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Complications in Operationalizing Lifelong Fatigue as an Exclusionary Criterion

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Abstract

The case definitions for chronic fatigue syndrome (CFS) and chronic fatigue syndrome/Myalgic Encephalomyelitis stipulate that the experience of lifelong fatigue is an exclusionary criterion (Fukuda et al., 1994; Carruthers et al., 2003). This article examines the lifelong fatigue construct and identifies potential validity and reliability issues in using lifelong fatigue as an exclusionary condition. Participants in the current study completed the DePaul Symptom Questionnaire (Jason et al., 2010), and responses were examined to determine if they had experienced lifelong fatigue. This article discusses the extensive process that was needed to confidently discern which participants had or did not have lifelong fatigue. Using the most rigorous standards, few individuals were classified as having lifelong fatigue. In addition, those with and without lifelong fatigue had few significant differences in symptoms and functional areas. This article concludes with a recommendation that lifelong fatigue should no longer be used as an exclusionary criterion for CFS or ME/CFS.

Keywords

chronic fatigue syndrome; Myalgic Encephalomyelitis; case definitions; exclusionary criteria; lifelong fatigue

Before a patient can be diagnosed with chronic fatigue syndrome (CFS) or Myalgic Encephalomyelitis (ME), clinicians and researchers must rule out certain exclusionary conditions. For example, the Fukuda et al. (1994) criteria, which is the most widely used CFS case definition, excludes those with lifelong fatigue from a CFS diagnosis. Specifically, to meet the Fukuda et al. criteria, a participant must have “persistent or relapsing chronic fatigue that is of new or definite onset (has not been lifelong).” Since the creation of the Fukuda et al. (1994) case definition, several additional case definitions have been released, all of which vary regarding the use of lifelong fatigue as an exclusionary criterion. The Canadian clinical ME/CFS (Carruthers et al., 2003) case definition is similar to the Fukuda et al. (1994) case definition in that it also requires a “significant degree of new onset” of fatigue. Alternatively, the recently published Myalgic Encephalomyelitis International Consensus Criteria case definition (Carruthers et al., 2011) does not specify that participants

who report lifelong fatigue should be excluded. Finally, although a revised Myalgic Encephalomyelitis case definition (Jason et al., 2012) requires an acute onset of the illness (due to a virus, infection, or other factors), it does not deem lifelong fatigue to be exclusionary.

Although neither the Fukuda et al. (1994) CFS case definition nor the Canadian clinical ME/CFS case definition (Carruthers et al., 2003) states the purpose of excluding those who have experienced lifelong fatigue, an article by Reeves et al. (2003) provides a partial explanation for this exclusionary criteria. The authors state that lifelong fatigue was noted as an exclusionary condition in order to exclude those with personality or somatization disorders. There are two problems with this explanation. First, these psychiatric disorders can be diagnosed directly, instead of relying on the presence of lifelong fatigue, a more indirect method. Second, there is no evidence that has been published to show that individuals with lifelong fatigue have more psychiatric problems.

If researchers are to use lifelong fatigue as an exclusionary criterion, there remain difficulties operationalizing the criteria. Neither the Fukuda et al. (1994) nor the Canadian clinical case definition (Carruthers et al., 2003) clearly specifies how lifelong fatigue should be defined or measured. Identifying true lifelong fatigue is possibly a subjective exercise that may be confounded by the limitations of a patient's memory. It is difficult to determine whether patients have not experienced a time without fatigue or they simply cannot *remember* a time without fatigue. This confound is especially apparent for older individuals, those who have suffered from CFS or ME/CFS for a prolonged period of time, or individuals with a childhood onset of CFS or ME/CFS. Furthermore, the Fukuda et al. (1994) case definition seems to equate having fatigue of new or definite onset with fatigue that is not lifelong. The Fukuda et al. (1994) case definition does not indicate which is most important in identifying lifelong fatigue: having a definite illness onset or not remembering a time without fatigue problems.

Published empirical evidence is not available regarding this exclusion, therefore, research needs to be conducted to empirically determine if lifelong fatigue should be used as an exclusionary criterion. This article explores the process that is needed to determine if participants in a research sample have lifelong fatigue and reviews the challenges and reliability issues involved in operationalizing this construct. This article also reports for the first time on possible differences in functional health or symptoms between participants who report lifelong fatigue versus those who do not.

Method

Participants

The sample collected was an international convenience sample of 217 adults between the ages of 18 and 65 who self-identified as having CFS, ME/CFS, or ME. Of these participants, 21 were excluded due to morbid obesity or other exclusionary medical or psychiatric conditions, as specified by the Fukuda et al. (1994) case definition. Participants were required to be capable of reading and writing English and were recruited through sources such as internet forums and support groups, as well as re-contacting individuals who had

previously expressed interest in participating in future DePaul University studies. Participants were given the option to complete questionnaires electronically, by hard-copy, over the phone, or in person at DePaul University's Center for Community Research. They were not given a deadline to complete the questionnaire due to the unpredictability of illness symptoms, but the first 100 participants to complete the questionnaire received a \$5.00 Amazon.com gift certificate.

The sample was 83.6% female and 16.4% male, and the mean age of participants was 51.6 ($SD = 11.1$). Of this sample, 97.4% identified as white, 0.5% as Asian, and 2.1% as "Other." The majority of the sample was not working, with 54.9% reporting that they were on disability and 13.3% working part- or full-time. Regarding education, 40.0% of participants had a graduate or professional degree; 35.4% had a college degree; 17.9% had completed at least one year of college; and 6.7% had a high school degree or equivalent.

Materials

The DePaul Symptom Questionnaire (DSQ)—Participants completed the DePaul Symptom Questionnaire (DSQ) (Jason et al., 2010), a self-report measure consisting of items related to core symptoms, illness onset, and other relevant information needed to determine whether participants met case definition criteria. The development of the DSQ was based upon the CFS Questionnaire (Jason et al., 1997), which evidences good inter-rater and test-retest reliability and sensitively distinguishes among individuals with CFS, individuals with Major Depressive Disorder, and healthy controls (Hawk, Jason, & Torres-Harding, 2006). For the DSQ, participants used 5-point Likert scales to rate each symptom's frequency and severity over the past six months. Frequency was rated on the following scale: 0=none of the time, 1=a little of the time, 2=about half the time, 3=most of the time, and 4=all of the time; and severity was rated on the following scale: 0=symptom not present, 1=mild, 2=moderate, 3=severe, 4=very severe. Frequency and severity scores were converted to a 100-point scale by multiplying the score by 25, and the frequency and severity scores were averaged to create a composite score for each symptom.

Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36 or RAND Questionnaire)—Participants also completed the SF-36, a 36-item questionnaire related to functional health (Ware & Sherbourne, 1992). Higher subscale scores indicate less impairment in functioning due to health. The SF-36 evidences internal consistency, significant discriminant validity among subscales, and can differentiate between patient and non-patient populations (McHorney, Ware, Lu, & Sherbourne, 1994).

Procedure

Figure 1 illustrates the process that was needed to determine whether participants should be excluded due to experiencing lifelong fatigue, and Figure 2 lists the questions used and specific responses participants could select for each question. Initially, participants' responses to the question, "*Have you always had persistent or recurring fatigue/energy problems, even back to your earliest memories as a child?*" (Question 67 in the DSQ) were noted. Of the participants who answered "Yes" to this question, responses to two additional questions related to lifelong fatigue were considered. The question "*How long ago did your*

fatigue/energy problem begin?” indicated whether participants remembered a time prior to their illness, and the question *“Over what period of time did your fatigue/energy related illness develop?”* indicated whether their illness had a new or definite onset (Questions 69 and 77 in the DSQ). Based on responses to these two questions, participants with suspected lifelong fatigue were re-contacted and asked five additional questions about the onset of their illness: (1) *Around what age did your fatigue/energy-related illness begin?* (2) *When did you first begin to experience symptoms?* (3) *Even if you have always dealt with fatigue/energy problems, was there a point of “onset” of your illness, or a time when your symptoms became significantly worse?* (4) *In the case that you do not remember a time without fatigue/energy problems, have friends or family ever told you that there was a time when you did not have fatigue/energy problems?* (5) *Are there other relevant details we should know about the timing or onset of your fatigue/energy-related illness?* Responses to these open-ended questions provided the information needed to determine which participants truly had lifelong fatigue.

Results

Of the 196 participants who did not report medical or psychiatric exclusionary conditions, 20 participants answered “Yes” to the initial screening question (Question 67), indicating they had always experienced fatigue or energy problems. However, of these 20 participants with suspected lifelong fatigue, 9 participants’ responses to the second set of questions (Questions 69 and 77) indicated that they could remember a time prior to their illness or that they had new or definite onset. The remaining 11 participants were re-contacted to request responses to the five open-ended questions, and 9 of these participants responded. Based on their responses, it was clear that 4 did not have lifelong fatigue, as they could identify an age when their problems with fatigue and energy began. The remaining 5 participants who responded to the follow-up questions did appear to have lifelong fatigue. For the 2 participants who did not respond, we counted them as lifelong fatigued, as we did not have sufficient evidence to indicate that they had a new or definite onset of their fatiguing illness. In summary, of the 20 participants who initially seemed as if they might have experienced lifelong fatigue (and had no other medical or psychiatric exclusionary conditions), only 7 truly needed to be excluded as having lifelong fatigue after examining more detailed descriptions of the onset of their illness.

The group of 7 participants with lifelong fatigue (henceforth referred to as the Lifelong^a group) was compared to the group of participants who met the Fukuda et al. (1994) case definition criteria. Because of the small sample size of the Lifelong^a group, the larger group of 20 participants who expressed always having had fatigue problems (hereupon referred to as the Lifelong^b group) was also compared to the participants who met the Fukuda et al. (1994) criteria. This second comparison allows us to determine if significant differences would be found had only one question been used to determine the presence of lifelong fatigue.

Table 1 summarizes the demographic characteristics of each group, as well as the presence of psychiatric illness; no significant demographic or psychiatric differences were found

between the Lifelong^a group and the Fukuda group or between the Lifelong^b group and the Fukuda group.

Table 2 displays the results of ANOVAs that compared the eight SF-36 subscale scores of the groups. One significant difference was found between the Lifelong^a group and the Fukuda group. The Lifelong^a group had significantly higher Role Emotional scores than the Fukuda group [$F(1, 187) = 7.85, p = 0.02$]. No significant differences were found between the Lifelong^b group and the Fukuda group.

Table 3 displays the results of ANOVAs that compared the groups' symptom scores. Of the 54 symptoms, only 1 symptom was significantly different between the Lifelong^a group and the Fukuda group. The Lifelong^a group had significantly worse scores related to needing to nap daily [$F(1,181) = 38.61, p < 0.001$]. When comparing the Lifelong^b group to the Fukuda group, only 4 symptoms showed significant differences: Needing to nap daily [$F(1,179) = 6.23, p = 0.01$], bladder problems [$F(1,185) = 4.72, p = 0.03$], irritable bowel problems [$F(1,184) = 13.23, p < 0.001$], and having no appetite [$F(1, 184) = 6.02, p = 0.02$]. For each of these symptoms, the Lifelong^b group reported worse symptom scores than the Fukuda group. Given the large number of comparisons and inflated risk of Type I error (a Bonferroni adjustment indicates that only symptoms that are significant at the $p < 0.001$ level should be interpreted as significant), several of the significant findings above may solely be due to chance.

Discussion

The current study found that when comparing the group of participants who reported always having had lifelong fatigue versus the others who did not have lifelong fatigue, few significant differences were found in SF-36 subscale scores or in the majority of symptom composite scores. An extensive process was required to determine which participants in this study had truly experienced lifelong fatigue and therefore should be excluded according to the Fukuda et al. (1994) and Canadian clinical (Carruthers et al., 2003) case definitions. Asking participants if they could not remember a time without fatigue was not sufficient to accurately determine the presence of lifelong fatigue. The primary difficulty involved parsing the participants who had true lifelong fatigue from those who had simply suffered from fatigue for a long time. Several participants reported not remembering a time without fatigue problems but could still identify a point of sudden, definite onset when their symptoms became disabling or significantly worse. For example, some participants who reported always having fatigue problems actually had sudden, infectious onsets (after contracting mononucleosis) during early adolescence. Therefore, this study suggest that some participants using the Fukuda et al. (1994) criteria and the Carruthers et al. (2003) criteria are being inappropriately excluded from a CFS or ME/CFS diagnosis due to lifelong fatigue, as their responses to several questions related to lifelong fatigue indicated that they did not have lifelong fatigue.

To confidently discern which participants in this sample truly had experienced lifelong fatigue, the original three discrete-answer questions that were used had to be supplemented with five open-ended questions, as detailed descriptions of illness onset were needed to

confidently exclude participants based on this criterion. The large number of questions required could introduce validity and reliability issues when researchers try to operationalize this criterion. If researchers cannot accurately and consistently identify participants with lifelong fatigue, then participants may be arbitrarily excluded. The need for open-ended questions also increases the chance of reliability issues, as most investigators will not use questionnaires that include all the needed questions.

This study needs to be replicated with other studies to determine if similar findings emerge. The low numbers of individuals in the lifelong fatigue group surely reduced power in a number of comparisons. However, this study found that an extensive effort was required to identify only a few cases of lifelong fatigue and accompanying risk of reliability issues. There was also a lack of significant differences in psychiatric comorbidity, functional status, or symptom scores between the two groups. In summary, the current study suggests that lifelong fatigue should no longer be used as an exclusionary criterion for CFS or ME/CFS case definitions.

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Figure 1.
Illustration of process used to determine if participants should be excluded due to lifelong fatigue

DePaul Symptom Questionnaire, Question #67:

Have you always had persistent or recurring fatigue/energy problems, even back to your earliest memories as a child? (By persistent or recurring, we mean that the fatigue/energy problems are usually ongoing and constant, but sometimes there are good periods and bad periods)

- Yes
- No
- Not having a problem with fatigue/energy

DePaul Symptom Questionnaire, Question #69:

How long ago did your problem with fatigue/energy begin?

- Less than 6 months
- 6-12 months
- 1-2 years
- Longer than 2 years
- Had problem with fatigue/energy since childhood or adolescence
- Not having a problem with fatigue/energy

DePaul Symptom Questionnaire, Question #77:

Over what period of time did your fatigue/energy related illness develop?

- Within 24 hours
- Over 1 week
- Over 1 month
- Over 2-6 months
- Over 7-12 months
- Over 1-2 years
- Over 3 or more years
- I am not ill

Follow-up questions, provided via email (open-ended):

1. Around what age did your fatigue/energy-related illness begin?
2. When did you first begin to experience symptoms?
3. Even if you have always dealt with fatigue/energy problems, was there a point of “onset” of your illness, or a time when your symptoms became significantly worse?
4. In the case that you do not remember a time without fatigue/energy problems, have friends or family ever told you that there was a time when you did not have fatigue/energy problems?
5. Are there other relevant details we should know about the timing or onset of your fatigue/energy-related illness?

Figure 2.

Questions and possible responses used to determine if participants should be excluded due to lifelong fatigue

Table 1

Demographics and Psychiatric Characteristics

Age	Lifelong ^a		Fukuda		Sig.		Lifelong ^b		Fukuda		Sig.	
	M (SD)	N (%)	M (SD)	N (%)	Sig.		M (SD)	N (%)	M (SD)	N (%)	Sig.	
	49.4 (9.5)		51.6 (11.3)				55.6 (10.1)		51.1 (11.3)			
Other Demographic Information:												
Gender												
Male		1 (14)		30 (17)				2 (10)		29 (17)		
Female		6 (86)		151 (83)				18 (90)		137 (83)		
Race												
Caucasian		6 (86)		177 (98)				19 (95)		163 (98)		
Asian/Pacific Islander		0 (0)		1 (1)				0 (0)		0 (0)		
Other		1 (14)		3 (2)				1 (5)		3 (2)		
Work status												
On disability		3 (43)		101 (56)				9 (45)		93 (56)		
Student		0 (0)		6 (3)				0 (0)		6 (4)		
Homemaker		0 (0)		9 (5)				2 (10)		7 (4)		
Retired		1 (14)		22 (12)				4 (20)		19 (11)		
Unemployed		1 (14)		22 (12)				3 (15)		20 (12)		
Working part-time		1 (14)		14 (8)				1 (5)		14 (8)		
Working full-time		1 (14)		7 (4)				1 (5)		7 (4)		
Educational level												
High school		0 (0)		13 (7)				1 (5)		12 (7)		
Partial college		2 (29)		32 (18)				4 (20)		30 (18)		
Standard college degree		2 (29)		64 (35)				8 (40)		57 (34)		
Graduate/Professional degree		3 (43)		72 (40)				7 (35)		67 (40)		
Lifetime psychiatric diagnosis												
Yes		3 (43)		77 (42)				9 (45)		71 (43)		
No		4 (57)		105 (58)				11 (55)		96 (57)		

Table 2

SF-36 Subscales (Higher score indicates **less** impairment)

	Lifelong ^a		Fukuda		Sig.		Lifelong ^b		Fukuda		Sig.	
	M	(SD)	M	(SD)			M	(SD)	M	(SD)		
Physical Functioning	35.7	(16.2)	29.6	(18.3)			33.6	(18.4)	29.4	(18.3)		
Role Physical	0.0	(0.0)	4.8	(15.1)			1.3	(5.6)	4.9	(15.6)		
Bodily Pain	50.6	(20.7)	41.4	(22.5)			41.9	(27.0)	41.7	(21.9)		
General Health	20.0	(15.5)	25.1	(14.3)			23.1	(18.2)	25.3	(13.9)		
Social Functioning	28.6	(24.7)	20.3	(20.3)			26.9	(23.7)	19.8	(19.9)		
Mental Health	66.9	(22.8)	71.7	(16.7)			70.2	(18.6)	71.7	(16.9)		
Role Emotional	95.2	(12.6)	79.9	(36.9)	*		75.0	(41.7)	80.8	(35.9)		
Vitality	12.1	(11.1)	12.9	(13.0)			10.3	(11.1)	13.4	(13.1)		

*
 $p < 0.05$

Table 3

Symptoms (Higher score indicates **more** impairment)

	Lifelong ^a		Fukuda		Sig.	Lifelong ^b		Fukuda	Sig.
	M	(SD)	M	(SD)		M	(SD)	M	(SD)
Fatigue	79.2	(10.2)	79.4	(16.0)		83.6	(11.8)	78.9	(16.3)
Post-exertional malaise									
Dead, heavy feeling after starting to exercise	76.8	(27.4)	68.0	(29.0)		73.8	(24.3)	67.3	(29.4)
Next-day soreness after non-strenuous activities	76.8	(22.2)	74.4	(20.7)		78.8	(19.9)	74.0	(20.6)
Mentally tired after slightest effort	71.4	(20.0)	62.7	(24.9)		68.8	(23.8)	62.0	(24.8)
Minimum exercise makes you tired	75.0	(16.1)	75.8	(23.5)		70.6	(23.7)	76.4	(23.3)
Physically drained/sick after mild activity	76.8	(16.8)	72.1	(24.0)		75.0	(18.6)	71.6	(24.2)
Sleep									
Unrefreshing sleep	75.0	(10.2)	78.7	(21.6)		79.4	(23.0)	78.3	(21.2)
Need to nap daily	85.7	(13.4)	51.3	(30.3)	***	69.1	(30.2)	50.9	(30.0)
Problems falling asleep	64.3	(36.4)	60.6	(31.4)		67.1	(36.4)	60.0	(31.1)
Problems staying asleep	64.6	(24.3)	62.3	(30.2)		70.8	(25.7)	61.6	(30.3)
Waking up early in the morning	53.6	(32.0)	49.0	(33.0)		58.1	(31.7)	48.2	(32.9)
Sleeping all day/staying awake all night	12.5	(23.9)	17.5	(28.0)		23.8	(33.4)	16.5	(27.2)
Pain									
Muscle pain	57.1	(26.9)	62.2	(26.0)		61.8	(30.8)	62.0	(25.6)
Pain in multiple joints	35.7	(32.6)	51.1	(33.0)		50.0	(36.7)	50.5	(32.8)
Eye pain	39.3	(28.3)	32.4	(28.4)		35.6	(27.9)	32.2	(28.6)
Chest pain	16.1	(23.6)	25.4	(24.5)		18.8	(23.8)	25.6	(24.5)
Bloating	53.6	(18.7)	44.8	(27.8)		53.8	(24.4)	44.3	(27.7)
Abdomen/stomach pain	51.8	(21.0)	37.4	(25.6)		45.4	(26.1)	37.0	(25.4)
Headaches	48.2	(23.3)	48.8	(25.1)		48.8	(26.9)	48.9	(24.9)
Neurocognitive									
Muscle twitches	37.5	(22.8)	31.6	(25.6)		38.8	(22.2)	30.9	(25.8)
Muscle weakness	64.3	(16.8)	60.2	(27.8)		61.9	(32.8)	60.0	(27.0)
Sensitivity to noise	64.3	(24.4)	60.9	(27.6)		59.7	(29.3)	60.8	(27.3)
Sensitivity to bright lights	60.7	(23.3)	57.0	(29.0)		63.8	(27.0)	56.0	(28.9)

	Lifelong ^a M (SD)	Fukuda M (SD)	Sig.	Lifelong ^b M (SD)	Fukuda M (SD)	Sig.
Problems remembering things	53.6 (23.7)	66.2 (22.5)		68.1 (24.7)	65.4 (22.6)	
Difficulty paying attention for long periods of time	55.4 (32.2)	72.0 (25.1)		69.4 (26.4)	71.5 (25.5)	
Difficulty expressing thoughts	60.7 (21.0)	62.4 (23.8)		68.8 (22.0)	61.3 (23.7)	
Difficulty understanding things	50.0 (19.1)	47.4 (23.7)		51.3 (22.8)	46.8 (23.7)	
Can only focus on one thing at a time	69.6 (18.9)	68.9 (27.7)		71.9 (27.8)	68.4 (27.5)	
Unable to focus vision/attention	48.2 (29.3)	49.1 (24.6)		56.9 (27.6)	47.8 (24.2)	
Loss of depth perception	16.1 (23.6)	26.3 (31.5)		30.3 (40.7)	25.0 (30.0)	
Slowness of thought	62.5 (14.4)	58.3 (24.2)		61.3 (26.3)	58.1 (23.8)	
Absent-mindedness	60.7 (21.0)	60.3 (26.9)		64.4 (27.0)	59.8 (26.8)	
Autonomic						
Bladder problems	37.5 (33.1)	29.7 (32.2)		44.4 (35.0)	28.1 (31.3)	*
Irritable bowel problems	64.3 (23.3)	45.2 (31.4)		69.4 (27.3)	43.1 (30.7)	***
Nausea	25.0 (21.7)	32.0 (23.9)		28.8 (20.3)	31.8 (24.1)	
Feeling unsteady on feet	51.8 (18.3)	41.5 (26.3)		50.6 (28.8)	40.3 (25.4)	
Shortness of breath	28.6 (23.6)	38.2 (26.3)		42.5 (29.6)	36.9 (25.7)	
Dizziness/fainting	45.8 (23.3)	38.2 (25.3)		42.1 (26.1)	37.8 (25.2)	
Irregular heart beats	35.4 (9.4)	31.6 (27.1)		37.5 (31.2)	30.6 (26.0)	
Neuroendocrine						
Losing/gaining weight without trying	39.3 (21.0)	37.8 (34.5)		51.3 (32.9)	36.0 (34.0)	
No appetite	19.6 (24.9)	22.2 (23.6)		33.8 (24.7)	20.3 (22.9)	*
Sweating hands	25.0 (36.1)	11.3 (20.6)		17.5 (30.7)	11.0 (20.0)	
Night sweats	50.0 (19.1)	33.9 (30.4)		41.3 (31.2)	33.5 (30.1)	
Cold limbs	53.6 (25.7)	52.1 (30.4)		58.1 (28.2)	51.2 (30.4)	
Chills/shivers	21.4 (17.3)	35.2 (27.9)		33.8 (26.9)	34.3 (27.7)	
Feeling hot/cold for no reason	51.8 (33.4)	51.0 (28.8)		56.3 (29.1)	50.2 (29.0)	
Feeling like you have a high temperature	37.5 (34.6)	31.4 (29.3)		40.0 (36.2)	30.7 (28.5)	
Feeling like you have a low temperature	30.4 (23.8)	28.1 (29.4)		30.0 (33.5)	27.5 (28.6)	
Alcohol intolerance	64.3 (45.3)	47.9 (39.7)		52.5 (45.1)	48.0 (39.2)	
Immune						
Sore throat	35.7 (28.3)	35.6 (23.3)		35.5 (27.1)	35.7 (23.2)	

	Lifelong ^a		Fukuda		Sig.	Lifelong ^b		Fukuda		Sig.
	M	(SD)	M	(SD)		M	(SD)	M	(SD)	
Tender lymph nodes	51.8	(31.0)	42.2	(28.5)		52.5	(28.6)	41.2	(28.5)	
Fever	10.7	(13.4)	14.8	(20.6)		24.4	(25.5)	13.4	(19.5)	
Flu-like symptoms	60.4	(30.0)	52.5	(26.6)		58.6	(30.9)	52.0	(26.3)	
Sensitivity to smells/foods/medications/chemicals	69.6	(35.2)	54.5	(35.8)		63.8	(33.4)	53.5	(35.9)	

* $p < 0.05$;
*** $p < 0.001$