SOME NOTES ON INCLUDED WORKS:

Since there are hundreds of studies on ME/CFS, post-polio syndrome, post-viral fatigue, myalgic encephalomyelitis, and chronic fatigue syndrome, this compilation represents a very small percentage of total 'important' works.

A confounding factor in ME/CFS research is the many research and clinical definitions of the disease, some of which are more inclusive than others. Research that utilized the Oxford Criteria alone, or the NICE criteria alone, was *de facto* excluded from the analysis, save for the PACE trial, due to its significant impact on research in (and treatment for) ME/CFS.

Many genetic studies that at first appeared intriguing were omitted due to a lack of repeatability.

Several studies were omitted that had very interesting results, but had very low sample sizes.

Finally: historically, funding for ME/CFS research has been low. This causes history to repeat itself in the form of tiny studies with small sample sizes that may arrive at the same conclusion every decade or so, without a large-scale study or meaningful validation (or a meta-analysis). Many studies from the 1980s and 1990s may have similar findings to what is presented here. For that reason, chosen studies are primarily within the past decade. For a complete analysis of published work on ME/CFS up to 2015, refer to the Institute of Medicine report linked in the first section.

SOME NOTES ON THIS DOCUMENT

SELECTED REFERENCES BY TOPIC (PP 2-5)

In order to cut to the chase for those who are more interested in a frank list of important studies, this precedes all in-depth analysis. Note that each section only includes what I considered most important to each topic. A full works cited can be found at the end of the document.

Researchers who will be attending the conference are marked in **gold**.

SEMINAL IDEAS AND IDEAS IN ME/CFS RESEARCH

This section goes into greater depth on the selected studies outlined in the first section. Other studies will also be cited here in support of chosen studies.

GENERAL INFORMATION (PP5)

This section describes documents that are useful for broad knowledge of ME/CFS.

METABOLOME (PP5-7)

Studies involving metabolites in ME/CFS

MICROBIOME (PP8-9)

Studies that examine gut microflora in ME/CFS

EXERCISE STUDIES (PP 10-15)

Studies that look at muscular function, post-exertional malaise, and exercise therapies in ME/CFS

NEUROENDOCRINE (PP 15-18)

Studies that examine signs of neurological dysfunction, including imaging studies; studies of HPA axis responsivity

CARDIAC AND ENDOTHELIAL DYSFUNCTION (PP 18-19)

Studies that demonstrate cardiac abnormalities not directly related to exercise testing

IMMUNOLOGICAL (PP 20-24)

Cytokine studies, autoimmunity, and studies involving various immune cells

LIST OF INTERESTING AUTHORS (PP 25)

An incomplete list of well-known authors and researchers in ME/CFS and why they are well-known

WORKS CITED (PP26-32)

All works cited here

SELECTED REFERENCES BY TOPIC

See the end of the document for a more traditional (and complete) Works Cited.

GENERAL INFORMATION

IOM (Institute of Medicine). (2015). Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness. Washington, DC: The National Academies. Retrieved June 21, 2016 from http://www.nationalacademies.org/hmd/Reports/2015/ME-CFS.aspx.

Carruthers et al. (2003) Myalgic encephalomyelitis/ chronic fatigue syndrome: clinical working case definition, diagnostic and treatment protocols.

- Summary of all current diagnostic criteria on MEpedia
- Canadian Consensus Criteria clinicians' guide
- Canadian Consensus Criteria full document

DePaul Questionnaire

Bell's Disability Scale

METABOLOME

Armstrong, C.W., McGregor, N.R., Lewis, D.P., Butt, H.L., & Gooley, P.R. (2015, December). Metabolic profiling reveals anomalous energy metabolism and oxidative stress pathways in chronic fatigue syndrome patients. *Metabolomics*, 11(6): 1626-1639.

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MICROBIOME

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Snell, C. R., Stevens, S. R., Davenport, T. E., & Van Ness, J. M. (2013, November). Discriminative Validity of Metabolic and Workload Measurements for Identifying People With Chronic Fatigue Syndrome [Electronic version]. *Phys Ther.*, *93*(11), 1482-1492. http://doi.org/10.2522/ptj.20110368

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Huth TK, Brenu EW, Nguyen T, Hardcastle SL, Johnston S, et al. (2014) Characterization of Natural Killer Cell Phenotypes in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis . *J Clin Cell Immunol, 5*(223). doi:10.4172/2155-9899.1000223

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SEMINAL STUDIES AND IDEAS IN ME/CFS RESEARCH

GENERAL INFORMATION:

THE INSTITUTE OF MEDICINE REPORT, 2015

Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness is a literature review conducted by the then-IOM. Reviewing over 9,000 separate studies, it's the place to go to find out if there is any ME/CFS research on Topic X or any findings for biomarker Y before 2015.

THE CANADIAN CONSENSUS CRITERIA, 2003

Diagnostic criteria are varied in ME/CFS. However, the Canadian Consensus Criteria identifies a very specific cohort in comparison to some of the more generalized criteria and is often used in research in conjunction with Fukuda or ICC.

- Summary of all current diagnostic criteria on MEpedia
- Canadian Consensus Criteria clinicians' guide
- Canadian Consensus Criteria full document

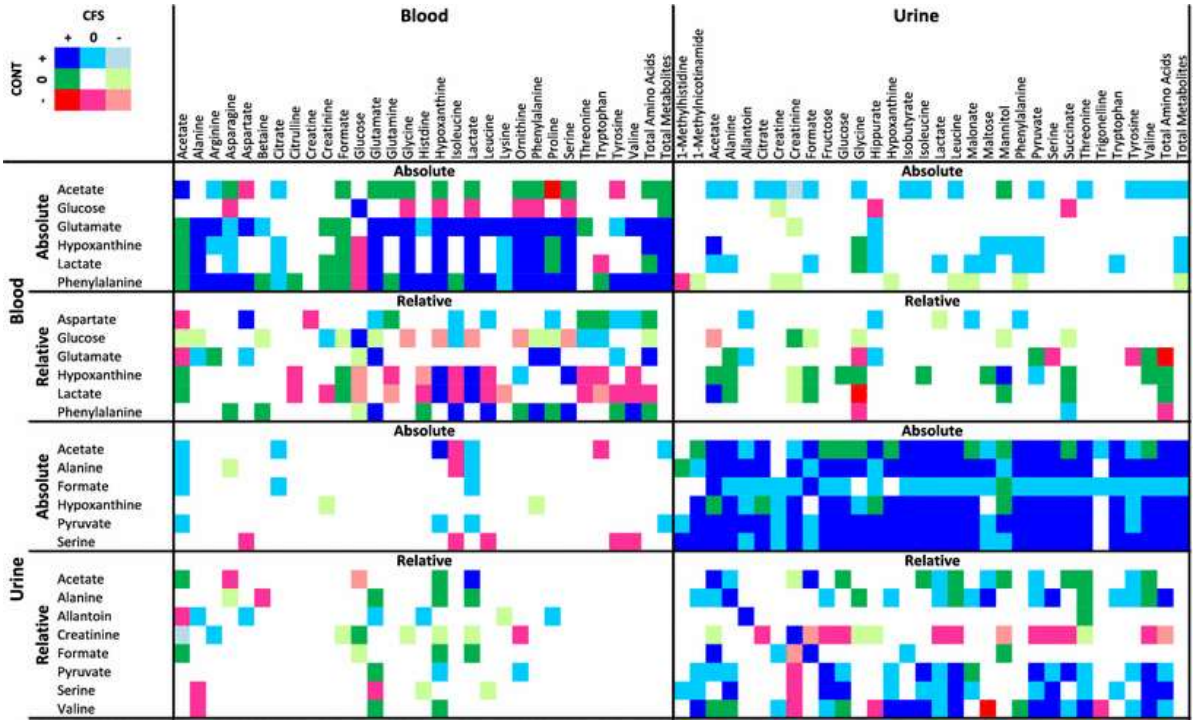
DEPAUL QUESTIONNAIRE AND BELL'S DISABILITY SCALE

Created by Leonard Jason's team at DePaul University, utilized in some ME/CFS studies diagnose and determine severity

METABOLOME:

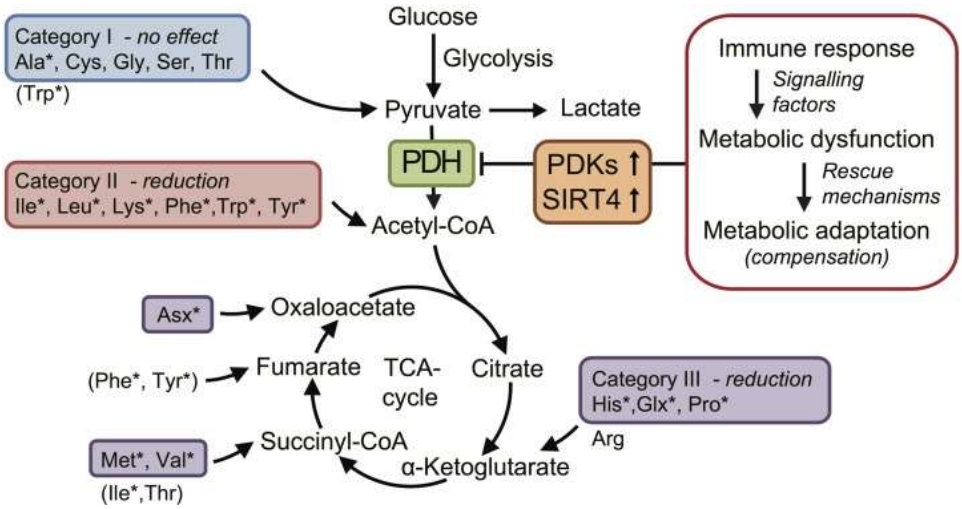
FLUGE AND MELLA 2016; ARMSTRONG ET AL, 2015

Research from Fluge and Mella in Norway, and Christopher Armstrong of Australia have identified errors in cellular energy metabolism in ME patients that differs from sedentary controls. They found reduced glycolysis, high blood glucose, and metabolites that demonstrate an uptick in mitochondrial activity in response. Other energy-producing reactions' metabolites were elevated, which may indicate compensatory metabolic mechanisms in people with ME. Women's amino acid stores in particular appear to be used in place of glucose. Women's diet showed no difference in protein intake than in controls.



(Armstrong et al., 2015: *Metabolic profiling reveals anomalous energy metabolism and oxidative stress pathways in chronic fatigue syndrome patients*)

Further analysis by Fluge and Mella impicated PDH inhibitors as a mechanism for decreased glycolysis.



(Fluge and Mella, 2016: *Metabolic profiling indicates impaired pyruvate dehydrogenase function in myalgic encephalopathy/chronic fatigue syndrome*)

Table 1. Serum levels of amino acids catabolized to pyruvate (category I), and to acetyl-CoA (category II), in nonfasting ME/CFS patients and healthy controls by sex

	All patients and controls				Women				Men			
	ME[A]	HC[B]			ME[A]	HC[B]			ME[A]	HC[B]		
	n = 153	*n* = 102	*P* value[C]	Effect size[D]	*n* = 124	*n* = 67	*P* value[C]	Effect size[D]	*n* = 29	*n* = 35	*P* value[C]	Effect size[D]
Category I (to Pyr) (μM, mean [SD])												
Gly	290.7 (79.8)	273.3 (76.3)	0.082	0.22	295.4 (85.6)	285.5 (83.5)	0.44		270.5 (43.3)	249.9 (54.1)	0.096	0.42
Ser	143.2 (28.5)	149.1 (27.7)	0.106		143.7 (29.0)	155.4 (30.3)	0.010	0.39	141.4 (26.6)	136.9 (16.3)	0.42	
Cys	259.0 (26.0)	258.9 (26.9)	0.98		257.8 (25.5)	257.8 (29.2)	0.99		264.0 (28.1)	261.0 (22.1)	0.65	
Thr	135.9 (32.7)	143.2 (34.4)	0.090	0.22	134.5 (33.8)	149.2 (38.8)	0.010	0.40	141.7 (26.8)	131.8 (19.8)	0.11	
Category II (to ac-CoA) (μM, mean [SD])												
Lys	179.8 (37.7)	196.8 (38.0)	0.001	0.45	175.5 (36.1)	196.6 (42.5)	0.001	0.54	197.9 (39.5)	197.4 (28.1)	0.95	
Leu	123.5 (31.6)	143.7 (36.0)	<0.001	0.60	118.0 (28.2)	139.6 (40.9)	<0.001	0.61	147.3 (34.6)	151.6 (22.6)	0.58	
Phe	68.2 (13.1)	76.6 (11.8)	<0.001	0.67	67.5 (12.5)	77.0 (12.7)	<0.001	0.75	71.4 (15.1)	75.8 (10.0)	0.19	
Tyr	63.1 (15.9)	73.0 (19.5)	<0.001	0.56	62.1 (15.8)	72.3 (21.6)	0.001	0.62	67.3 (16.4)	74.1 (14.8)	0.086	0.44
Ile	70.3 (20.0)	80.7 (23.4)	<0.001	0.48	67.0 (17.3)	77.9 (26.3)	0.003	0.49	84.4 (24.8)	86.0 (15.4)	0.76	
Trp[E]	73.4 (14.6)	77.8 (12.0)	0.009	0.28	72.0 (14.4)	76.7 (12.7)	0.022	0.35	79.3 (14.2)	79.9 (10.3)	0.85	
Ala[F] (category I)	423.5 (93.5)	447.9 (81.0)	0.027	0.28	420.3 (91.0)	449.9 (87.2)	0.029	0.33	437.1 (104.1)	444.1 (68.7)	0.76	

[A]ME, ME/CFS patients, nonfasting. [B]HC, healthy controls, nonfasting. [C]*P* values from independent *t* tests (equal variances not assumed). [D]Effect sizes from Cohen's *d* test. [E]Trp may also be catabolized to Pyr through Ala. [F]Ala was excluded from category I in this analysis, since it is involved in the glucose-Ala cycle transporting amino groups from peripheral tissues to liver via blood. This cycle exerts major influence on the serum concentration of Ala, masking potential effects due to Ala oxidation. Pyr, pyruvate; ac-CoA, acetyl-CoA.

(Fluge and Mella, 2016: *Metabolic profiling indicates impaired pyruvate dehydrogenase function in myalgic encephalopathy/chronic fatigue syndrome*)

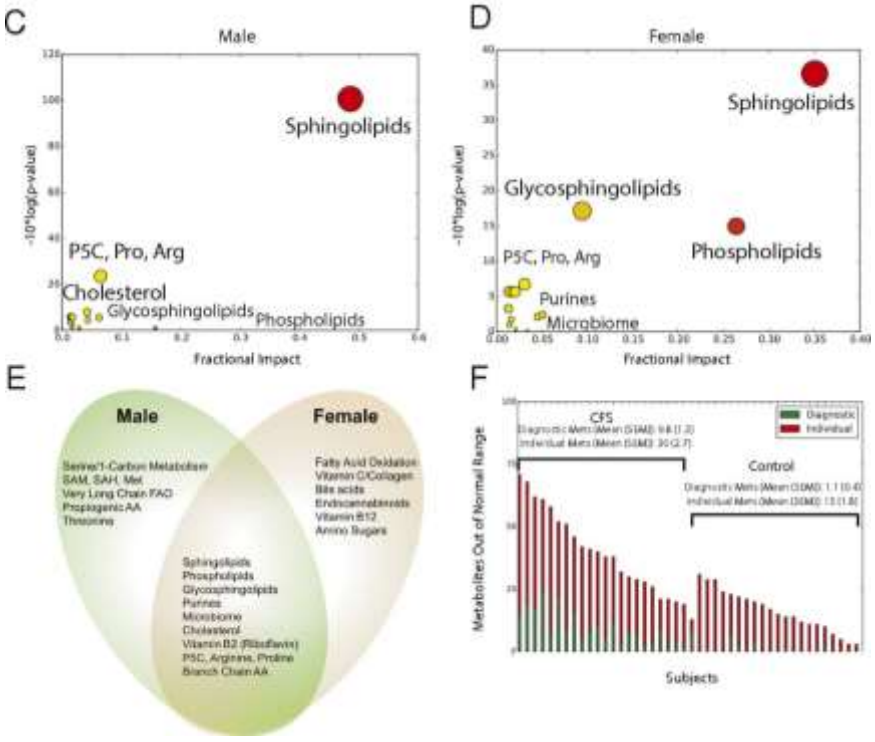
Finally, bathing culture-grown cells in ME patients' serum caused them to exhibit the same metabolic abnormalities as patients' cells.

NAVIAUX ET AL, 2016

Naviaux found significant decreases in metabolites that led to an overall hypothesis of hypometabolism in ME/CFS patients. Sphingolipid, phospholipid, purine, cholesterol, microbiome, pyrroline-5-carboxylate, riboflavin, branch chain amino acid, peroxisomal, and mitochondrial metabolism were found to be dysregulated. He also found that some of the alterations in plasma metabolites were gender-specific:

	Women	*Men*
1	Sphingolipids	Sphingolipids
2	Phospholipids	Phospholipids
3	Glycosphingolipids	PSC, Arg, Ornithine, Pro
4	Purines	Glycosphingolipids
5	Microbiome metabolism	Cholesterol, non-gonoidal steroids
6	Fatty acid oxidation / synthesis	Branched chain amino acids
7	PSC, Arg, Ornithine, Pro	Purines
8	Cholesterol, non-gonoidal steroids	Microbiome metabolism
9	Collagen/hydroxyproline metabolism	Riboflavin
10	Riboflavin	Serine, 1-carbon metabolism
11	Bile salt metabolism	SAM, SAH, methionine, glutathione
12	Endocannabinoids	Very long chain fatty acid oxidation
13	Branched chain amino acids	Propiogenic amino acids
14	Vitamin B12 metabolism	Threonine metabolism
15	Amino-sugar, galactose, and nonglucose	

(Seltzer, 2016 – *Naviaux's metabolism paper is about as big as you think*)



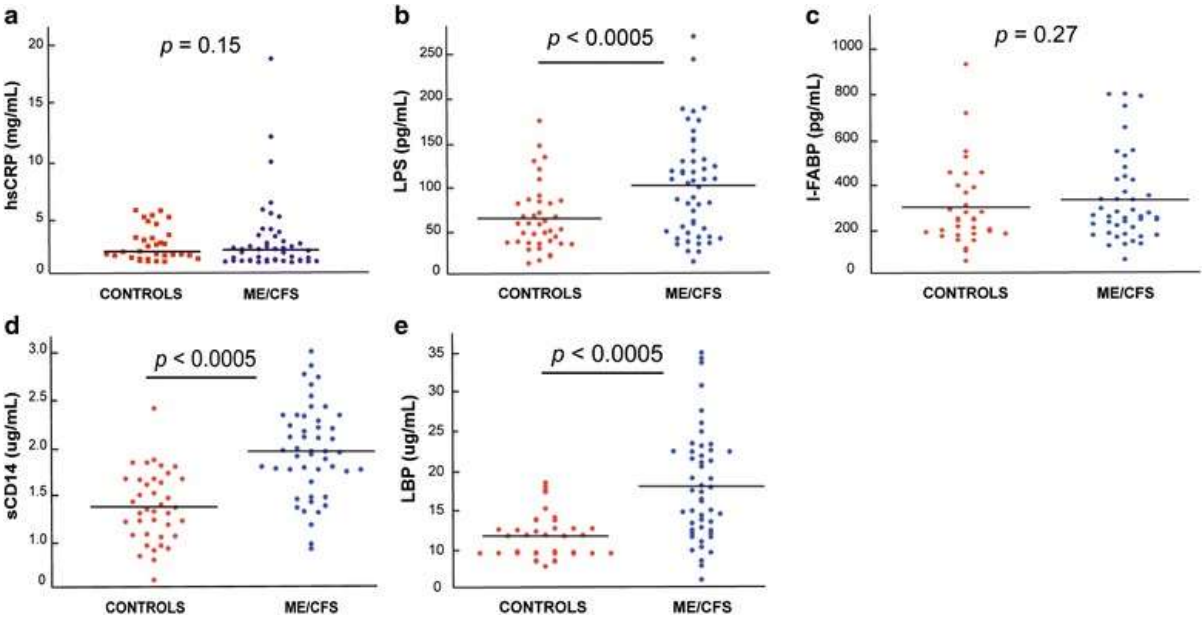
(Naviaux et al., 2016 – *Metabolic features of chronic fatigue syndrome*)

Naviaux's group also discovered that they could identify patients 19 times of 20 using a mix of 8 metabolites in women and 13 in men. However, the sample size means that this finding needs to be repeated.

MICROBIOME:

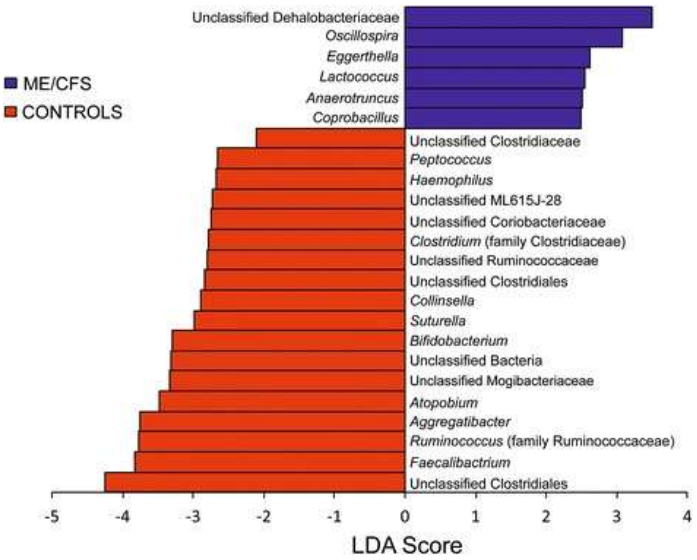
GILOTEAUX ET AL., 2016

Maureen Hanson of Cornell's team (Giloteaux, 2016) as well as researchers from the University of Melbourne (citation) have confirmed previous results showing that ME patients have gut bacteria that is not just generally different from controls, but with specific phyla elevated (*Firmicutes* and *Bacterioides*). Using a machine-learning approach, the Melbourne team was able to identify the right patient utilizing a sample of their gut bacteria over 80% of the time.



(Giloteaux et al., 2016 – *Reduced diversity and altered composition of the gut microbiome in individuals with myalgic encephalomyelitis/chronic fatigue syndrome*.

Signs of infection and bacterial translocation in ME/CFS patients, including elevated LPS, LBP, and sCD14)

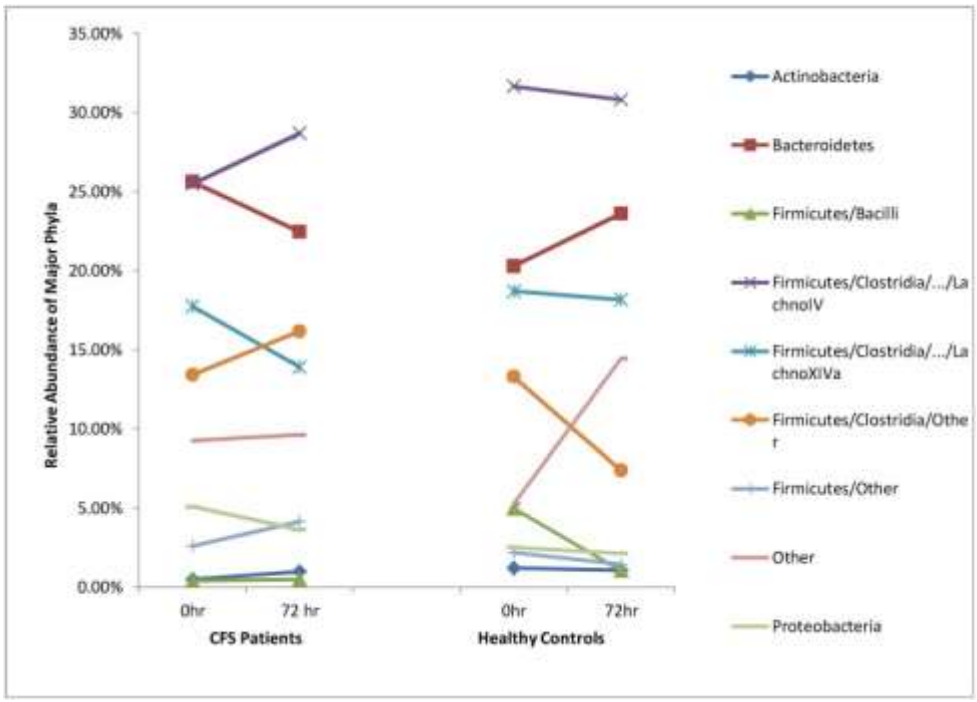


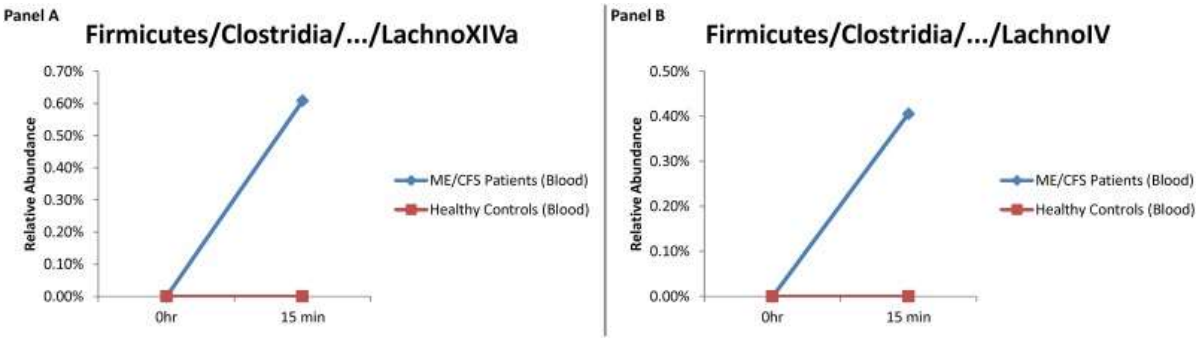
(Giloteaux et al., 2016 : *Reduced diversity and altered composition of the gut microbiome in individuals with myalgic encephalomyelitis/ chronic fatigue syndrome* -- Histogram of the LDA scores computed for genera differentially abundant between ME/CFS and healthy individuals. ME/CFS-enriched genera are indicated with a positive LDA score, and genera enriched in healthy individuals have a negative score.)

SHUKLA AT AL., 2015: SEPSIS AS A FEATURE OF PEM

Post-exertionally, Shukla et al. (2015) found that both blood and stool sample microbiota differed significantly in ME/CFS patients in the abundance of "several major bacterial phyla", especially *Bacilli* in blood 48 hours post-exercise and *Clostridium XIVa* and *IV* (Firmicutes) in blood samples collected 15 minutes after exercise. Following exercise challenge,

> "there was an increase in relative abundance of 6 of the major 9 bacterial phyla/genera in ME/CFS patients from baseline to 72 hours post-exercise compared to only 2 of the 9 phyla/genera in controls (p=0.005). There was also a significant difference in clearance of specific bacterial phyla from blood following exercise... in ME/CFS patients versus... controls" (Shukla et al., 2015).





(Shukla et al. 2015 -- *Changes in Gut and Plasma Microbiome following Exercise Challenge in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)*)

Other studies have verified dysregulation in the intestinal microbiota in patients, using all modern classifications of ME/CFS (CCC, Fukuda, and Ramsay). Moreover, these findings were consistent with those in the previous study, featuring a significant dysregulation in the Firmicutes phylum in Norwegian ME patients over controls, including a fifty-fold decrease in *Holdemania*, a 20-fold increase in *Lactonifactor*, and Bacteriodes genera *Alistipes* (Frémont, Coomans, Massart, & De Meirlier, 2013).

NAVANEETHARAJA ET AL, 2016

This is a relatively complete review of microbiome studies in ME/CFS as of 2016.

EXERCISE STUDIES

Numerous studies have found paradoxical reactions to exercise in ME, including reduced blood flow to the brain and heart (Neary et al., 2008; Peterson et al., 1994), reduced oxygen uptake in hemoglobin (Miller et al., 2015) and reduced VO2 on second-day exercise testing (Jones et al., 2012; Keller, Pryor, & Giloteaux, 2014) not caused by a general lack of physical activity (Vermeulen, & Vermeulen van Eck, 2014). See Shukla et al. (2015), above, a microbiome study performed post-exercise.

Note that *in vivo* exercise studies are self-selecting for minor or minor-moderate-presenting patients.

LIGHT ET AL., 2009: GENE EXPRESSION POST-EXERCISE

Light's group found that the mRNA expression of certain genes was upregulated in Fukuda CFS patients post-exercise, as were several cytokines. The difference was dramatic in comparison to that of healthy controls:

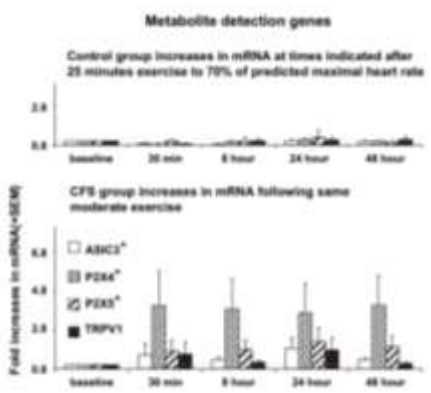


Figure 2. Amount of mRNA for ASIC3, P2X4, P2X5, and TRPV1 expressed as fold increases relative to baseline levels at each of the times indicated before (baseline) and after the end of 25 minutes of moderate exercise. *$P < .05$ compared with control subjects for the area under the curve (AUC) of mRNA across all time points after exercise. Faint dotted line indicates the baseline levels.

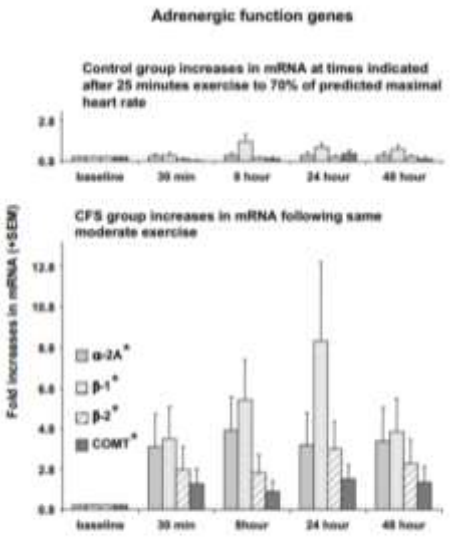


Figure 3. Amount of mRNA for α-2A, β-1, β-2 adrenergic receptors and catechol-o-methyl-transferase (COMT) relative to baseline levels. *$P < .05$ compared with control subjects for the area under the curve (AUC) of mRNA across all time points after exercise. Faint dotted line indicates the baseline levels.

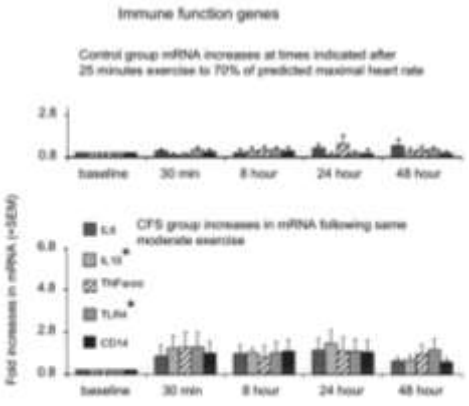


Figure 4. Amount of mRNA for IL6, TNF-α, IL10, TLR4, and CD14 relative to baseline levels. *$P < .05$ compared with control subjects for the area under the curve (AUC) of mRNA across all time points after exercise. Faint dotted line indicates the baseline levels.

Light et al., 2009 -- *Moderate Exercise Increases Expression for Sensory, Adrenergic, and Immune Genes in Chronic Fatigue Syndrome Patients But Not in Normal Subjects*

- The ASIC3 gene is acid-sensing, and is expressed primarily in the nervous system.
- P2X4 and P2X5 are purinergic receptors that help regulate cardiac function, ATP-mediated cell death, synaptic strengthening, and activate the inflammasome. They require ATP input.
- TRPV1 receptors are responsible in part for temperature maintenance and perception of pain and, like ASCI3, are activated under acidic conditions
- Note that alpha and beta adrenergic response is also significantly elevated, implicating an SNS response to exercise
- CD14, IL-6, IL-10, TNF-α, and TLR4 mRNA expression was all elevated compared to controls.

SNELL ET AL., 2013, KELLER ET AL., 2014, VERMEULEN & VERMEULEN, 2014: SECOND-DAY CPET AND VO_2

Patients find that they often do not experience symptoms during exercise, but after; and some patients only experience symptoms 8, 24, or 48 hours later.

Snell et al. (2013) found that, while a single CPET showed no appreciable differences between 51 female CFS patients and ten age-and-gender-matched controls, a second test performed 24 hours later showed significant abnormalities in VO_2 peak and workload.

In Keller's study (2014), they measured VO_2, heart rate, minute ventilation, workload, and respiratory exchange ratio (RER) at both maximal and ventilatory threshold (VT) intensities in 22 individuals with Fukuda CFS.

Canonical Correlation Coefficients, Standardized Function Coefficients, F Values, and *P* Values for Test 2[a]

Variable	Canonical Correlation Coefficient With Discriminant Function	Standardized Function Coefficient	F[b]	*P*
$\dot{V}O_2$peak, mL/kg/min	.308	−.308	5.23	.026
V_{TO_2}, mL/kg/min	.254	.375	7.78	.007[c]
WLpeak, W	.559	.563	17.54	<.001[d]
VTWL, W	.781	.877	42.57	<.001[d]

[a] $\dot{V}O_2$peak=volume of oxygen consumed at peak exertion, V_{TO_2}=volume of oxygen consumed at ventilatory threshold, WLpeak=workload at peak exertion, VTWL=workload at ventilatory threshold.
[b] *df*=1,59.
[c] Statistically significant at *P*<.01.
[d] Statistically significant at *P*<.001.

(Snell et al., 2013, *Discriminative Validity of Metabolic and Workload Measurements for Identifying People With Chronic Fatigue Syndrome*).

Table 2 Physiological and work variables for Tests 1 and 2 at peak and ventilatory threshold (VT) intensities, N = 22 (mean ± SD)

Peak exercise	Test 1	Test 2	%diff*	P
VO_2peak (ml·kg^{-1}·min^{-1})	21.9 (4.75)	18.6 (4.06)	−13.8%	.000*
%predVO_2peak†	77.1% (20.22)	65.2% (15.74)	—	.000*
HRpeak (bpm)	159.4 (21.10)	150.0 (23.05)	−5.9%	.001*
%predHRpeak†	91.0% (10.75)	85.2% (11.93)	—	.002*
Work@peak (W)	122.7 (28.77)	105.7 (33.57)	−12.5%	.012‡
Ve peak (L·min^{-1})	54.5 (17.56)	44.6 (12.63)	−14.7%	.003*
VCO_2peak (L·min^{-1})	1.91 (.477)	1.58 (.464)	−16.1%	.000*
O_2 pulse@peak (ml·beat^{-1})	10.48 (3.068)	9.46 (2.697)	−8.8%	.003*
%predVO_2peak†	77.1% (20.22)	65.2% (15.74)	—	.000*
RERpeak	1.17 (0.079)	1.14 (0.081)	−1.9%	.157
Ventilatory threshold				
VO_2@VT (ml·kg^{-1}·min^{-1})	12.2 (3.68)	9.9 (2.89)	−15.8%	.003*
HR@VT (bpm)	113.5 (21.78)	107.9 (20.61)	−4.9%	.086
Work@VT (W)	51.4 (24.97)	41.4 (28.8)	−21.3%	.030‡
Ve@VT (L·min^{-1})	21.2 (6.07)	18.8 (4.86)	−7.4%	.035‡
VCO_2@VT (L·min^{-1})	0.86 (.345)	0.72 (.265)	−11.3%	.014‡
O_2 pulse@VT (ml·beat^{-1})	8.15 (2.603)	7.00 (2.323)	−12.6%	.003*

*A negative %diff value indicates a decrease from Test 1 to Test 2.
†Percent of age-predicted maximum heart rate achieved.
‡% predicted VO_2peak for sedentary subjects from Bruce et al. [23].
§Statistically significant difference between Test 1 and Test 2 at $P < 0.05$.
*Statistically significant difference between Test 1 and Test 2 at $P < 0.01$.

(Keller et al., 2014, *Inability of myalgic encephalomyelitis/chronic fatigue syndrome patients to reproduce VO_2 peak indicates functional impairment*)

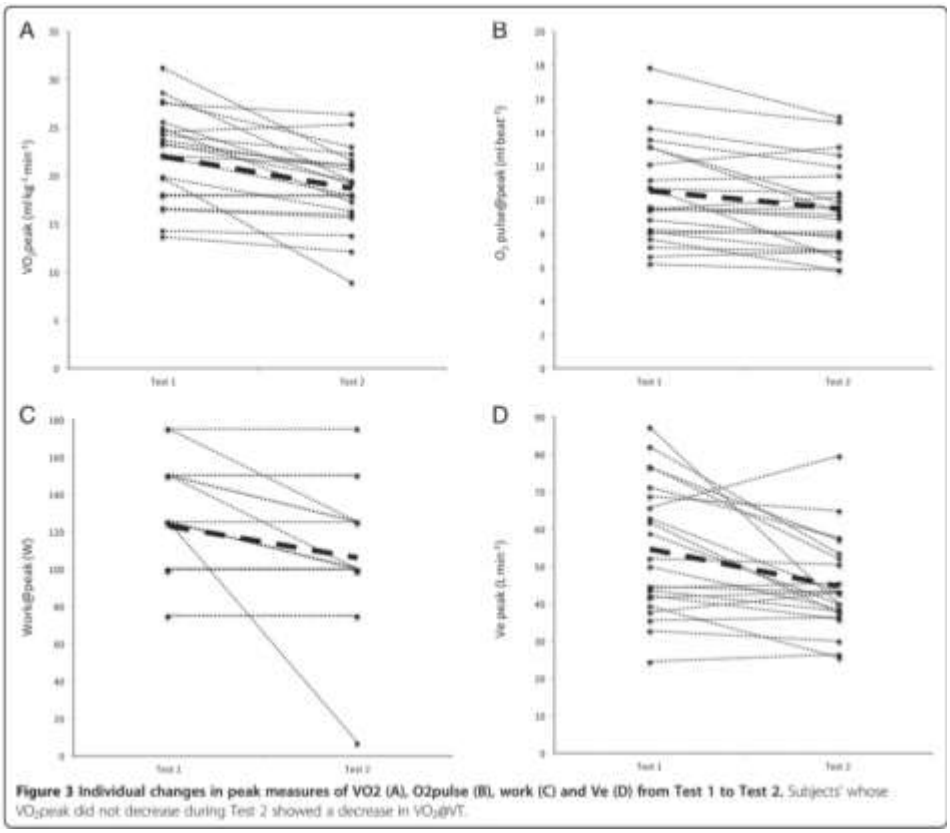


Figure 3 Individual changes in peak measures of VO2 (A), O2pulse (B), work (C) and Ve (D) from Test 1 to Test 2. Subjects' whose VO_2peak did not decrease during Test 2 showed a decrease in VO_2@VT.

(Keller et al., 2014 -- *Inability of myalgic encephalomyelitis/chronic fatigue syndrome patients to reproduce VO_2 peak indicates functional impairment*)

Finally, Vermeulen et al. (2014) compared sedentary controls (active <1 hr / week) to ME/CFS patients to ensure that the differences between patients and controls was not merely a matter of low activity level. Vermeulen also included patients with the symptom of fatigue but who did not meet Fukuda (1994) criteria.

Note that the patients who were being utilized as sedentary controls were those who had visited a cardiovascular clinic, but were not on medication known to affect pulmonary, cardiovascular, immunologic system or cellular respiration. These were unlikely to be truly healthy individuals.

Despite this, O_2 extraction at peak was found to be less than half of that of these 'healthy' controls.

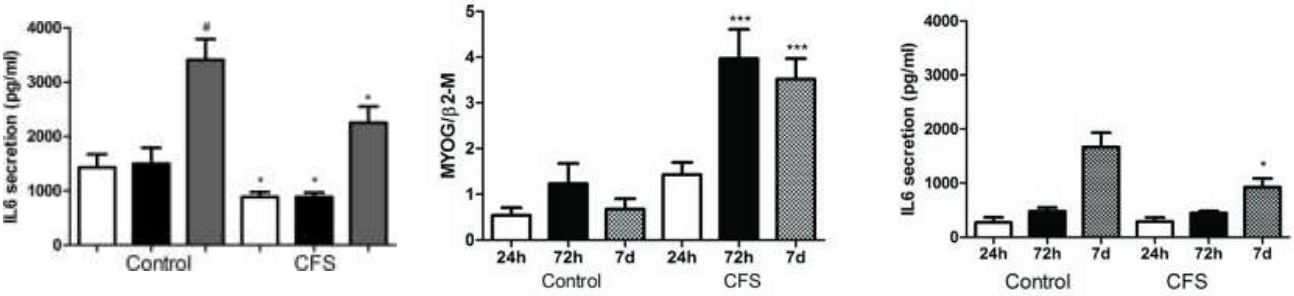
Results were analyzed by gender:

Female					
		CFS	**CFI**	**Healthy**	**ANOVA**
		n=178	**n=172**	**n=11**	***P***
Age	(years)	37.3 ± 12.1	37.9 ± 12.3	42.2 ± 14.8	0.421
Weight	(kg)	69.5 ± 15.0	67.5 ± 13.1	68.6 ± 13.2	0.412
BSA	(m^2)	1.81 ± 0.20	1.78 ± 0.18	1.79 ± 0.17	0.497
Haemoglobin	(mmol/l)	8.45 ± 0.55	8.46 ± 0.51		0.846
Rest					
HR	(beats/min)	96.1 ± 14.9	93.5 ± 16.8	87.7 ± 11.1	0.113
VO_2	(ml/min/kg)	5.46 ± 0.99	5.41 ± 0.93	5.18 ± 0.98	0.635
O_2 pulse	(ml/beat)	4.00 ± 0.85	3.95 ±0.82	4.09 ± 0.90	0.784
RER		0.86 ± 0.07	0.86 ± 0.07	0.81 ± 0.03	0.073
VE/VCO_2		34.2 ± 4.3	34.3 ± 4.1	34.7 ± 3.0	0.924
SVI	(ml/m^2)	42.8 ±7.0	42.3 ±7.6	43.4 ± 10.4	0.797
Cardiac index	($L/min/m^2$)	4.10 ± .081	3.97 ± 0.92	3.80 ± 0.95	0.294
O_2 extraction	(ml/100ml)	6.48 ± 1.65	6.58 ± 1.72	6.96 ± 1.63	0.620
Anaerobic threshold					
HR	(beats/min)	112.0 ± 15.6	112.3 ± 15.2	113.3 ± 8.7	0.955
VO_2	(ml/min/kg)	10.9 ± 2.6	11.6 ± 2.7	13.7 ± 3.6	0.001
O_2 pulse	(ml/beat)	6.75 ± 1.63	6.95 ± 1.67	8.33 ± 2.31	0.009
RER		0.84 ± 0.07	0.85 ± 0.08	0.81 ± 0.06	0.216
VE/VCO_2		29.7 ± 3.5	28.8 ± 3.5	27.6 ± 1.7	0.025
SVI	(ml/m^2)	45.7 ± 7.9	45.0 ± 8.2	48.2 ± 11.8	0.382
Cardiac index	($L/min/m^2$)	5.12 ± 1.10	5.11 ± 1.21	5.52 ± 1.64	0.534
O_2 extraction	(ml/100ml)	8.30 ± 2.08	8.77 ± 2.23	9.86 ± 2.37	0.019
Peak exercise					
HR	(beats/min)	158.4 ± 19.3	159.6 ± 18.6	164.1 ± 11.3	0.250
VO_2	(ml/min/kg)	20.3 ± 5.0	22.2 ± 5.3	27.4 ± 7.2	0.000
VO_2/pred.	%	80.6 ± 17.9	83.1 ± 18.0	105.4 ± 18.8	0.000
O_2 pulse	(ml/beat)	8.89 ± 2.17	9.26 ± 2.08	11.36 ± 2.89	0.001
RER		1.16 ± 0.10	1.18 ± 0.10	1.20 ± 0.11	0.094
VE/VCO_2		30.2 ± 3.7	29.7 ± 3.7	27.9 ± 2.4	0.103
SVI	(ml/m^2)	45.9 ±7.9	45.4 ± 8.3	47.6 ± 11.2	0.797
Cardiac index	($L/min/m^2$)	7.33 ± 1.77	7.39 ± 1.78	7.87 ± 1.96	0.618
O_2 extraction	(ml/100ml)	10.83 ± 2.80	11.62 ± 2.90	13.45 ± 2.72	0.001
Slope					
$\Delta Q/\Delta VO_2$	(L/L)	7.35 ± 2.40	6.80 ± 1.99	5.85 ± 1.23	0.012
Male					
		CFS	**CFI**	**Healthy**	**ANOVA**
		n=25	**n=51**	**n=7**	***P***
Age	(years)	41.6 ± 12.3	41.8 ± 9.9	49.4 ± 13.8	0.215
Weight	(kg)	88.9 ± 15.7	80.0 ± 12.8	94.3 ± 13.9	0.005
BSA	(m^2)	2.12 ± 0.21	2.02 ± 0.17	2.19 ± 0.16	0.016
Haemoglobin	(mmol/l)	9.34 ± 0.66	9.53 ± 0.56		0.263

(Vermeulen et al., 2014 -- *Decreased oxygen extraction during cardiopulmonary exercise test in patients with chronic fatigue syndrome*)

BROWN ET AL., 2015: MUSCULAR CELL FUNCTION

Julie Newton and her team discovered that cultured muscle cells of patients with ME had increased myogenin expression but decreased IL-6 secretion in comparison to controls and, when an electrical pulse was sent through the tissue to simulate exercise, muscle cells of ME patients demonstrated impaired AMPK activation and impaired uptake of glucose. Cells responded normally to insulin.



(Brown et al., 2015: *Abnormalities of AMPK Activation and Glucose Uptake in Cultured Skeletal Muscle Cells from Individuals with Chronic Fatigue Syndrome* – IL-6 secretion and myogenin expression in CFS vs healthy control cultured cells)

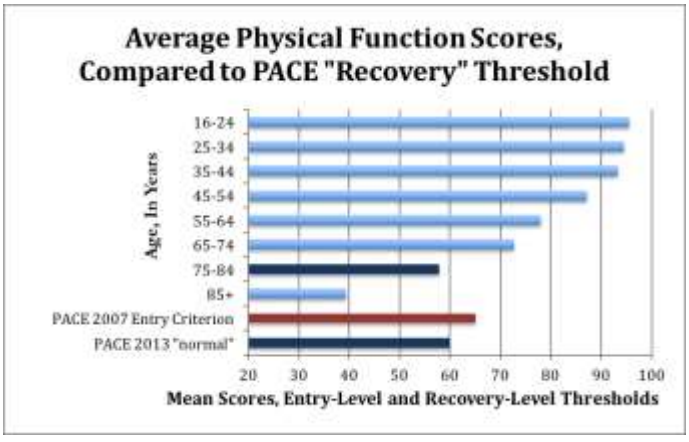
PACE TRIAL AND REFUTATIONS

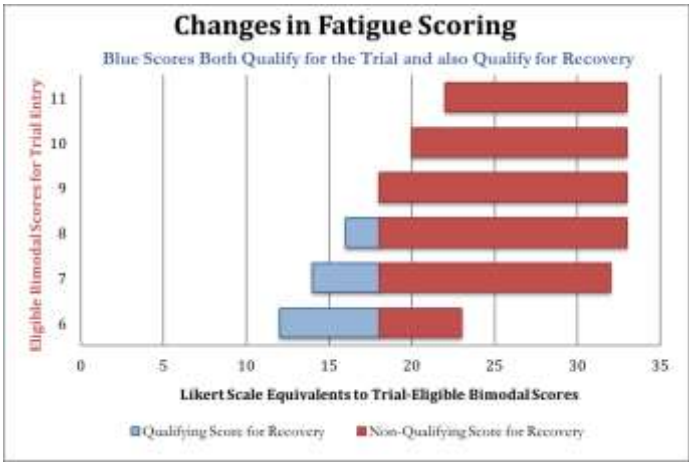
The PACE trial recommends exercise therapy and cognitive behavioral therapy for ME/CFS. PACE was met with skepticism by patients who observed that exercise, even gradually implemented, worsened their condition. This skepticism eventually led to widespread refutation, including a series of peer-reviewed rebuttals in the Journal for Health Psychology, several features on Retraction Watch, a letter signed by 40+ academics denouncing the trial (including Ron Davis), and a series of blistering articles in the press.

It was years before the poor quality of the 2011 PACE trial and its subsequent sister-trials came to public attention, however. As a result, PACE influenced years of patient care; and the biopsychosocial model is still the prevailing narrative in the UK today in part due to a conflict of interest: a researcher on the board of the UK's Science Media Centre was a principal investigator on many of these trials.

Here is a brief summary of some of the noted issues in the PACE trial:

- The Oxford Criteria, which solely requires fatigue of new origin lasting longer than 6 months in the absence of organic brain disease or severe mental illness, identified patients. A recent article demonstrated that the Oxford criteria could be used to identify ¼ men and 1/5 women as CFS patients in a 6,000+ -individual epidemiological survey performed as a matter of course by the US Census. The same study identified only 1.8% of women and 2.3% of men as having CFS as defined by Fukuda. CCC's prevalence is generally placed at 0.42% of the population (Jason et al., 1999).
- The SF-36 for physical functioning was used to determine whether patient exercise ability had improved.[1] The level for recovery was initially set in the 80s. Later, the recovery level was dropped to 60, even though entry for the study was at 65. This meant that 13% of patients had 'recovered' on at least some measures as of trial entry. These patients were not omitted from the authors' interpretation of their data.

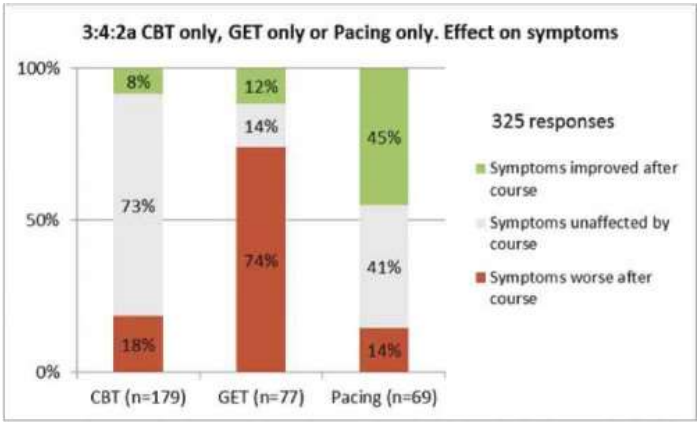




Goldin, 2017 – PACE: the research that sparked a patient rebellion and challenged medicine : Patient 'recovery' was set to the approximate physical function of an 80-year-old; a significant number of patients qualified to be included in the study who were already classified as 'recovered' on some measures.

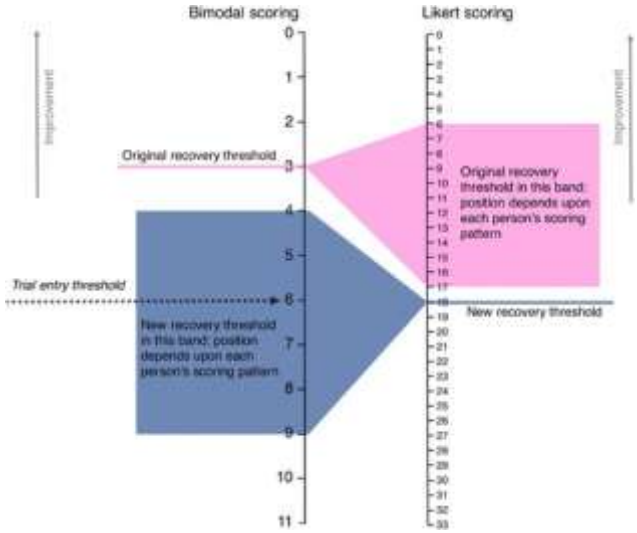
[1] The SF36PF has 10 items, each of which asks about patient ability to perform a task that should pose no difficulty to a healthy individual, such as 'walking up a flight of stairs' or 'washing / bathing'. If the task presents no difficulty, the patient should reply '10'. If the task presents difficulty, the patient should reply '5'. If the patient cannot complete the task, the answer should be '0'. An SF36PF for a healthy middle-aged individual should be 90-100.

- Actometer use was scrapped partway through the trial,[2] eliminating the most significant objective measure in the study.
- Promotional materials for GET (graded exercise therapy) and CBT (cognitive behavioral therapy) were disseminated to participants while the trial was underway. The newsletter implied that CBT and GET were known to be the therapies most likely to lead to recovery and included glowing testimonials from patients enrolled in the study still underway (and still recruiting). The materials also expressed skepticism regarding biomedical therapies and biomedical findings in ME/CFS.
- PACE trial practitioners employed 'directive' CBT to guide patients to eliminate their false illness beliefs (Burgess & Chalder, 2004). Patients were taught that their disease is due to false interpretations of natural bodily sensations; then, they were asked to respond to surveys gauging symptom-experience as the sole outcome measure. It stands to reason that a compliant patient would report improved symptoms in hopes of getting / feeling well, since they were taught that it was their perceptions of illness that were causing the illness itself. It has been argued that this interpretation of CBT has obviated its conventional use as a therapy for patients dealing with the grief and isolation of a chronic illness (Friedberg, 2016).
- Graded exercise therapy made a significant number of patients worse, which was not reported by the authors. An 1800-patient study from the ME Association reported the following incidence of harms in GET treatment, CBT treatment, and pacing strategies[3]:



(*Our CBT, GET and pacing report calls for major changes to therapies offered for ME/CFS*, 2015)

- Authors denied requests to release raw, anonymized data to other researchers on the grounds that the requests were vexatious, despite publication in an open-access journal and funding from institutions in which the promise of open-access is necessary to receive funding. A UK tribunal decision mandated the release of the raw data (McCook, 2016),[4] upon which reanalysis using the authors' original definitions of improvement found no statistical difference in improvement scores between control, CBT, and GET groups (Wilshire et al., 2017).



(Wilshire, Kindlon, Matthees, & McGrath, 2017 -- *Can patients with chronic fatigue syndrome really recover after graded exercise or cognitive behavioural therapy? A critical commentary and preliminary re-analysis of the PACE trial* : Chalder fatigue scores required for entry vs what is required for recovery)

[2] "…a test that required participants to wear an actometer around their ankle for a week was too great a burden [for them]," the authors said in a public statement.
[3] Pacing involves gearing activity around symptom-experience: more activity when feeling well, less activity when feeling ill.
[4] The offical tribunal decision and response itself is lengthy, but an interesting read.

- Authors initially reported 60% improvement. When they re-analyzed their own data, they arrived at a 20% improvement. However, perhaps most significantly, the same authors found no difference between activity levels on follow-up in their similar FINE trial (Wearden et al., 2010), and on a long-term follow-up with PACE participants themselves (Sharpe et al., 2015)[5]: even the subjective improvements that were reported dissipated within a few months.
- Although authors declared their connections to and funding from disability insurers in the paper itself, this conflict of interest was not disclosed to study participants as is required by law.

The Lancet has not yet retracted the study, but PLOS ONE has flagged it and issued an expression of concern.

There have been a series of counter-articles discussing the flaws of the PACE trial, notably David Tuller of Berkeley's series, Trial By Error, posed on Racaniello of Columbia's Virology Blog. The Journal of Health Psychology just released a series of solicited opinions on PACE, and the Journal of Health Psychology editor's preface is worth reading.

NEUROENDOCRINE

While there is a paucity of neurological research on ME/CFS, many symptoms are neurological, with particular emphasis on autonomic dysfunction. For example, OI (orthostatic intolerance) has been found in nearly all ME/CFS patients in some studies, with POTS having a prevalence of as many as 70% of ME/CFS patients (Okamoto et al., 2012).

White matter lesions on MRI are included in the Canadian Consensus Criteria's diagnostic algorithm; however, some studies have found no differences between ME/CFS patients and controls on MRI (Perrin et al., 2010).

MATHEW ET AL., 2008; 2010; 2012; 2017 : INCREASED VENTRICULAR LACTATE

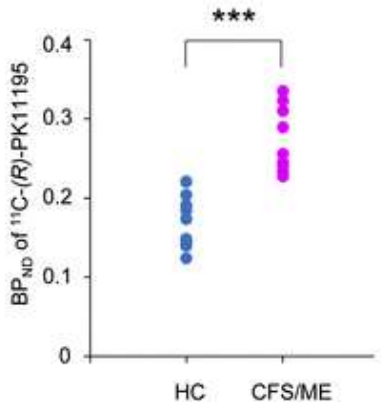
Several imaging studies (with a great deal of author overlap) show **increased ventricular cerebrospinal lactate** in ME/CFS patients as compared to various control groups:

- Versus generalized anxiety disorder (Mathew et al., 2008)
- Versus major depressive disorder (Murrough et al., 2010)
- Versus fibromyalgia (Natelson et al., 2017)
- Relationship of ventricular lactate to glutathione: evidence for oxidative stress (Shungu et al., 2012)

NAKATOMI ET AL, 2014 : NEUROINFLAMMATION

Nakatomi et al. (2014) also performed a small PET imaging study using 11C-(R)-PK11195, a protein used to visualize brain inflammation, since it is a marker for neuronal damage.

The BP_{ND} values of ^{11}C-(*R*)-PK11195 in the cingulate cortex, hippocampus, amygdala, thalamus, midbrain, and pons were between 1.5 and 3 times as high as that of healthy controls (Nakatomi et al., 2014).



(Right: Nakatomi et al., 2014 -- *Neuroinflammation in Patients with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis: An 11C-(R)-PK11195 PET Study* : BP_{ND} of ME/CFS patients versus healthy controls)

BARNDEN ET AL., 2016 : A FAILURE TO COMMUNICATE

Barnden et al. correlated heart rate and blood pressure to MRI results. Patients were diagnosed via the CCC, and monitoring of BP and HR was monitored using 24-hour Holter monitor.

[5] Their abstract reports the opposite to be the case. Reading the full text is necessary.

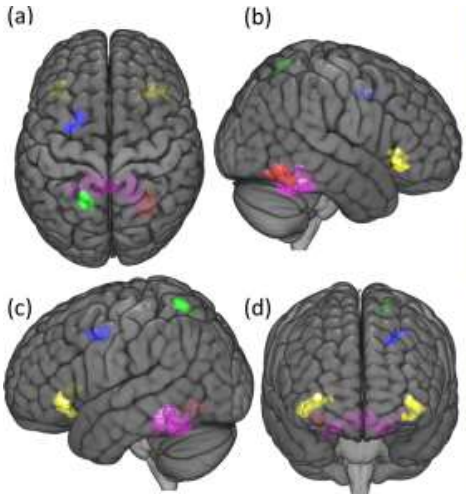
In order to measure ANS dysfunction, Barnden et al. compared autonomic function interaction-with-group regressions to find where regression slopes differed in ME/CFS from that of healthy controls. Barden et al. also measured MRI regressions in the ME/CFS and HC groups alone to detect additional locations with abnormal correlations in ME/CFS.

Abnormal regressions were found in the brainstem vasomotor center, the midbrain reticular formation, the hypothalamus, the limbic nuclei involved in stress responses and in prefrontal white matter. Group comparisons between ME/CFS and HC groups did not find MRI differences in these locations. The researchers posited that two-way communication between the CNS and peripheral sensors / effectors may be dysregulated, resulting in inverted or magnified responses.

Barnden also performed a study showing increased myelination in ME/CFS patients (2015). There are a very few preliminary studies on myelination in ME/CFS, but nothing that could be called definitive.

SHAN ET AL., 2016 AND PURI ET AL., 2012: BRAIN CHANGES ON MRI

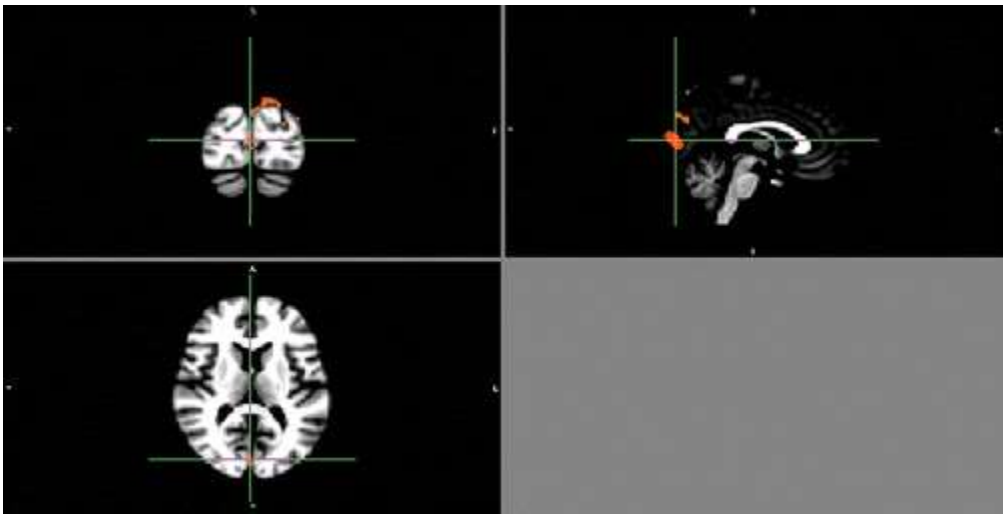
Shan et al. (2016) examined patients that met both Fukuda and CCC definitions, and found that white matter volume (MWV) had decreased in the IFOF and adjacent regions, and that the grey matter volume (GMV) had decreased in contralateral regions. These changes correlated to symptom scores on the Bell's Disability Scale, the Somatic Symptoms Scale and Neurological Symptoms Scale in patients.



Regressions	P_{FWE}	*k*	T	MNI
GM vol vs NeuroSS (+) (red)	0.006	599	6.76	27 -60 -15
GM vol vs NeuroSS (-) (green)	0.006	286	6.8	-18 -56 64
GM vol vs SomaticSS (+) (magenta)	< 0.001	3115	6.51	-2 -48 -22
WM vol vs SomaticSS (+) (blue)	0.03	371	4.94	-21 6 40
T2 vs NeuroSS (-) (yellow)	0.01	393	5.61	-38 32 -6
T2 vs NeuroSS (-) (yellow)	0.02	562	5.61	32 27 0

Shan et al., 2016 -- *Progressive brain changes in patients with chronic fatigue syndrome: A longitudinal MRI study*

Puri et al., (2012) identified Fukuda patients. Using high-resolution structural 3 T cerebral MRI scanning and interpreting the data using voxel-wise generalised linear modelling with corrections for multiple comparisons, they found significant differences in the MRI results of CFS patients versus that of healthy controls. The advantage of using these analysis methods is that they do not require operator decisions regarding what to scan or focus on; and they are therefore far less subject to bias regarding what areas of the brain 'should' show dysfunction.



Puri et al., 2012 -- *Regional grey and white matter volumetric changes in myalgic encephalomyelitis (chronic fatigue syndrome): a voxel-based morphometry 3 T MRI study*

Reduced grey matter volume was found in the occipital lobes (right and left occipital poles; left lateral occipital cortex, superior division; and left supracalcrine cortex), the right angular gyrus and the posterior division of the left

parahippocampal gyrus; and reduced white matter volume in the left occipital lobe.

The findings support subjective patient reports of impaired memory, visual processing, and discrepancies between intended actions and consequent movements.

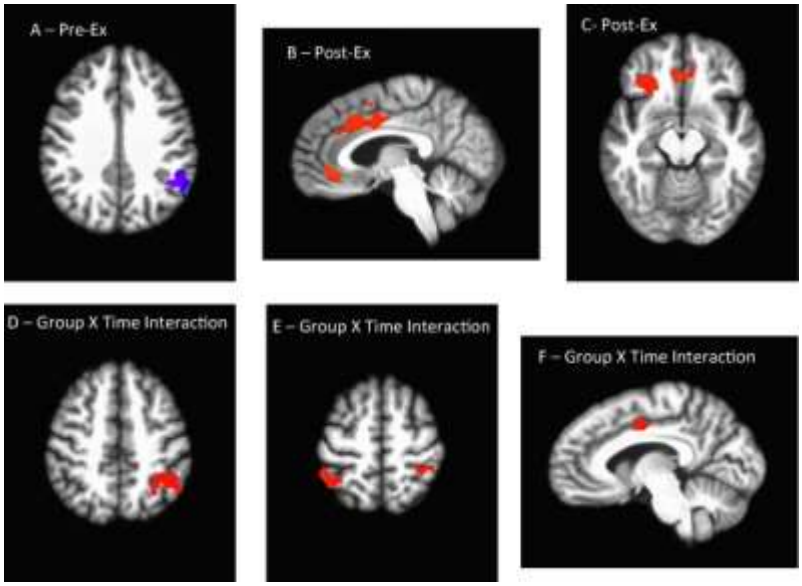
COOK ET AL., 2017 : MRI ABNORMALITIES POST-EXERTION

Cook et al. (2017) showed significant differences pre- and post-exertion between ME/CFS patients and healthy controls. Patients met both Fukuda (1994) and CCC criteria.

Patients were given four tasks:

	Fatiguing	**Non-fatiguing**
Physical	30-min sub-maximal exercise test	Finger-tapping
Cognitive	Paced auditory serial addition	Simple number recognition

Patients and healthy controls had similar physiological responses to the initial fatiguing exercise test, but they could not replicate the level of effort of healthy controls, and experienced greater pain and fatigue on exertion. Patient response to other tasks was then examined post-exercise.



(Above, Right)

(Cook et al., 2017 -- *Neural consequences of post-exertion malaise in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome* : Between-groups comparisons of brain responses pre- and post-exercise during the PASAT (Paced Auditory Serial Addition Task). A. Pre-exercise ME/CFS patients show less activity in the inferior and superior parietal cortices and the supramarginal gyrus. B & C. Post-exercise, ME/CFS patients show greater brain activity in the mid and anterior cingulate cortex and the right inferior frontal cortex. D, E & F Group X Time interaction for brain responses during the PASAT. ME/CFS patients show a greater change from to pre- to post-exercise compared to controls bilaterally for the inferior and superior parietal cortices and the cingulate cortex.

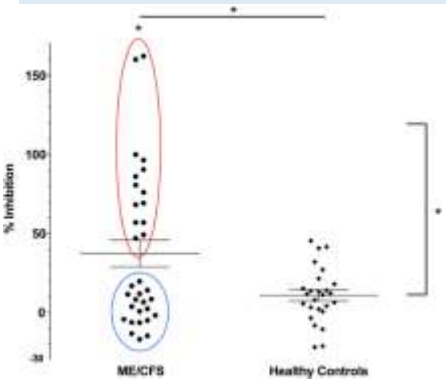
	PHYSICAL	**COGNITIVE**	
	NON-FATIGUING		FATIGUING
	Finger-tap	Number recognition	Paced auditory serial addition
Patients	No difference pre- and post-exercise	No difference pre- and post-exercise	Worse performance post-exertion
Healthy controls		Increased activity in posterior cingular gyrus pre-exercise only	Better performance post-exertion

Healthy controls performed better in strenuous cognitive tasks post-exercise. Patients performed significantly worse.

The paced auditory serial addition task showed significant differences between patients and healthy controls on MRI as well, with a greater activity post-exercise in the inferior and superior parietal and cingulate cortices.

It was also found that the degree of increased activity in patients correlated to symptoms.

DE VEGA ET AL., 2017 : GLUCOCORTICOID SENSITIVITY

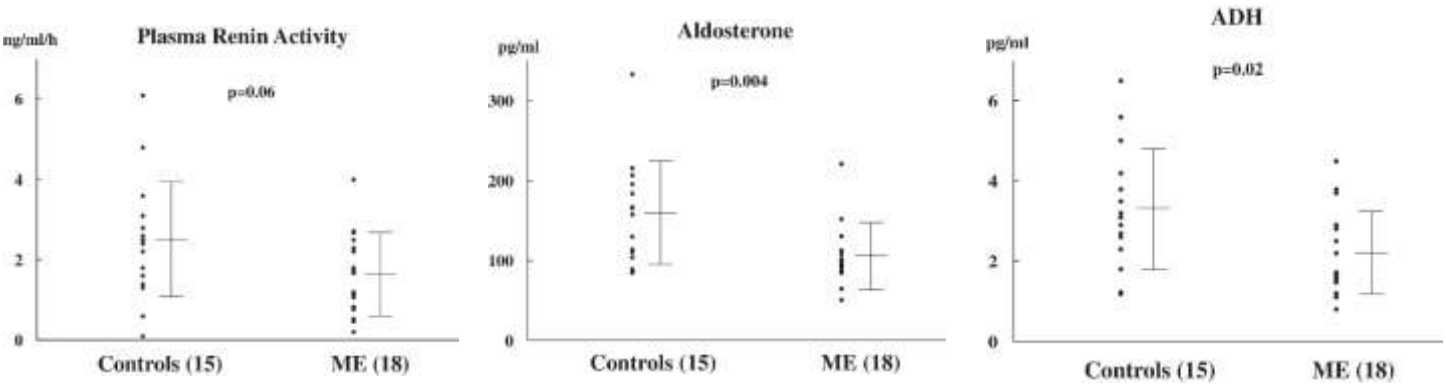


A recent endocrine study show increased sensitivity to glucocorticoids in a significant subset of ME/CFS patients via response of female patient PBMCs to dexamethasone (de Vega et al., 2017). While glucocorticoids are peripherally anti-inflammatory, they may cause inflammation in the CNS. Clinicians had in the past noted a high incidence of adverse events on the administration of glucocorticoids (often prescribed in fatigue-related chronic disease) (Twisk, 2015). The common finding of low ACTH in ME/CFS patients (Di Giorgio et al., 2003; Gaab et al., 2004) may in part be in order to maintain lower levels of cortisol to prevent neuroinflammation.

(de Vega et al., 2017 -- *Epigenetic modifications and glucocorticoid sensitivity in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)*): Percent inhibition of cortisol production in PBMCs exposed to dexamethasone suppression. The red circle represents the hypersensitive subset.

MIWA ET AL., 2017 : RENIN-ANGIOTENSIN SYSTEM

Low ADH and low aldosterone is a common finding in ME/CFS (Institute of Medicine, 2015). Miwa et al. (2017) is the latest group to find low renin activity, low anti-diuretic hormone, and low aldosterone in ME/CFS patients:



(Miwa et al., 2017: *Down-regulation of renin–aldosterone and antidiuretic hormone systems in patients with myalgic encephalomyelitis/chronic fatigue syndrome*)

CARDIAC AND ENDOTHELIAL DYSFUNCTION

Multiple studies have found cardiac and circulatory system abnormalities in ME patients.

NEWTON ET AL., 2016: REDUCED CARDIAC VOLUMES

Newton et al. performed cardiac magnetic resonance examinations in Fukuda CFS patients and matched case-by-case controls, as well as total blood volume, red cell volume, and plasma volume. The researchers found significantly reduced end-systolic and end-diastolic volumes with reduced end-diastolic wall masses ($p<0.0001$), which was positively correlated to TV, RCV, and PV, in CFS patients. Additionally, fatigue severity correlated to a low plasma volume. Because no relationships could be found between any of these markers and disease history, the study concluded that these abnormalities were unlikely to be the result of deconditioning (Newton et al., 2016). Miwa & Fujita (2011) also found reduced blood volume in CFS patients with OI.

Cardiac magnetic resonance parameters in CFS compared with matched controls

	N	Age (yrs)	Females	Heart rate / min	Systolic blood pressure	Diastolic blood pressure	Stroke volume	ED volume (mL)	ES phase (ms)	ES volume (mL)	ED wall mass (g)	ED wall+Pap mass (g)
Controls	47	47 (13)	34 (72%)	64 (12)	124 (25)	76 (10)	73 (16.2)	121 (30.7)	334 (44)	48 (18)	95 (28)	102 (28)
CFS	47	46 (12)	34 (72%)	67 (12)	109 (18)	70 (12)	57 (12.7)	91 (21.4)	320 (47)	34 (11)	70 (20)	77 (22)
P value		NS	NS	NS	**0.002**	**0.02**	**0.0002**	**<0.0001**	NS	**0.0006**	**<0.0001**	**<0.0001**

Values expressed as mean (SD) normalised for body surface area unless stated.

Values in bold typeface statistically significant.

CFS, chronic fatigue syndrome; ED, end diastolic; ES, end systolic; NS, not significant.

Newton et al., 2016 : *Reduced cardiac volumes in chronic fatigue syndrome associate with plasma volume but not length of disease: a cohort study*

Numerous studies have found altered heart rate and blood pressure variability in ME and CFS patients, particularly during sleep (Boneva et al., 2007; Hurum, Sulheim, Thaulow, & Wyller, 2010; Meeus et al., 2013; Togo, & Natelson, 2013).

Endothelial dysfunction may have a role in the pathophysiology of the cardiovascular abnormalities seen in ME patients. One study tested large-vessel endothelial dysfunction using flow mediated dilation (FMD) and microvascular endothelial dysfunction using post-occlusive reactive hyperemia, two measures associated with cardiovascular risk and outcome. Patients with ME showed reduced FMD in the brachial artery and reduced post-occlusive reactive hyperemia in the forearm skin microcirculation (Newton et al., 2012).

Though there is abundant evidence that something is irregular in the cardiovascular system of ME patients, these findings need to be validated with larger samples and differing patient populations.

IMMUNOLOGICAL

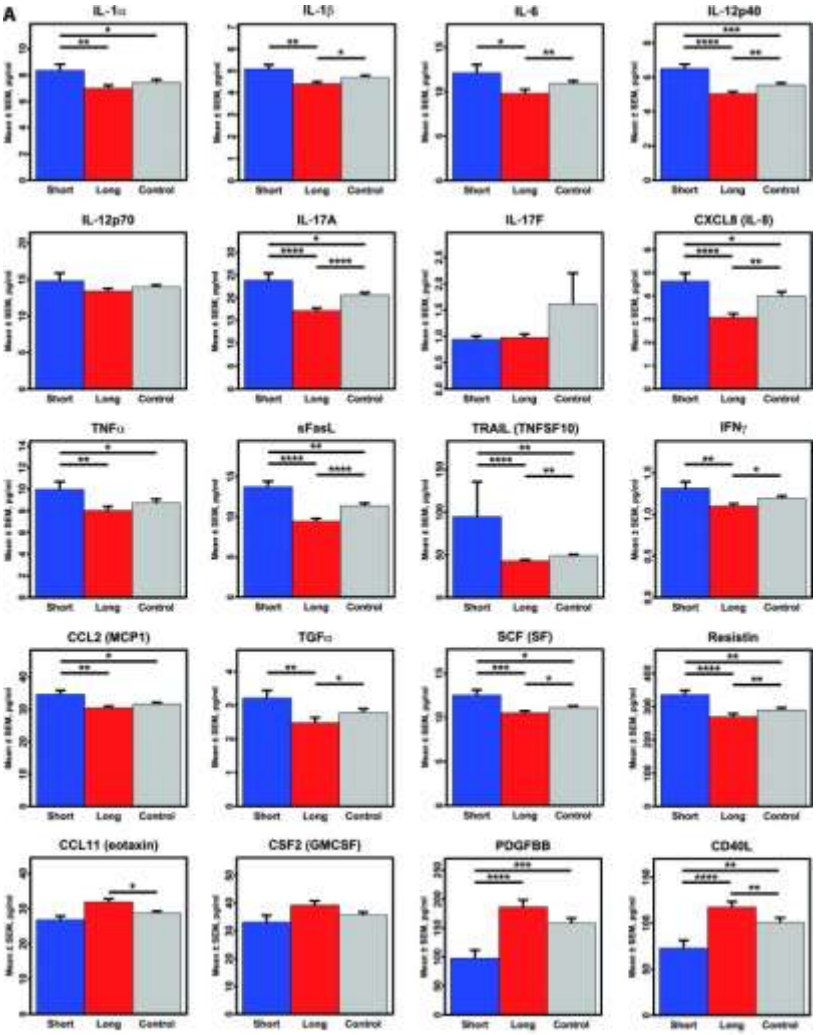
Numerous findings demonstrate that ME/CFS patients show dysregulated immune function.

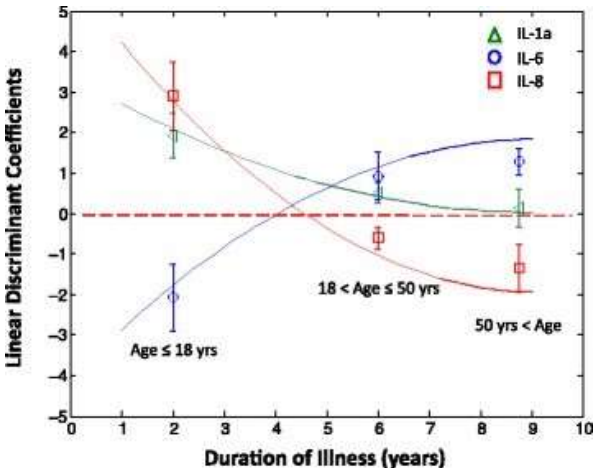
The search for a specific, causative pathogen has not been successful, although there is evidence that certain infectious organisms are more likely to result in the illness, including Epstein-Barr Syndrome and other herpes viruses, echovirus, and enterovirus (Institute of Medicine, 2015)[6]. ME/CFS may appear in epidemic outbreaks[7], implicating a vital role for an infectious agent or agents, coupled with a genetic susceptibility; in one study of those who contracted *Giardia*, for example, only 5% went on to develop ME/CFS (Naes, 2012).

Several authors have proposed that ME/CFS is a disease of chronic inflammation due to to mitochondrial dysfunction and oxidative/nitrosative stress (Morris & Maes, 2015, Pall, 2001).

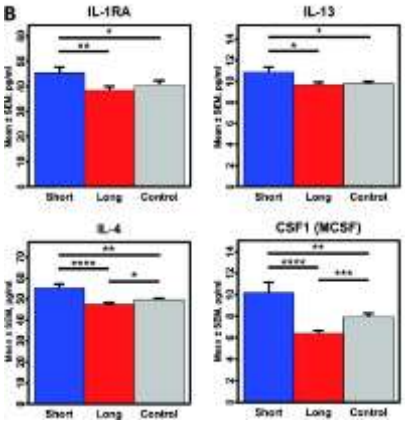
CYTOKINE STUDIES

Inflammatory cytokines that have been found to be elevated in patient serum include: IL-1, TNF-α, Il-4, -5, -6, -8, and -12, neopterin, and lysozyme.[8] Elevated IL-1, TNF-α, IL-6 and IL-8 are common findings in patient serum. Some researchers have discovered a general pattern of increased inflammation early in the disease and a more immunosuppressed picture after long-term illness (Lipkin & Hornig, 2015; Russell et al., 2016).





Above: Russell et al., 2016 -- *Illness progression in chronic fatigue syndrome: a shifting immune baseline* : different patterns of cytokine expression over disease progression



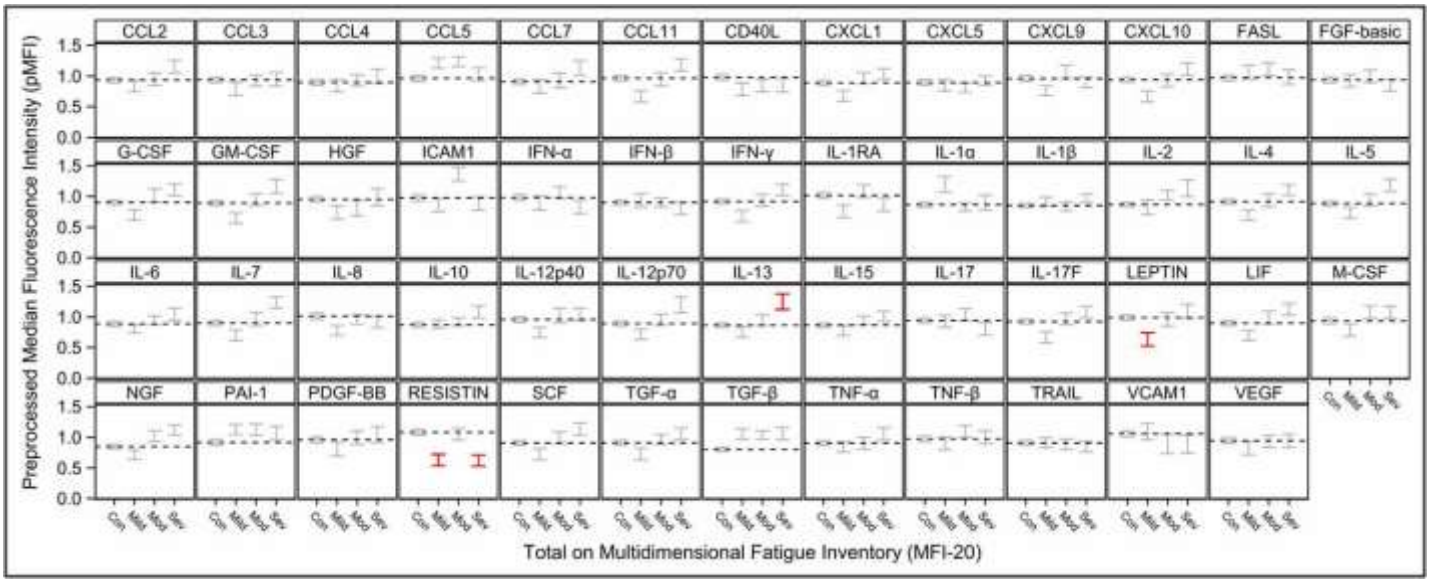
Lipkin & Hornig, 2015 -- *Distinct plasma immune signatures in ME/CFS are present early in the course of illness*

[6] You can find a patient-created list of enteroviral research with links here.

[7] You can find a list of outbreaks of myalgic encephalomyelitis 1934-1980 with attendant references here.

[8] See the following studies: (Broderick et al., 2010, Chao et al., 1991, Fletcher et al., 2009, Hardcastle et al., 2015, Maes et al., 2012 1, 2, Montoya et al., 2017, Russell et al., 2016)

A second set of researchers found that these cytokines fluctuated with severity rather than timecourse (Montoya et al., 2017).



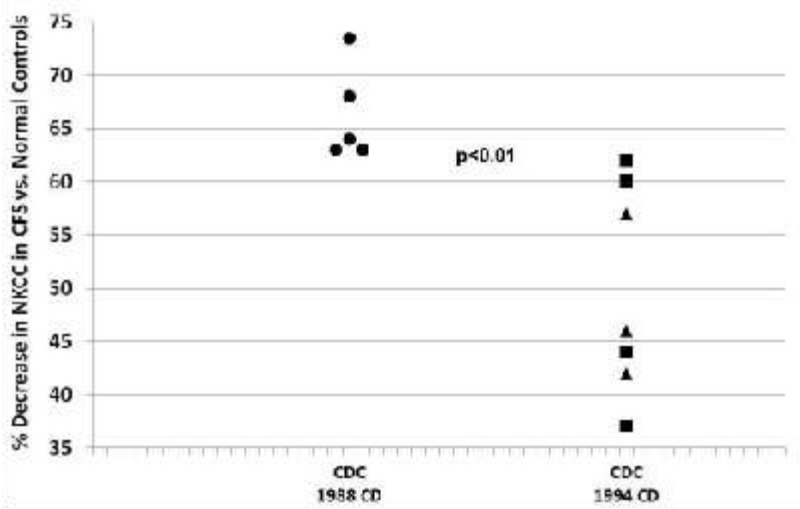
(Montoya et al., 2017 -- *Cytokine signature associated with disease severity in chronic fatigue syndrome patients*)

The difference may be due to the way severity has been gauged: Montoya et al. used the MFI (multi-dimentional fatigue inventory) to determine ME/CFS severity, but this is a measure of fatigue only. It may be more accurate to state that the severity of fatigue in ME/CFS patients is directly related to the level of many cytokines.

Cytokine findings are often inconsistent, perhaps due to patient population heterogeneity, the relapsing-remitting course of the illness, differences in measurement techniques, or the transient nature of the cytokines themselves, which (apart from IL-6) do not tend to travel a great distance from the cell in which they were produced.

NK FUNCTION STUDIES

A summary by Strayer et al. (2015) found that out of 17 studies in ME/CFS studying natural killer cell function, 15 had discovered lowered NK cell function in patients:



Strayer et al., 2015 -- *Low NK Cell Activity in Chronic Fatigue Syndrome (CFS) and Relationship to Symptom Severity*

The 1988 criteria is Ramsay's criteria, while the 1994 criteria refers to the far more relaxed Fukuda. However, even utilizing the Fukuda criteria to identify patients, NK cell function shows a significant decrease in comparison to that of healthy controls.

One of the most recent study is by Fletcher et al., 2010: *Biomarkers in Chronic Fatigue Syndrome: Evaluation of Natural Killer Cell Function and Dipeptidyl Peptidase IV/CD26*. Fletcher shows a significant difference between NK cell function in healthy controls and patients with ME/CFS.

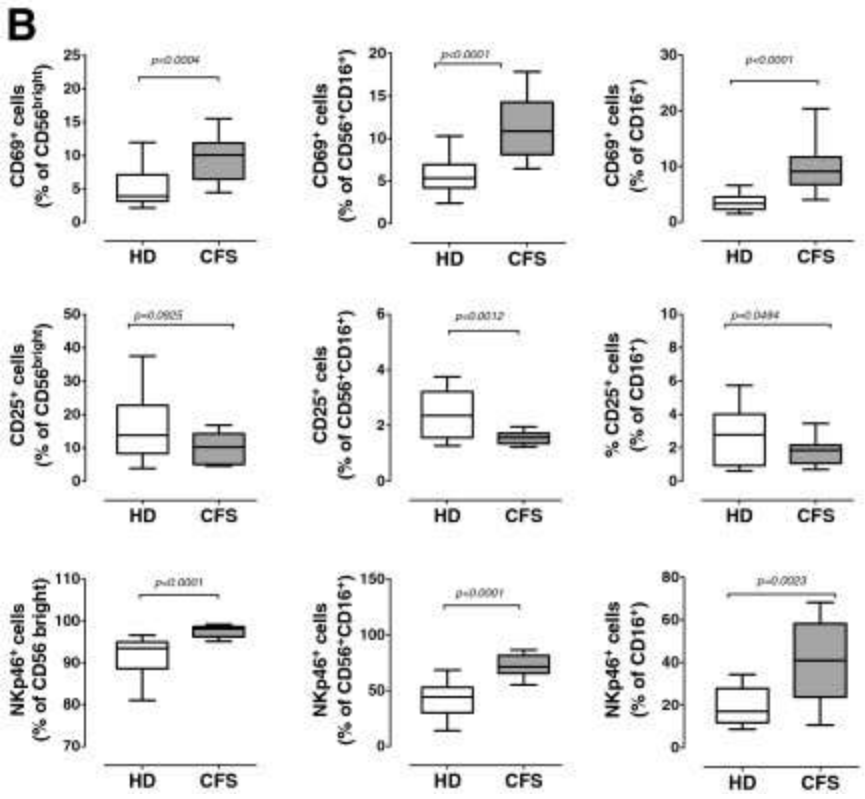
Natural killer cell cytotoxicity and dipeptidyl peptidase IV/CD26 in chronic fatigue syndrome cases[a] compared to controls[b].

VARIABLE	NUMBER OF CFS CASES	MEDIAN (25–75TH PERCENTILE)	NUMBER OF HEALTHY CONTROLS	MEDIAN (25–75TH PERCENTILE)	P
NKCC%	176	12 (8–21)	230	28 (20–37)	.000
% CD26+CD2+ Cells	75	61 (55–66)	100	52 (47–59)	.000
sCD26 in Serum (ng/ml)	73	489 (396–643)	122	671 (496–871)	.000
rMol CD26/CD2+ Cell	77	3625 (2844–4633)	102	4388 (3600–5388)	.001

[a]>80% female, average age 48;
[b]>80% female, average age 47.

(Fletcher et al., 2010 -- *Biomarkers in Chronic Fatigue Syndrome: Evaluation of Natural Killer Cell Function and Dipeptidyl Peptidase IV/CD26*)

A recent study (Curriu, 2013) showed unusual subsets of NK cells in ME/CFS patients, showing a high percentage of NKp46+ and CD69+ cells, and a relatively lower number of CD25+.



(Curriu, 2013 -- *Screening NK-, B- and T-cell phenotype and function in patients suffering from Chronic Fatigue Syndrome*: relative numbers of NK cell types)

The low numbers of CD3+CD56+ cells relative to total lymphocytes are interesting, as low levels have been linked to poor outcome / low resistance to HIV in HIV-infected patients (Jiang et al., 2014), and to autoimmune disease (Korek et al., 2002).

The same paper also analysed T and B cells; see the following section on B and T cell findings.

Both Huth et al. (2014) and Brenu et al. (2014) found increased degranulation in NK cells. Huth found decreased CD2 and CD8 (adhesion markers) in NK cells, and both Huth and Brenu found depleted Granzyme B activity with increased CD57 expression – a mature-cell surface marker in NK cells.

Although ≈ 9 / 10 papers on NK cell function have found an assocation between poor function and ME/CFS, there is one notably well-done paper that shows a lack of association (Theorell et al., 2017). It is worth mentioning, however, that the PBMCs in this study were suspended in fetal bovine serum and frozen, rather than stored in patient plasma.

B-CELLS, T-CELLS, AND RITUXIMAB

One of the most important recent studies showed that Rituximab, an anti-CD20 clonal antibody used in oncology, resulted in complete remission for some patients. Accidental discovery in a patient with cancer and ME/CFS led to a phase I, II, and III clinical trial using the drug by Fluge and Mella's team.

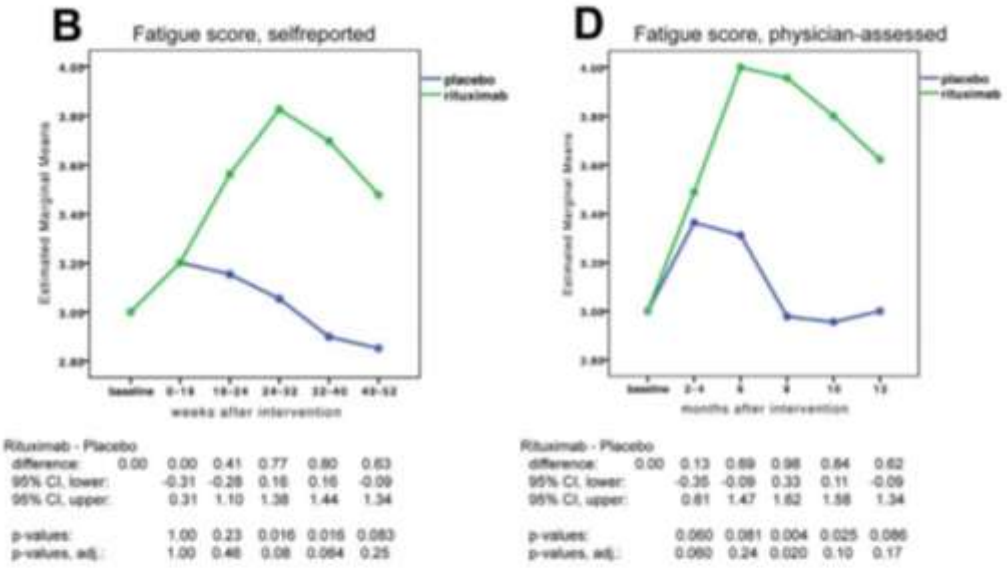


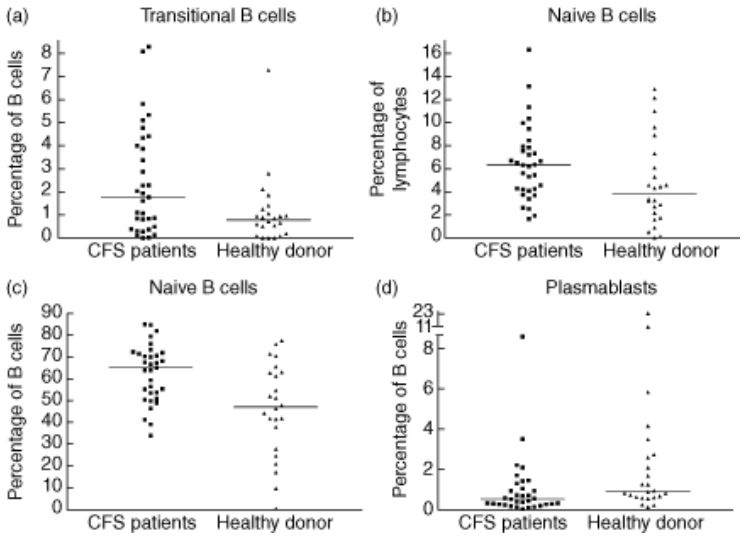
Figure 2. Fatigue scores in Rituximab and Placebo groups, self-reported and physician-assessed. In panel A, the self-reported *Fatigue scores* were calculated for each patient every second week, from the mean of the four symptoms: Fatigue, Post-exertional exhaustion, Need for rest, Daily functioning. Then the mean values in *Fatigue scores* for the time intervals during follow-up were plotted. In panel C, the physician-assessed *Fatigue scores* were calculated from the mean of the same four symptoms, registered by the physician at the visits in the outpatient clinic. In panel B and D, estimated marginal means for self-reported and physician-assessed *Fatigue scores* during follow-up are shown. The scales on Y-axes were 0–6 (0: Major worsening; 1: Moderate worsening; 2: Slight worsening; 3: No change; 4: Slight improvement; 5: Moderate improvement; 6: Major improvement). The differences in distribution of *Fatigue scores* during follow-up, between the Rituximab and Placebo groups, were assessed by General Linear Model (GLM) for repeated measures, analysing the effects of time, the interaction time by intervention group, and the overall

(Fluge and Mella et al., 2011 -- *Benefit from B-Lymphocyte Depletion Using the Anti-CD20 Antibody Rituximab in Chronic Fatigue Syndrome. A Double-Blind and Placebo-Controlled Study*)

The paper posited that the B cell depletion's success provided evidence for ME/CFS as an autoimmune disease.

Bradley et al. (2013) found that CFS patients had greater numbers of naive B cells as a percentage of total lymphocytes. Transitional B cells were also elevated, and parmablast levels were low as a percentage of total B cells. These findings might imply a tendency to autoimmunity in ME/CFS patients.

Curriu et al. (2013) found different levels of different types of lymphocytes in ME/CFS patients than healthy controls, as did Loebel et al., 2014.



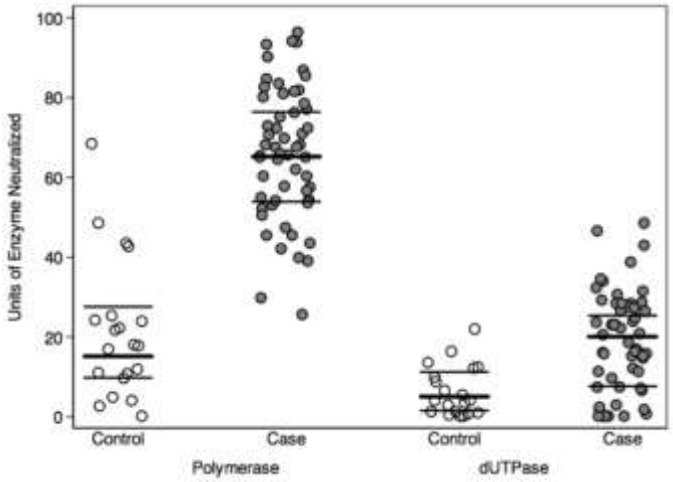
(Curriu, 2013 -- *Screening NK-, B- and T-cell phenotype and function in patients suffering from Chronic Fatigue Syndrome*: relative numbers of various immune cells)

Finally, Curriu and colleagues also found significant elevations of the T cell exhaustion markers PD-1 and CD95 (2013).

Altered immune reactions to EBV infection have recently been identified in ME in several studies, including a deficiency in EBV-specific B- and T-cell memory response in CFS patients (Lerner et al., 2012):

(Right)

Lerner et al., 2012 -- *Antibody to Epstein-Barr Virus Deoxyuridine Triphosphate Nucleotidohydrolase and Deoxyribonucleotide Polymerase in a Chronic Fatigue Syndrome Subset*



AUTOANTIBODY STUDIES

Multiple studies have found signs of autoimmunity in ME/CFS patients, including:

- Elevated ANA[9, 6]
- Anti-cholinergic muscarinic antibodies (Loebel et al., 2016)[10]
- B-adrenergic antibodies (Loebel et al., 2016)
- Anti-serotonin antibodies elevated in nearly 2/3 of patients in a 117-Fukuda-diagnosed patient study (Maes et al., 2013)
- Anti-P_i (phosphatidylinositol) antibodies modestly elevated in patients in comparison to healthy controls (Maes et al., 2007)

[9] Skowera et al., (2002) found no difference between ANA levels in Fukuda CFS patients and healthy controls.

[10] Patients were also found to have anti-cholinergic muscarinic antibodies by Tanaka et al., 2003, but the patient cohort was poorly characterized. Tanaka also found elevated ANA in over half of CFS patients, and anti-mu-opioid receptor antibodies. Anti-cholinergic muscarinic antibodies correlated to self-reported muscle weakness.

LIST OF INTERESTING AUTHORS

Armstrong	Metabolomics of blood, urine, fecal matter in ME/CFS
Bell, D.	hypoxia, blood volume, clinician, Bell's Disability Scale
Carruthers	lead author of Canadian Consensus Criteria
Chia	enteroviral research, clinician; part of CCC committee
Cook	Exercise studies, MRI post-exertional study
DeMeirlier	microbiome research, immunology research, clinician; part of CCC committee
Fluge & Mella	originally oncologists, now study Rituximab in ME/CFS patients; some metabolomics and genetics
Giloteaux	microbiome research
Hanson	microbiome research
Hornig, Mady	cytokines in ME/CFS
Hyde, B.	differential diagnosis, clinician; part of CCC committee
Klimas	natural killer cell function, immunology/genetics; part of CCC committee
Light & Light	post-exertional studies in gene expression
Jason, L.	Epidemiology, DePaul scale, mortality studies
Lipkin	viruses in ME/CFS; cytokines paper
Maes and/or Morris, G.	oxidative stress (ROS) model of ME/CFS, often compares to other inflammatory illnesses
McGowan	glucocorticoids in ME/CFS
Miwa	cardiovascular and autonomic studies
Myhill	Mitochondrial studies in ME/CFS, clinician
Nakatomi	Neuroinflammation via PET
Nath, A.	head of current NIH post-exertional study
Naviaux	metabolomics of human plasma, findings in fats and phospholipids, 'dauer' state idea
Newton, Julia	muscle studies in ME/CFS patients, some innovative experimental designs
Twisk, Frank	astute review articles on epidemiology and current state of the disease
VanElzakker	vagus nerve hypothesis
Vernon, Suzanne	Clinician, researcher
Unger	CDC, some genetics research

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