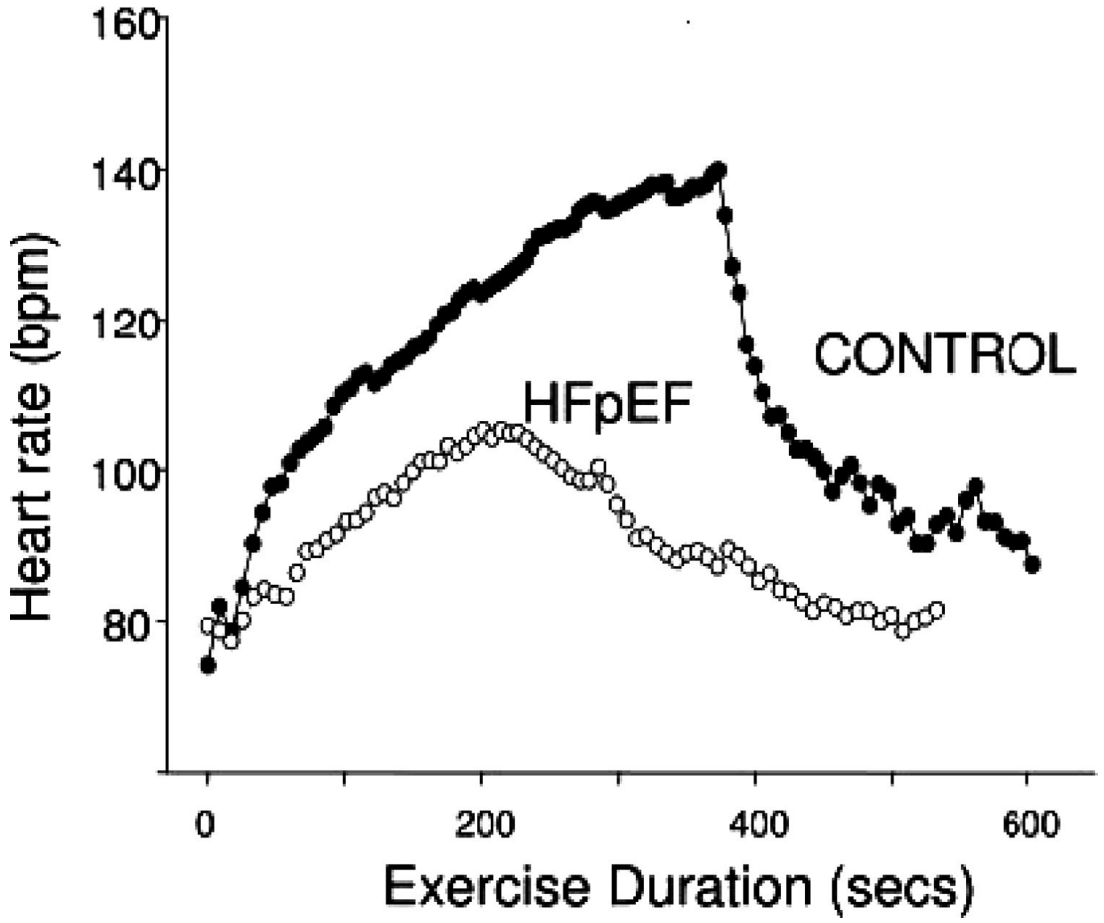




Chronotropic Incompetence Part One

- HRR
  - ME/CFS—33% did not meet 80%criteria
  - Control—14%
- Peak HR
  - ME/CFS—21% did not meet 85% criteria
  - Controls—9%
- CTI
  - ME/CFS—ranged from 4-17% below slope of 0.8 for a given stage
  - Controls—1-13%
  - 100% for each group achieved a slope of > .8 at some point during exercise

Chronotropic Incompetence Part Two



- ≥ 85% of age-predicted maximal HR (APMHR)
- ≥ 80% of adjusted heart rate reserve (HRR/APMHR – HR_{rest})
- Chronotropic index (CTI – Wilkoff Model):
  - Based on estimated HR stages
  - measured HR_{stage} / estimated HR_{stage}
    - Ratios ≤ 0.80 are indicative of chronotropic incompetence

Brubaker and Kitzman, 2011-Chronotropic Incompetence Causes, Consequences, and Management. Contemporary Reviews in Cardiovascular Medicine

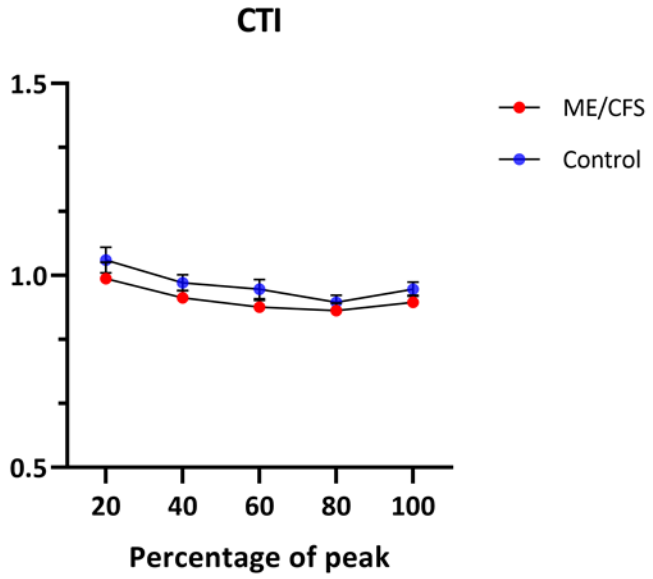
Statistical Analyses

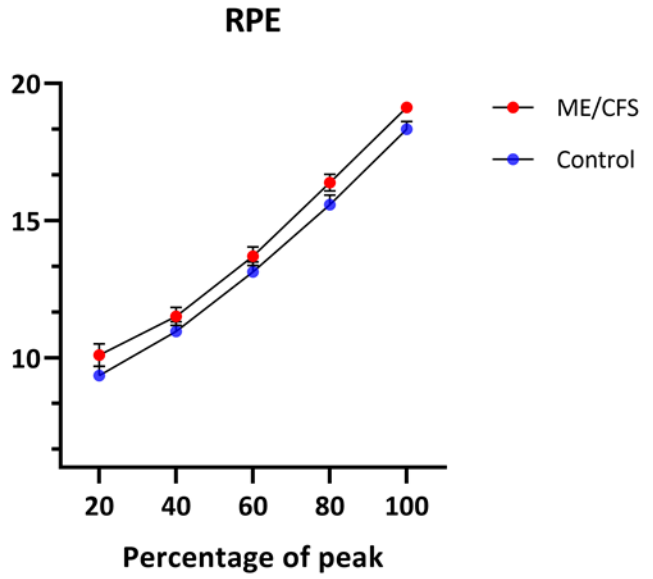
- Normality
  - Skewness, kurtosis, Q-Q plots, and the Shapiro-Wilk test
  - Data were normalized using a two-step approach as described by Templeton[1]
- Levene's Test
  - Equal variances between groups
- Hedge's *d* effect size with 95% confidence intervals[2]:
  - Subject characteristics, measures at the VT, OUES, and peak exercise
- Linear Mixed Effects models with repeated measures
  - VE, fR, V_T, VE/VO2, VE/VCO2, HR, O_2 pulse, CTI & RPE
  - $\alpha = 0.05$; Holm-Bonferroni Sequential Method
- Fitness-matched subset
  - ± 1 ml/kg/min peak VO_2
  - ± 5 years age

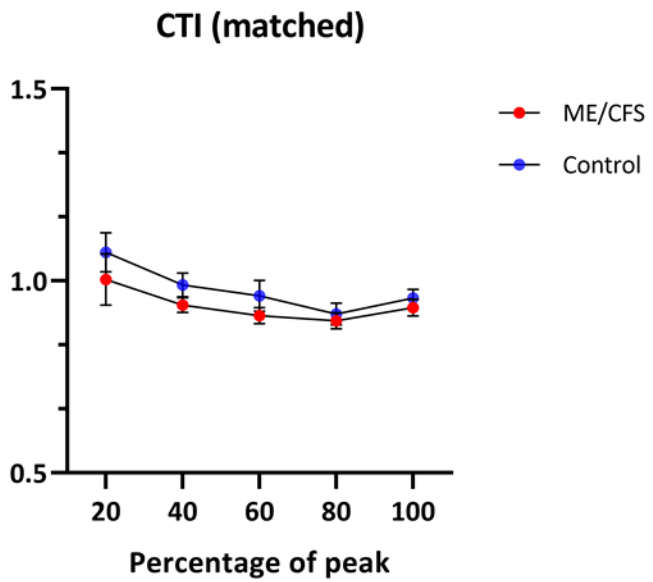
[1]Templeton GF. A two-step approach for transforming continuous variables to normal: implications and recommendations for IS research. Communications of the Association for Information Systems. 2011;28(1):4.;

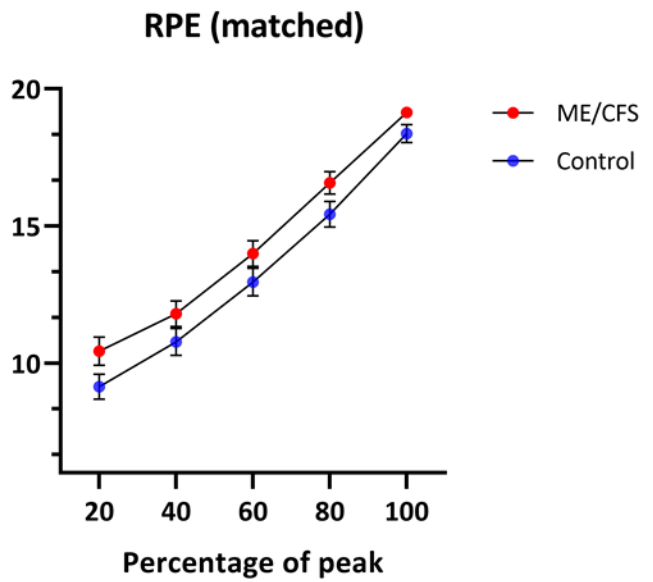
[2]Fritz CO, Morris PE, Richler JJ. Effect size estimates: current use, calculations, and interpretation. Journal of experimental psychology: General. 2012;141(1):2.

Dynamic Exercise Responses View Three









Demographic & Baseline	Entire Sample			Fitness –Matched		
	ME/CFS (n=179)	Controls (n=169)	ES (CI)	ME/CFS (n=99)	Controls (n=99)	ES (CI)
% Female	65	68	na	61	70	na
Age (yrs)	49.4 (13.2)	42.5 (14.0)	0.51** (.29 – .72)	47.3 (13.2)	47.1 (12.7)	0.02 (-0.38 – 0.41)
Height (m)	1.7 (0.1)	1.7 (0.09)	0.0 (-0.21 – 0.21)	1.7 (0.09)	1.7 (0.08)	0.35 (-.05 – 0.75)
Weight (kgs)	78.5 (18.7)	73.0 (16.0)	0.32** (0.10 – 0.53)	77.4 (16.5)	76.0 (16.6)	0.08 (-.31 – 0.48)
BMI (kg/m^2)	27.3 (6.9)	26.0 (5.1)	0.21** (0.00 – 0.42)	26.7 (5.6)	27.2 (5.2)	-.09 (-0.49 – 0.30)
HR (bpm)	67.9 (11.6)	62.2 (10.0)	0.53** (0.31 – 0.74)	68.7 (11.3)	63.5 (10.6)	0.47** (.19 – 0.76)
SBP (mmHg)	121.8 (14.0)	121.5 (15.8)	0.02 (-0.19 – 0.23)	120.5 (13.5)	120.5 (15.8)	0.00 (-0.21 – 0.21)
DBP (mmHg)	79.6 (9.8)	76.7 (10.6)	0.28** (0.07 – 0.50)	79.7 (9.5)	76.6 (9.9)	0.32** (0.04 – 0.60)
Physical Function***	40.7 (5.3)	59.0 (6.5)	-3.10** (-3.42 – -2.78)	41.3 (5.7)	57.6 (6.9)	-2.58** (-2.96 – -2.20)
IPAQ Total (min/week)	46.1 (79.5)	106.7 (103.7)	-0.66** (-0.89 – -0.43)	44.8 (78.0)	109.7 (113.0)	-0.67** (-0.98 – -0.36)
IPAQ Recreation (min/week)	8.9 (23.9)	26.2 (30.8)	-0.63** (-0.86 – -0.40)	9.6 (27.1)	20.9 (28.9)	-0.40** (-0.71 – -0.10)
IPAQ Sitting Total (hrs/week)	60.1 (25.3)	54.9 (42.1)	0.15 (-0.08 – 0.38)	58.6 24.3	55.4 (40.0)	0.10 (-0.20 – 0.40)

Ventilatory Threshold	Entire Sample			Fitness –Matched		
	ME/CFS (n=179)	Controls (n=169)	ES (CI)	ME/CFS (n=99)	Controls (n=99)	ES (CI)
%peak VO_2	52.9 (0.1)	51.2 (0.1)	0.15 (-.06 – 0.36)	52.8 (0.1)	51.3 (0.09)	0.12 (-0.16 – 0.40)
$\dot{V}O_2$ (ml)	947.1 (396.7)	1089.3 (503.6)	-0.31** (-0.53 – -0.10)	997.5 (407.4)	944.4 (395.7)	0.13 (-0.15 – 0.41)
$\dot{V}CO_2$ (ml)	801.6 (351.8)	937.2 (462.8)	-0.33** (-0.54 – -0.12)	849.2 (360.9)	816.8 (352.1)	0.09 (-0.19 – 0.37)
RER	0.84 (0.07)	0.86 (0.08)	-0.25 (-0.46 – 0.04)	0.85 (0.07)	0.87 (0.08)	-0.23 (-0.51 – 0.05)
$\dot{V}E$ (L/min)	18.8 (7.1)	22.3 (9.5)	-0.42** (-0.63 – -0.20)	19.8 (7.4)	20.1 (8.2)	-0.03 (-0.31 – 0.25)
fR (breaths/min)	19.9 (5.2)	22.1 (4.8)	-0.45** (-0.66 – -0.23)	**19.5 (4.9)**	**21.6 (5.1)**	**-0.41** (-0.69 – -0.13)**
V_T (L/min)	1.02 (0.41)	1.03 (0.40)	-.02 (-0.24 – 0.19)	**1.10 (0.46)**	**0.96 (0.35)**	**0.34** (0.06 – 0.62)**
$\dot{V}E/\dot{V}O_2$	25.5 (5.2)	23.5 (3.2)	0.47** (0.25 – 0.68)	**25.0 (4.9)**	**23.6 (3.7)**	**0.33** (0.04 – 0.61)**
$\dot{V}E/\dot{V}CO_2$	30.4 (6.5)	27.7 (3.4)	0.52** (0.30 – 0.73)	**29.7 (6.2)**	**27.7 (3.4)**	**0.41** (0.13 – 0.69)**
HR (beats/min)	103.2 (17.6)	108.7 (19.8)	-0.29** (-0.51 – -0.08)	105.2 (17.2)	107.2 (20.0)	-0.10 (-0.38 – 0.17)
O_2 pulse ($\dot{V}O_2$/HR)	9.2 (3.5)	10.0 (4.1)	-0.22 (-0.43 – -0.01)	9.5 (3.6)	9.0 (4.0)	0.14 (-0.14 – 0.41)
CTI	0.92 (0.13)	0.97 (0.15)	-0.36** (-0.57 – -0.14)	0.94 (0.13)	0.98 (0.17)	-0.25 (-0.67 – -0.11)
Watts	56.0 (27.7)	73.0 (35.2)	-0.54** (-0.75 – -0.32	59.2 (29.9)	64.1 (28.1)	-0.17 (-0.45 – 0.11)

Peak Reponses	Entire Sample			Fitness –Matched		
	ME/CFS (n=179)	Controls (n=169)	ES (CI)	ME/CFS (n=99)	Controls (n=99)	ES (CI)
Peak VO_2 (ml/kg/min)	23.4 (8.6)	29.9 (10.9)	-0.66** (-0.88 – -0.45)	25.2 (9.2)	25.1 (9.0)	0.02 (-0.19 – 0.23)
VO_2 (ml)	1817.3 (704.9)	2121.2 (761.8)	-0.41** (-0.63 – -0.20)	1915.6 (720.3)	1865.5 (694.9)	0.07 (-0.14 – 0.28)
VCO_2 (ml)	2111.0 (766.2)	2423.9 (787.9)	-0.40** (-0.62 – -0.19)	2210.6 (782.7)	2159.2 (731.0)	0.07 (-0.14 – 0.28)
RER	1.18 (0.1)	1.16 (0.08)	0.21 (0.00 – 0.42)	1.17 (0.09)	1.17 (0.09)	0.00 (-0.21 – 0.21)
VE (L/min)	54.7 (21.3)	63.0 (21.2)	-0.39** (-0.60 – -0.18)	57.0 (22.8)	56.3 (20.2)	0.03 (-0.18 – 0.24)
f_R (breaths/min)	34.7 (10.5)	38.9 (8.8)	-0.43** (-0.65 – -0.22)	**33.7 (10.1)**	**37.5 (9.2)**	**-0.39** (-0.60 – -0.18)**
V_T (L/min)	1.79 (0.59)	1.74 (0.59)	0.08 (-0.13 – 0.30)	**1.92 (0.64)**	**1.63 (0.57)**	**0.48** (0.19 – 0.76)**
VE/VO_2	38.5 (9.5)	34.0 (6.2)	0.57** (0.35 – 0.78)	**37.4 (9.1)**	**33.6 (6.7)**	**0.47** (0.26 – 0.68)**
VE/VCO_2	32.8 (7.4)	29.6 4.7	0.51** (0.30 – 0.72)	**32.1 (7.4)**	**29.1 (4.8)**	**0.48** (0.27 – 0.69)**
HR (beats/min)	156.0 (20.2)	166.5 (17.6)	-0.55** (-0.77 – -0.34)	157.7 (19.1)	161.7 (17.7)	0.22 (-0.50 – 0.06)
O_2 pulse (VO_2/HR)	11.6 (4.2)	12.8 (4.6)	-0.26** (-0.47 – -0.05)	12.1 (4.2)	11.5 (4.4)	0.15 (-0.06 – 0.36)
CTI	0.93 (0.12)	0.96 (0.12)	-0.25** (-0.46 – -0.04)	0.93 (0.11)	0.95 (0.11)	-0.18 (-0.46 – 0.11)
Watts	138.6 (42.3)	163.3 (50.1)	-0.53** (-0.75 – -0.32)	144.7 (44.6)	146.4 (47.3)	-0.04 (-0.25 – 0.17)
RPE (6-20)	**19.2 (1.0)**	**18.2 (2.0)**	**0.63** (0.42 – 0.85)**	**19.2 (1.0)**	**18.1 (2.2)**	**0.64** (0.43 – 0.86)**