



Evaluation of a functional medicine approach to treating fatigue, stress, and digestive issues in women



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ABSTRACT

Fatigue, stress, and digestive disorders are common among adults, especially women. We conducted a 28-week pilot study to assess the efficacy of a functional medicine approach to improving stress, energy, fatigue, digestive issues, and quality of life in middle-aged women. Findings showed significant improvements in many stress, fatigue, and quality-of-life measures. The treatment program increased mean salivary dehydroepiandrosterone levels and the cortisol-dehydroepiandrosterone ratio. Stool sample analyses suggested that these treatments reduced *Helicobacter pylori* infections. This study suggests that functional medicine may be an effective approach to managing stress and gastrointestinal symptoms.

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1. Introduction

Fatigue and stress are common in the United States, especially among women [1]. Digestive disorders are also commonly reported among women, and stress is a contributor [2]. One type of treatment approach, functional medicine, may be useful for addressing these common conditions.

Functional medicine is a systems approach to chronic illness which addresses the whole person rather than an isolated set of symptoms [3]. The functional medicine model is focused on restoring optimal functioning of 3 body systems: hormonal, digestive, and detoxification. Restoring these 3 body systems has positive effects on stress, energy, fatigue, digestive issues, and quality of life. Laboratory assessments in functional medicine include measurement of salivary cortisol and dehydroepiandrosterone (DHEA) to assess the hypothalamus-pituitary-adrenal (HPA) axis. "Dysregulation of the HPA axis resulting in hypercortisolism has been proposed as a mechanism by which depression may evolve from chronic stress" [4]. Functional medicine testing may also include stool analysis to evaluate the possible presence of

pathogenic organisms; stool analysis to determine the proper functioning of the gastrointestinal tract may be used but is considered unconventional [5].

This functional medicine study focused on the hormonal and gastrointestinal systems. The primary purpose of this 28-week pilot study was to assess the efficacy of a specific functional medicine approach for improving stress, energy, fatigue, digestive issues, and quality of life in middle-aged women exposed to high-stress work environments. The approach included lifestyle factors coupled with specific nutritional supplement protocols to treat HPA axis dysregulation and gastrointestinal infections. Changes in gastrointestinal health over the course of the program, in addition to the participants' satisfaction with the functional medicine program, were also evaluated.

2. Methods

2.1. Participants

The study protocol was approved by MaGil IRB, Inc, review board. Participants screened included women aged 30–55 years living in Northern California. Participants were recruited from Internet advertising on social networks and flyers in the local area; they were enrolled in August 2014, and the study was conducted from September 2014 through April 2015. All participants self-reported that they experienced stress from their work and/or home lives. Inclusion criteria were providing written consent to

Abbreviations: DHEA, dehydroepiandrosterone; HPA, hypothalamus-pituitary-adrenal; POMS, profiles of mood states; SF-36, short Form Health Survey; VAS, visual analog scale.

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participate, allowing the use of their data for the study and for contact by the study personnel, and having access to a home computer. Exclusion criteria were: a history of cancer; current use of thyroid medication; a history of thyroid or pituitary disorder or adrenal disorder other than adrenal fatigue; diabetes mellitus; a diagnosis of hypertension; pregnant or breastfeeding; childbearing potential but not using acceptable methods of birth control (eg, spermicide with condom, diaphragm, or cervical cap; intrauterine device; hormonal contraception; vasectomy; or abstinence—Plan B or rhythm methods were not considered reliable methods); current smokers; current participation in another clinical trial; active drug or alcohol abuse or dependence; and other conditions that, in the opinion of the investigator, would interfere with adherence to study requirements.

Upon enrollment, demographic data were collected, a medical history was obtained, and a physical examination was performed by the functional medicine provider. A negative pregnancy test was required before enrollment. Vital signs and anthropometrics were obtained at enrollment and at the end of the study. Responsibilities regarding study guidelines and requirements were outlined, and informed consent was obtained.

2.2. Clinical measurements

2.2.1. Assessment of mood, quality of life, fatigue, stress, and satisfaction

The Profiles of Mood States (POMS) questionnaire, Visual Analog Scale (VAS), Short Form Health Survey (SF-36) quality of life questionnaire, and the global satisfaction questionnaire were administered at enrollment, week 4, week 8, and the end of the study (week 28).

POMS is a widely used questionnaire to assess mood states [6]. All study participants completed the self-administered POMS questionnaire (Educational and Industrial Testing Service). The questionnaire measures 6 mood subscales that include tension-anxiety, depression, anger-hostility, vigor, fatigue, and confusion. Lower scores in the tension-anxiety, depression, anger-hostility, fatigue, and confusion subscales indicate positive mood, whereas higher vigor scores reflect a positive mood.

The VAS is commonly used to measure and compare change in various parameters within individuals [7]. This study used a VAS for fatigue and for stress. The SF-36 is a multipurpose health survey that measures the generic health concepts of physical functioning, role functioning (physical and emotional), vitality, emotional well-being, social functioning, pain, and general health [8].

At the end of the study (28 weeks), patients were asked to rate their experience with a global product satisfaction scale. Questions addressed satisfaction with the overall performance of the study; likelihood of recommending this methodology to family or friends; whether the protocol helped improve stress, energy, fatigue, digestive level, and quality of life; whether the protocol allowed them to feel more energetic; and whether they tolerated the protocol well.

Salivary cortisol and DHEA were measured at weeks 0 and 24. A salivary test kit from Biohealth Laboratory was collected in the morning, noon, evening, and before bed. DHEA was a 1-time salivary measurement.

Fecal specimens were examined for ova and parasites using a commercial, 4-day home stool kit from Biohealth Laboratory. The ova and parasites measured in the stool analysis included protozoa, flatworms, roundworms, *Cryptosporidium parvum*, *Giardia lamblia* antigens, bacteria, fungi (including yeasts), occult blood, *Clostridium difficile* colitis toxins A and B, and the *Helicobacter pylori* antigen measured via stool antigen fecal smear.

2.3. Lifestyle and nutritional counseling

Weekly telephone calls were made to eligible participants during the 4-week run-in period for lifestyle and nutritional counseling. At baseline, a 1-h in-person coaching session with a functional medicine practitioner, including review of saliva and stool sample test results, was performed, and a participant-specific supplementation protocol was issued. Compliance and counseling telephone calls were made at weeks 6, 10, 12, 16, 20, and 24 post screening. In-clinic visits occurred at weeks 8 and 28 post screening. Online group sessions with the nutritionist occurred once per month for nutrition coaching and follow-up with diet compliance.

2.4. Study treatment protocol

Participant-specific supplementation protocols were issued after the in-person coaching session. The personalized program involved a combination of adrenal and digestive cleanse protocols. The protocols are detailed in the [Appendix](#).

Compliance with the supplemental protocol was measured using a supplement diary. Participants were required to complete a daily dosing diary to determine if they followed their designated protocol. In addition, participants were required to return their empty supplement bottles at the end of the study as an additional measure of compliance.

2.5. Statistical analysis

We expected to recruit 25 participants and anticipated a small attrition rate, allowing the study to reach an anticipated minimum of 20 participants. Because this was a pilot study, there was no formal sample size calculation. All variables under investigation were summarized by time point. End points measured in interval/ratio scales and their changes from baseline were presented as mean (SD) or median (range). All missing values of efficacy variables were imputed with the most recent previously available value (last value carried forward imputation). All interval/ratio scale end points were tested for normality and log normality. Log-normally distributed variables were analyzed in the logarithmic domain. Variables that were intractably non-normal were analyzed by an appropriate nonparametric test. The changes from baseline of interval/ratio-scaled variables were tested using the paired Student *t*-test. In cases of intractable non-normality, the Wilcoxon signed-rank test was used. $P < 0.05$ was considered statistically significant. All evaluations were carried out using the software package R, version 3.03.

3. Results

3.1. Demographics, screening characteristics, and compliance

A total of 25 women were screened; 24 participants were enrolled in the study, and 21 completed the trial. Most participants had demanding professional schedules that included running their own businesses, managing large companies, and frequent travel. A modified per-protocol population was used for the analysis of efficacy end points, which consisted of all participants receiving a functional medicine treatment and completing at least 1 postdose visit, regardless of compliance, protocol deviations, or withdrawal ([Fig. 1](#)).

The mean (SD) age of enrolled participants was 44.9 [5] years ([Table 1](#)). No screening characteristics were outside clinically acceptable ranges. The average compliance exhibited by participants was more than 80% for the adrenal and gastrointestinal protocols. However, individual compliance varied, with 1 participant having a

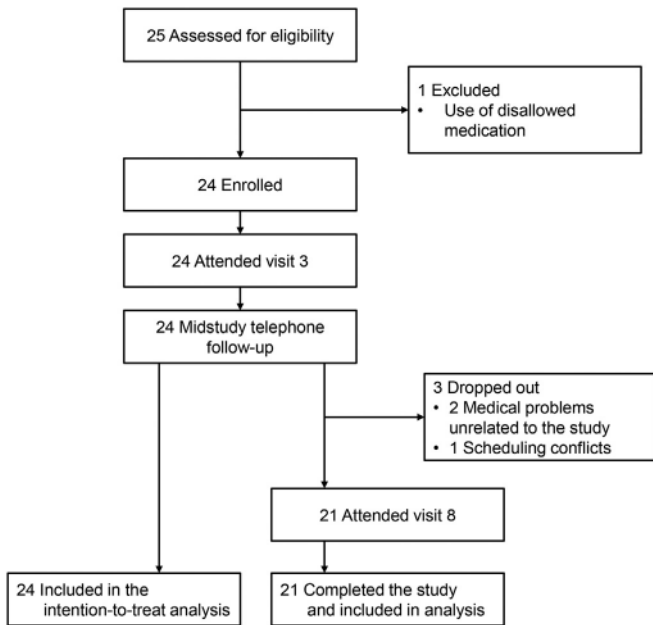


Fig. 1. Study participant flow diagram.

mean overall compliance of less than 50% and 5 participants having a mean overall compliance between 50% and 80%.

3.2. Efficacy results

3.2.1. POMS findings

There was a significant decrease in the mean fatigue (9.0 [6.0] to 5.6 [5.2]; $P = 0.005$) and confusion (7.9 [4.1] to 6.2 [4.7]; $P = 0.02$) POMS subscale scores from baseline to end of the study (Table 2). This equated to a 38% decrease in the fatigue subscale score and a 22% decrease in the confusion subscale score. There were no significant differences in the scores for tension-anxiety, depression, anger-hostility, and vigor.

Table 1
Demographics, vitals, and anthropometric measurements.

Variable	Value (N = 24) ^a
Age, y	44.9 (5.0) (n = 23)
Race	
Asian	1 [4]
White	18 (75)
Latino/Hispanic	2 [8]
Mixed descent	3 (12)
Relationship	
Divorced	3 (12)
Domestic partnership	2 [8]
Married	12 (50)
Single	7 (29)
Study status	
Completed	21 (88)
Dropped out	3 (12)
Blood pressure, mm Hg	
Systolic	119.8 (9.6)
Diastolic	76.0 (9.7)
Heart rate, beats/min	68.0 (5.6) (n = 23)
Height, cm	166.3 (6.5)
Weight, kg	71.0 (18.0)
Body mass index, kg/m ²	25.5 (5.5)

^a Values are mean (SD) or No. of participants (%).

Table 2
POMS questionnaire results (N = 24).

Scale	Score ^a		Change from baseline		Change from baseline	
	Screening (Week -4)	Baseline (Week 0)	To visit 3 ^a	To end of study ^b	P	P
Total mood disturbance	34 (-21–119)	24.5 (-22–97)	-4.5 (-50–98)	-12 (-59–98)	0.69	0.23
Tension	12.5 (2–24)	10 (1–23)	0 (-13–14)	-0.5 (-13–14)	0.77 ^b	0.59 ^b
Depression	9 (0–39)	7 (0–27)	0.5 (-14–31)	-1 (-16–31)	0.28 ^b	0.11 ^b
Anger	5.5 (0–32)	2 (0–24)	0.5 (-10–13)	0 (-12–13)	0.49 ^b	0.68 ^b
Fatigue	12.5 (0–25)(12.7 [6.7])	10 (0–23)(9.0 [6.0])	-2 (-13–13)(-2.0 [5.7])	-3.5 (-14–13)(-3.4 [5.9])	0.16 ^b	0.005 ^b
Confusion	8 (1–22)(9.5 [5.7])	7 (1–16)(7.9 [4.1])	-1 (-9–11)(-0.7 [4.0])	-2 (-7–11)(-1.7 [4.4])	0.17 ^b	0.02 ^b
Vigor	12 (0–24)	13 (3–29)	1 (-16–14)	4 (-16–13)	0.34 ^b	0.13 ^b

Abbreviation: POMS, Profiles of Mood States.

^a Values are median (range) or median (range) (mean [SD]).

^b Logarithmic transformation was required to achieve normality.

Table 3
Fatigue and stress VAS results (N = 24).

Scale	Score ^a				Change from baseline		Change from baseline	
	Screening (Week–4)	Baseline (Week 0)	Visit 3 (Week 4)	End of study (Week 24)	To visit 3 ^a	P	To end of study ^a	P
Fatigue	50.9 (25.9)	42.5 (25.4)	31.4 (22.6)	29.3 (22.2)	–13.7 (–59.3–70.7)(–11.0 [28.0])	0.07	–13 (–55–71) (–13 [30])	0.04
Stress	69.9 (26.0)	59.6 (26.9)	47.6 (29.1)	43.8 (25.7)	–8 (–78–36) (–12.0 [26.0])	0.03	–13.3 (–80–36) (–15.8 [29.8])	0.02

Abbreviation: VAS, Visual Analog Scale.

^a Values are mean (SD) or median (range) (mean [SD]).

3.3. VAS findings

Both the fatigue and stress VAS scores decreased significantly from baseline to end of study ($P = 0.04$ and $P = 0.02$, respectively) (Table 3). The fatigue score decreased by 31% and the stress score decreased by 27%. A significant decrease in the stress scores ($P = 0.03$) was observed 4 weeks after commencement of the protocol, and fatigue also decreased nonsignificantly ($P = 0.07$) in the same time period.

3.4. SF-36 quality of life questionnaire findings

Results of the SF-36 questionnaire indicated that participants experienced significant increases in vitality (39%; $P < 0.001$), role functioning–emotional (39%; $P = 0.007$), role functioning–physical (28%; $P = 0.005$), pain (14%; $P = 0.03$), and emotional well-being (11%; $P = 0.045$) subscale scores from baseline to end of study (Table 4). The vitality subscale score was the only SF-36 category to reach significance ($P = 0.03$) by 4 weeks post baseline. There were no significant differences in physical functioning, social functioning, or general health.

3.5. Salivary cortisol and DHEA

Total salivary cortisol levels, as well as levels assessed during the day (morning, noon, afternoon, and night) showed no significant differences between screening and end-of-study measurements (Table 5). A significant increase was seen in mean salivary DHEA concentration, with an initial value of 4.7 (4.8) ng/mL and an end-of-study value of 5.7 (15.4) ng/mL ($P = 0.047$). However, the median DHEA concentration decreased from baseline to end of study (3.1–2.2 ng/mL), which suggests that the mean value may not accurately reflect the effect of the protocol on DHEA levels. In addition, 1 participant had a 36-fold increase in salivary DHEA level, which affected the mean. The cortisol:DHEA ratio increased

significantly from the beginning to the end of the study ($P = 0.04$).

In the aggregate statistics for this group of women, the daily 4-point measure of cortisol showed a decrease in the percentage deviance from the median in the morning, noon, and afternoon levels (Fig. 2). The nighttime measure showed an increase from the median.

3.6. Stool microbial analysis

At screening and end of the study, there was no detection of ova and parasites with tests #2, #3, and #4, and no *G. lamblia* antigen, occult blood, or *C. difficile* toxins A and B (Table 6). On the ova and parasites test #1, 1 participant had a positive result at the end of study only. Two participants' results for *Cryptosporidium* antigen changed during the study, 1 positive to negative and 1 negative to positive. Other tests that showed differences in results between the time points were those for trichrome stain, fungi, yeast, and *H. pylori* antigen (Table 6).

3.7. Global satisfaction questionnaire findings

Of the 6 questions on the global satisfaction questionnaire, 4 received all positive feedback (questions #1–4) and 1 received positive and null feedback (#5) (Table 7). One question received positive, null, and negative feedback (#6) related to tolerance to the protocol; 2 participants disagreed with the statement, “I tolerated the protocol well, had no complaints.”

4. Discussion

The 6-month implementation of this functional medicine program resulted in significant improvements in many stress, fatigue, and quality-of-life measures. In a personalized medical approach to address chronic stress, it is difficult to define a specific mechanism; however, the DHEA effect on the HPA axis, combined with the

Table 4
SF-36 questionnaire results (N = 24).

Scale	Score ^a				Change from baseline		Change from baseline	
	Screening (Week–4) (n = 23)	Baseline (Week 0)	Visit 3 (Week 4)	End of Study (Week 24)	To visit 3 ^a	P ^b	To end of study ^a	P ^b
Physical functioning	87.0 (19.5)	89.8 (12.5)	92.9 (9.7)	91.2 (17.6)	0 (–15–25) (3.1 [8.8])	0.10 ^c	0 (–70–20) (1.5 [17.2])	0.08 ^c
Role functioning–physical	60 (35)	71 (34)	77 (35)	90.6 (28.4)	0 (–50–50) (6.2 [22.4])	0.21 ^c	0 (–25–75) (19.8 [27.6])	0.005 ^c
Role functioning–emotional	46 (42)	53 (42)	50 (45)	85 (31)	0 (–100–67) (–3 [35])	0.70	50 (–100–100) (32 [52])	0.007
Vitality	39.3 (21.3)	47.4 (24.5)	56.0 (19.0)	66.0 (17.5)	7.5 (–30–65) (8.7 [18.2])	0.03	15 (–30–55) (18.7 [20.8])	<0.001
Emotional well-being	57.9 (17.3)	65.5 (16.9)	69.0 (17.0)	72.5 (15.8)	4 (–28–44) (3.5 [13.2])	0.21	8 (–28–44) (7.0 [16.2])	0.045
Social functioning	70.7 (22.2)	73.4 (20.3)	71.4 (25.1)	77.6 (25.3)	0 (–50–37.5) (–2.1 [21.1])	0.63	0 (–50–37.5) (4.2 [22.0])	0.36
Pain	72.0 (16.8)	74.1 (23.9)	79.7 (15.4)	84.5 (16.1)	0 (–22.5–77.5) (5.6 [20.9])	0.20	10 (–22.5–77.5) (10.4 [21.7])	0.03
General health	68.5 (16.5)	71.7 (19.7)	72.9 (16.9)	76.6 (12.9)	0 (–20–25) (1.2 [10.0])	0.55	0 (–20–45) (4.9 [14.3])	0.10

Abbreviation: SF-36, Short Form Health Survey.

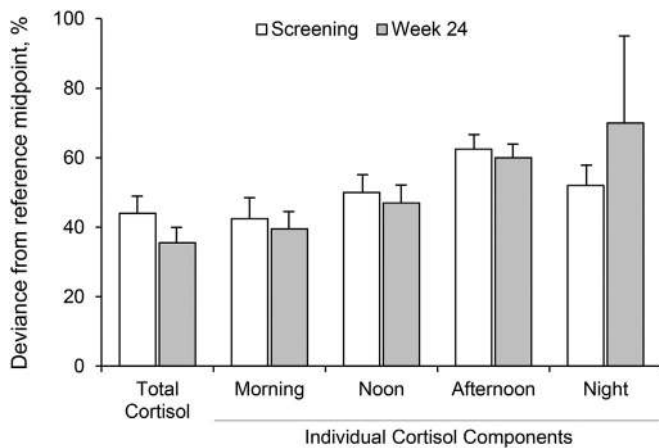
^a Values are mean (SD) or median (range) (mean [SD]).^b Paired Student *t*-test, unless otherwise noted.^c Signed-rank test.

Table 5

Cortisol and DHEA levels over time (N = 24).

Measurement	Value ^a		Change ^a	p ^b
	Screening (Week-4)	End of study (Week 24)		
Cortisol, nmol/L				
Total	17.9 (2.8–133.3)	21.6 (10.1–42.6)	0 (–105.2–21.7) (–1.0 [23.5])	0.35
Morning	11.1 (0.3–120)	13.2 (4.6–34.8)	0.4 (–100.1–20.3) (–1.7 [22.0])	0.31
Noon	3.45 (0.6–7.1)	3.15 (1.4–11.7)	0.15 (–5.1–7) (0.43 [2.31])	0.27
Afternoon	2.1 (0.6–6.9)	2.1 (0.6–4.3)	0 (–2.6–2.1) (–0.13 [1.25])	0.97
Night	1.25 (0.1–4.1)	1.25 (0–13.6)	–0.05 (–2.4–12.2) (0.31 [2.66])	0.80
DHEA, ng/mL	3.1 (0.2–20.6)	2.2 (0.2–77.4)	–0.9 (–13.6–75.3) (1.0 [16.2])	0.047
Cortisol/DHEA ratio	5.2 (1–137.5)	12 (0–188)	4.6 (–11.4–57.9) (13.1 [19.1])	0.04

Abbreviation: DHEA, dehydroepiandrosterone.

^a Values are median (range) or median (range) (mean [SD]).^b Paired Student *t*-test. All values required logarithmic transformation to achieve normality.**Fig. 2.** Deviance from Median Normal Cortisol Levels Throughout the Day at Screening and Week 24 (n = 22). Lower values suggest a better health outcome.

lifestyle changes, most likely contributed to the results observed in this study. A substantial improvement was seen in the *H. pylori* infections in the program, with 9 participants testing positive at the beginning of the study and only 1 remaining positive at the end. This open-label pilot study suggests that functional medicine

Table 6

Stool microbial analysis for participants completing the study (n = 21).

Test	Positive result ^a		Relevant changes ^b
	Screening	End of study	
Ova & parasites			
#1	0 (0)	1 (5)	1 Neg → pos
#2	0 (0)	0 (0)	
#3	0 (0)	0 (0)	
#4	0 (0)	0 (0)	
Trichrome stain	5 (24)	4 (19)	5 Pos → neg 4 Neg → pos
<i>Cryptosporidium</i> antigen	1 (5)	1 (5)	1 Pos → neg 1 Neg → pos
<i>Giardia lamblia</i> antigen	0 (0)	0 (0)	
Fungi	3 (14)	1 (5)	3 Pos → neg 1 Neg → pos
<i>Clostridium difficile</i> toxin			
A	0 (0)	0 (0)	
B	0 (0)	0 (0)	
Yeast	2 (10)	5 (24)	1 Pos → neg 4 Neg → pos
Occult blood (n = 20)	0 (0)	0 (0)	
<i>Helicobacter pylori</i> antigen	9 (43)	1 (5)	8 Pos → neg

Abbreviations: neg, negative result; pos, positive result.

^a Values are No. of participants (%) with a positive test result.^b No. of participants whose test result changed from screening to end of study.

programs may be an effective approach to combat chronic stress and potentially any stress-associated gastrointestinal symptoms in the population studied.

In the aggregate statistics for this group of women, the daily 4-point measure of cortisol showed a decrease in the percentage deviance from the median in the morning, noon, and afternoon levels. This reflects a shift in the study participants' cortisol circadian profile toward physiologically normal profiles for the morning, noon, and afternoon points after 6 months using this specific functional medicine method and possibly suggests a reversal in the HPA axis dysregulation.

This laboratory-based program, which used a functional medicine (or whole-person) approach, relies heavily on lifestyle changes that pose little risk to participants, along with nutritional supplements researched in past studies. This study comes at an important time, because functional medicine assessment for HPA axis dysfunction and gastrointestinal infections has become popular with the public and with integrative physicians, yet there is little research to show which clinical protocols may prove to be safe and effective. This pilot study provides the initial foundation for future research to build upon in the growing field of functional medicine.

4.1. Limitations

This study had several limitations. The sample size of 24 participants is small, and results on a much larger scale would need to be conducted. Due to the holistic nature of functional medicine, multiple interventions were applied and the resulting outcomes were measured. Functional medicine is inherently a multifactorial practice that uses unique approaches for individual patients. Therefore, it is difficult to discern which interventions contributed to the positive findings, whether it was the lifestyle interventions, the protocols to treat HPA-axis dysfunction, the protocols to treat various gut infections, or all of the interventions combined. However, the definition of functional medicine is to assess and treat the whole person; therefore, the results should be viewed collectively. There was no control group, so positive outcomes could have been attributed to the placebo effect.

5. Conclusions

This study used a personalized holistic functional medicine approach in women to manage chronic stress often associated with high stress/pressure work environments. Women who received multiple counseling sessions with a functional medicine practitioner and nutritionists, along with a 24-week regimen of participant-specific adrenal and digestive protocols, had significant improvements in POMS fatigue and confusion subscale scores, VAS stress and

Table 7
Satisfaction questionnaire for participants completing the study (n = 20).

Statement	Responses ^a				
	Strongly agree	Agree	No opinion	Disagree	Strongly disagree
I am satisfied with the overall performance of the study.	16 (80)	4 (20)	0 (0)	0 (0)	0 (0)
I would recommend the methodology to family or friends.	17 (85)	3 (15)	0 (0)	0 (0)	0 (0)
I feel the protocol helped me improve my stress, energy, fatigue and digestive level.	15 (75)	5 (25)	0 (0)	0 (0)	0 (0)
I feel the protocol helped improve the quality of my life.	11 (55)	9 (45)	0 (0)	0 (0)	0 (0)
I feel the protocol allowed me to feel more energetic.	12 (60)	7 (35)	1 (5)	0 (0)	0 (0)
I tolerated the protocol well, had no complaints.	8 (40)	9 (45)	1 (5)	2 (10)	0 (0)

^a Values are No. of participants (%).

fatigue subscale scores, and SF-36 vitality, physical and emotional role functioning, and emotional well-being subscale scores. The SF-36 pain subscale score also decreased significantly during the study. The treatment program increased mean salivary DHEA levels and the cortisol-DHEA ratio. However, the mean salivary DHEA level was biased by the results of 1 participant with a 36-fold increase and does not reflect the protocol's effect on the cohort. Stool sample analyses suggest that these treatments may reduce *H. pylori* infections, which can be associated with decreased occurrence of ulcers. The participants gave predominantly positive feedback relating to their satisfaction with this functional medicine approach.

Further examination into this therapy is warranted. Additional randomized studies are needed and would offer additional information on the effects and efficacy of these types of approaches.

Conflict of interest statement

There are no competing interests among the authors of this work.

Table 1
Adrenal Protocols for Participants With Initial Low or High Cortisol Levels

12-Week nutritional supplement protocol	Adrenal protocol A (Low cortisol)			Adrenal protocol B (High cortisol)		
	With breakfast	With lunch	With dinner	With breakfast	With lunch	With dinner
DHEA drops	3	3	3	4	4	4
Pregnenolone drops	10	10	10	6	6	6
Support Essentials ^a	1 pack		1 pack	1 pack		1 pack
Licorice Root Extract drops	10	10				2
Balance 5 – Adrenal Repair ^b	1	1	1	1	1	1
C-Flav ^c	1	1	1	1	1	1
Support Glucose ^d	1	1	1	1	1	1

Abbreviation: DHEA, dehydroepiandrosterone.

^a Support Essentials (Biomatrix International, LLC) is a multivitamin that contains vitamins, minerals, antioxidants, and essential fatty acids. Ingredients: vitamin A, vitamin C, vitamin D₃, vitamin E, thiamine, riboflavin, niacin/niacinamide, vitamin B₆, folate, vitamin B₁₂, vitamin K, biotin, pantothenic acid, calcium, copper, iodine, magnesium, zinc, selenium, manganese, chromium, molybdenum, potassium, choline, inositol, citrus bioflavonoid complex, vanadium, boron, eicosapentaenoic acid, docosahexaenoic acid, hesperidin, rutin. Other ingredients: cellulose, ultrarefined fish oil concentrate, gelatin (capsule), silica, vegetable stearate, glycerin, water, rosemary extract, ascorbyl palmitate, mixed tocopherols, ethylcellulose, coconut oil, ammonium hydroxide, sodium alginate, and stearic acid. (Krebs = citrate, fumarate, malate, glutarate, and succinate complex.)

^b Balance 5 – Adrenal Repair (Douglas Laboratories) is a herbal product that supports adrenal health. Ingredients: calcium, magnesium, zinc, selenium, copper, manganese, chromium, molybdenum, potassium, betaine HCl, vanadyl sulfate, boron. Other ingredients: natural vegetable capsules (may contain one or more of the following: calcium silicate, magnesium stearate, microcrystalline cellulose, and silicon dioxide).

^c Vitamin C (Ortho Molecular Products). Ingredients: vitamin C, acerola fruit extract, quercetin, hesperidin complex, hibiscus flowers, rutin. Other ingredients: natural vegetable capsules (may contain one or more of the following: calcium silicate, magnesium stearate, microcrystalline cellulose, and silicon dioxide).

^d Support Glucose (Biomatrix International, LLC) is natural blood sugar support. Ingredients: chromium, *Gymnema* leaf extract, alpha lipoic acid, cinnulin, vanadyl sulfate hydrate, bitter melon extract, *Lagerstroemia speciosa* L. leaf extract. Other ingredients: natural vegetable capsules (may contain one or more of the following: calcium silicate, magnesium stearate, microcrystalline cellulose, and silicon dioxide).

Table 2
Digestive Cleanse Protocols

8-Week nutritional supplement protocol	Protocol		
	With breakfast	With lunch	With dinner
Protocol 1 (Stomach Issues)			
Mastic ^a	2	2	2
Pepti Guard ^b	2	2	2

Table 2 (continued)

8-Week nutritional supplement protocol	Protocol		
	With breakfast	With lunch	With dinner
Protocol 2 (Intestinal Issues)			
Clear 2 – <i>Candida</i> Clear ^c	3	3	3
Protocol 3 (Intestinal Issues)			
Clear 1 – Herbs for digestive repair ^d	1 pack	1 pack	1 pack
Protocol 4 (Gastrointestinal Support)			
Clear 6 – Probiotics ^e	2		2
Clear 7 – Enzymes ^f	2	2	2
Clear 8 – <i>S. boulardii</i> ^g	2		2

^a Mastic (Biomatrix International, LLC Biomatrix International, LLC should be replaced with Allergy Research Group, LLC). Ingredients: *Pistacia lentiscus* (resin). Other ingredients: hydroxypropyl methylcellulose, microcrystalline cellulose, magnesium stearate, silicon dioxide.

^b Pepti Guard (Thorne Research). Ingredients: deglycyrrhizinated licorice extract (root) (*Glycyrrhiza* spp), bismuth citrate, aloe vera (gel, dehydrate powder) (*Aloe barbadensis*), berberine HCl (from Indian barberry extract) (root) (*Berberis aristata*). Other ingredients: hypromellose (derived from cellulose) capsule, leucine, silicon dioxide.

^c Clear 2 – *Candida* Clear (Ortho Molecular). Ingredients: coconut oil powder, garlic powder (deodorized), oregano powder extract (leaf), olive leaf extract, *Uva ursi* extract (leaf), grapefruit seed extract, berberine sulfate, alpha lipoic acid, milk thistle extract (80% silymarin), *N*-acetylcysteine. Other ingredients: gelatin (capsule).

^d Clear 1 – Herbs for digestive repair (Douglas Laboratories). Ingredients: berberine sulfate hydrate, olive extract, sweet wormwood, grapefruit seed, and clove. Other ingredients: calcium silicate, magnesium stearate, microcrystalline cellulose, natural vegetable capsule, silicon dioxide, stearic acid.

^e Clear 6 – Probiotics (Douglas Laboratories). Ingredients: *Bifidobacterium bifidum*, *B. lactis*, *Lactobacillus acidophilus*, *L. rhamnosus*, *B. longum*, *L. gasseri*, *Streptococcus thermophilus*, fructooligosaccharides, *Ulmus fulva* (bark). Other ingredients: gelatin (capsule), cellulose, vegetable stearate, and silica.

^f Clear 7 – Enzymes (Douglas Laboratories). Ingredients: betaine, glutamic acid, pancreatin, pepsin, papain, *Aspergillus oryza*, lipase, ox bile extract, rennin, malt diastase, beet root powder, citrus pectin. Other ingredients: cellulose, vegetable stearate, myrrh gum, and silica.

^g Clear 8 – *S. boulardii* (Ortho Molecular). Ingredients: *Bifidobacterium longum*, *Lactobacillus acidophilus*, *Saccharomyces boulardii*. Other ingredients: fructooligosaccharide, magnesium silicate, magnesium stearate (vegetable), vegetable cellulose (capsule).

References

- [1] J.A. Ricci, E. Chee, A.L. Lorandeanu, J. Berger, Fatigue in the U.S. workforce: prevalence and implications for lost productive work time, *J. Occup. Environ. Med.* 49 (1) (2007 Jan) 1–10.
- [2] S. Saha, S.D. Esposti, Meeting the need for women's health training in gastroenterology: creation of a women's digestive disorders program at Brown University, *J. Womens Health (Larchmt)* 19 (7) (2010 Jul) 1409–1415.
- [3] Institute for Functional Medicine, What Is Functional Medicine? (Internet), 2015 (cited 2015 Dec 30). Available from: <https://www.functionalmedicine.org/about/whatisfm/>.
- [4] A. Levine, O. Zagoory-Sharon, R. Feldman, J.G. Lewis, A. Weller, Measuring cortisol in human psychobiological studies, *Physiol. Behav.* 90 (1) (2007 Jan 30) 43–53. Epub 2006 Oct 19.
- [5] Institute for Functional Medicine, Functional Medicine in Clinical Practice (Internet), 2015 (cited 2015 Dec 30). Available from: <https://www.functionalmedicine.org/page.aspx?id=790>.
- [6] M. Morfeld, C. Petersen, A. Kruger-Bodeker, S. von Mackensen, M. Bullinger, The assessment of mood at workplace: psychometric analyses of the revised Profile of Mood States (POMS) questionnaire, *Psychosoc. Med.* 4 (2007 May 10). Doc06.
- [7] D. Gould, D. Kelly, L. Goldstone, J. Gammon, Examining the validity of pressure ulcer risk assessment scales: developing and using illustrated patient simulations to collect the data, *J. Clin. Nurs.* 10 (5) (2001 Sep) 697–706.
- [8] J.E. Ware Jr., B. Gandek, Overview of the SF-36 health survey and the international quality of life assessment (IQOLA) project, *J. Clin. Epidemiol.* 51 (11) (1998 Nov) 903–912.