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The Association of Hormone Levels with the Risk of

Chronic Fatigue Syndrome

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The Association of Hormone Levels with the Risk of Chronic Fatigue Syndrome

By

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B.S., Dankook University, 2009
MSPH, Emory University
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2011

Advisor: Michael J. Haber, Ph.D.

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Abstract

The Association of Hormone Levels with the Risk of Chronic Fatigue Syndrome

By Jiin Ahn

Background - Chronic fatigue syndrome (CFS) is characterized by profound fatigue that substantially interferes with daily activities and at least 4 of 8 other symptoms. The condition is more common in women and especially in the 40-50 age range. The causes of CFS illness are not yet understood. Except for cortisol, other hormones have barely been studied in CFS. The objective of this study is to investigate the association of hormones and CFS illness.

Methods - We used the dataset from the first follow up study CFS in GA. Wilcoxon non-parametric tests were applied to the mean differences of hormones between CFS and Non-CFS. Logistic regression and sex-adjusted logistic regression were used to investigate the association of hormones and CFS, and ordinal logistic regression models were used to explore the association of hormones and the functional scores from several SF-36 subscales among women.

Results - There was a significantly higher proportion of women in the CFS group. The means of hormones differed between CFS and Non-CFS by sex, but not by race. The means of cortistol, DHEAS, testosterone, and BMI were significantly different between CFS and Non-CFS persons. After adjusting for sex in the logistic regression analysis, prolactin ($p=0.0232$) and BMI ($p=0.0054$) were the best predictor of CFS. In most SF-36 subscales among women, when CFS status is not considered, some hormones are related to most of the SF-36 subscales. However, among women with CFS, there is no significant association between hormonal levels and SF-36 scores.

Conclusion - We found that there is an association between some hormones and CFS, but there is no significant association between SF-36 scores and hormones in women with CFS.

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Table of Contents

1. Introduction

Chronic fatigue syndrome (CFS) is defined as: (a) severe chronic fatigue for at least 6 months or longer that is not relieved by rest and not due to other known medical or psychiatric conditions associated with fatigue and (b) the concurrent presence of at least four of eight other symptoms. The latter include impaired short-term memory or concentration severe enough to cause substantial reduction in previous levels of occupational, educational, social, or personal activities; sore throat (frequent or recurring), tender cervical or axillary lymph nodes, muscle or multi-joint pain (without redness or swelling), unrefreshing sleep, post-exertional malaise lasting more than 24 hours, headaches of new type, pattern, or severity [1]. CFS is a major health problem, but the causes of CFS have not been discovered yet [2]. Because no certain cause of CFS has been discovered, it is often misdiagnosed as depression, but it is different from depression [3]. However, CFS is defined as long-lasting fatigue, which usually produces tiredness [4]. CFS occurs in both sexes, at all ages, and in all racial and ethnic groups, however it is several times more common in women and most common in the 40-50 year-old age group [5]. Having experienced higher number of stress events in the past has been associated with CFS [2]. Lower levels of the adrenal hormone cortisol or of other hormones can be associated with fatigue. Studies that have examined hormones in CFS have usually addressed one or two hormones with major focus on the adrenal steroid hormones such as cortisol, aldosterone, testosterone, DHEA, DHEAS, androstenedione and estrogens. For example, the level of sex hormones binding globulin drops in men with CFS as compared to men without CFS [6]. Most patients with CFS tend to have lower blood levels of both rennin and aldosterone [7]. In addition to the individual effects of each hormone, it is possible that the combination of abnormal levels of several hormones could be associated with CFS.

2. Background/ literature review

CFS is chronic severe fatigue for at least 6 months without any disease and at least 4 other specific symptoms that occur at the same time. However, the primary cause of chronic fatigue syndrome has not yet been found. It is currently believed that CFS might result from multiple causes, not from a single cause. Although the causes have not been discovered yet, identifying high-risk groups can explain what kinds of patients are more likely to be diagnosed with CFS [8].

In this thesis, we explore the relationship between CFS and hormones. Although sex hormones are not the factor that causes CFS, one study by Robyn [9] found that women with CFS are more likely than men with CFS to experience pain. Furthermore, although one study insisted that there is no significant difference in cortisol levels between patients with CFS and healthy controls [10], most studies reported that cortisol levels were significantly lower in patients with CFS compared to healthy controls [11]. Moreover, dehydroepiandrosterone (DHEA) is a hormone secreted by the adrenal glands, and is a precursor of the sex hormones like estrogen and testosterone [12]. Similarly, to cotisol levels, DHEA levels appear to be related to CFS as well. One study found that DHEA levels were significantly lower in patients with CFS [13].

Laura Solomon and colleagues [14] studied 2762 patients including only CFS and CFS-like, of whom 1795 had CFS. The study showed that there are differences in health and quality of life between persons with CFS and persons with a chronic fatigue syndrome-like illness. They also demonstrated that persons with CFS have reported that they have less energy to do activities compared to persons without CFS. On the other hand, although patients with CFS are less physically active compared to asymptomatic controls, the variation of activities was similar between the two groups [15]. The study of health and quality of life in an Australian CFS population found that CFS has negative impacts on quality of life, and patients with CFS experienced higher level of pain compared to those without CFS. For example, a high proportion of students with CFS reported (>50%) school absence for the

past 6 months [16]. Further, patients with CFS tend to get more stress than those of without CFS [17], and some studies found that higher number of the patients with CFS had personality disorders in depression compared to control groups such as a depression group and healthy controls [18]. In addition to the mental distress, aspects of job performances such as punctuality, public dealing, obedience, efficiency, knowledge of nursing, and interpersonal communication, nurses with CFS had difficulty in working as a nurse compared to normal nurses [19]. One study found that, compared to healthy controls, patients with CFS showed a reduced activation in the brain region related with working memory [20]. Therefore, CFS is associated with decreased functioning in various aspects of daily activities.

Objectives

The primary goal for this thesis is to investigate the association of hormones and characteristics of patients with Chronic Fatigue Syndrome (CFS). The second goal is to explore hormones' effects on health-related items in women with and without CFS.

3. Methods

Data sources and sample

The dataset contains observations from the First Follow study of CFS and unwellnes in GA. The study participants were grouped into four different groups, which are: patients with CFS, Non-CFS controls, excluded because of conditions incompatible with CFS diagnosis, and Insufficient Symptoms/Fatigue (ISF). Although the original dataset consists of four different groups, we consider two groups that are a chronic fatigue syndrome group (CFS) and non-fatigue group (Non-CFS). In this thesis, 752 patients were examined to determine if subjects meeting criteria for CFS have hormonal abnormalities compared to

non-fatigued subjects. Using statistical methods, the association between the level of hormones and CFS will be investigated.

Variables/ Measures

The present study considers 12 different hormones: aldosterone, cortisol, dehydroepiandrosterone sulfate (DHEA_S), estradiol, follicle stimulating hormone (FSH), luteinizing hormone (LH), progesterone, prolactin, sex hormone-binding globulin (shbg), free thyroxin (T4 or T-4), testosterone, tyroid stimulating hormone (TSH). Demographic variables such as sex, age, race, and body mass index (BMI) will be used as covariates and potential confounders. Lastly, the outcome variable of this study is named Wager_Clean_T1, which includes four different groups, but only the CFS group and Non-CFS group are considered as the outcome categories for the logistic regression analyses in this study.

This report also evaluates health status of persons with CFS and Non-CFS by a questionnaire called sf36s (Short-Form-36 Health Survey) (the questionnaire is attached). Each patient scored 11 questions, and each question has a different point scale. A higher score means better health functions, and the maximum score of each variable is 100 (the method of coding and the scales of each formula is attached). Using information gathered through a survey on CFS and Non-CFS respondents, we check whether the responses to each question are different between the two groups. The meanings of questions and variables' names are as follows:

1) Physical functioning (sf36_pf)

2) Role limitations due to physical health problems (sf36_rp)

3) Bodily pain (sf36_bp)

4) Social functioning (sf36_sf)

5) General mental health (covering psychological distress & well-being) (sf36_mh)

6) Role limitations due to emotional problems (sf36_re)

7) Vitality, energy or fatigue (sf36_vef)

8) General health perceptions (sf36_hp)

Statistical Analysis

Descriptive statistics

We calculate the mean, median, and standard deviation of each hormone in each group (CFS and Non-CFS). In addition, through histograms of each hormone by CFS status and sex, we can identify outliers and missing values. We used the Wilcoxon non-parametric test to compare the level of each hormone between CFS and Non-CFS participants by sex and race.

Multivariable analyses

For the first aim of this study, logistic regression analyses, with the group (CFS or non-CFS) as the binary outcome variable, and the 12 hormones as the main exposure variables will be conducted. Covariates will be included to adjust for possible confounding. Manual model selection (dropping independent variables when p-value is less than 0.2) will be used to find a subset of hormones that are most closely related to the differences between persons with and without CFS. After that, we conduct logistic regression analyses by sex to find out which hormones have a significant effect for men and women

We used ordinal logistic regression models to examine the relationships between hormonal levels and health status (as measured by SF-36 subscales' scores) among women with CFS. However, different from the first logistic regression analysis, we only include five hormones (TSH, T4, FSH, LH, progesterone) and demographic variables (sex, age, race, and BMI). Since TSH causes T4, and FSH and LH induce progesterone, we have chosen those five hormones to see how those similar hormones influence on SF-36 subscales' scores among CFS patients differently. We categorized each SF36 subscale into four or less ordinal categories using its quantiles. For example, the first category contains persons who score less than Q1 of the subscale's score, the second category includes persons who scores

between Q1 and Q2, and so on. However, for the subscales SF36_re and SF36_rp, we use original categories for the outcome variables because the number of outcome categories was quite small. Statistical analyses were done using SAS version 9.3 (SAS Institute, Cary, NC). A p-value less than .05 was considered significant.

4. Results

A total of 70 CFS patients and 212 healthy controls (Non-CFS) were included in the study. The two groups were compared regarding sex, age, race, BMI, and each hormone. There is a statistically significant difference between cases and controls by sex ($p<.0001$), but not by race ($p=0.5139$) (**Table 1, 2**). There are statistically significant mean differences between the CFS and Non-CFS groups in cortistol, dheasulf, FSH, LH, testosterone, and BMI (**Table 3**). Comparing between women and men, DHEA_S, FSH, LH, prolactin, SHBG, testosterone, and BMI means are statistically different (**Table 4**).

The final logistic model for comparing CFS and Non-CFS subjects (men and women combined) includes aldosterone, cortisol, progesterone, prolactin, and BMI (cutoff: $p<.2$). The risk of CFS increased with low levels of aldosterone and cortistol, but increased with the higher level of progesterone, prolactin, and BMI (**Table 6**). When we look at logistic models by sex, the final model for women includes aldosterone, cortisol, progesterone, prolactin, testosterone, TSH and BMI (cutoff: $p<.2$). The risk of CFS increased with higher levels of aldosterone, cortistol, testosterone, and TSH, and increased with lower levels of the rest of covariates (**Table 7**). On the other hand, the model for men includes LH (luteinizing hormone), progesterone, and TSH. In this model, higher values of LH, progesterone and TSH were associated with a lower risk of CFS (**Table 8**).

For the SF-36 analysis, the means of the scores for the various SF-36 subscales are very different between CFS and Non-CFS ($p<.0001$) (**Table 9**). In the final logistic regression including all patients with and without CFS, Bodily pain was associated with

TSH), progesterone and BMI (cutoff: p<.2). The general health perceptions score was associated with TSH (thyroid stimulating hormone), progesterone, and BMI in the final model. The final model for General mental health (sf36_mh) included TSH and progesterone. In addition, progesterone, age, and BMI are included as significant factors in the final model of physical functioning (sf36_pf). The final model for Role limitations due to emotional problems (sf36_re) only includes progesterone and BMI. The final logistic model of Role limitations due to physical health problems (sf36_rp) included FSH, progesterone, and BMI. The final model for Social functioning (sf36_sf), included progesterone and BMI. Lastly, the hormones TSH (tsh3rdge), LH (luteinizing hormone), and progesterone, along with the variables age, and BMI were included in the final model for sf36_vef (Vitality, energy or fatigue) (**Table 10**).

For the group of patients with CFS only, the final logistic regression models of each SF-36 variable are as follows (most time 0.2 was used as cutoff, but when none of covariates had a p-value less than 0.2, then we dropped covariates if the p-value was less than 0.5). The final model for role limitations due to physical problems (SF36_rp) included FSH, LH, age, and T4. The final model for the physical functioning score included LH, age, and BMI. Two models - for vitality/energy score (SF36_Vef) and for mental health score (SF36_mh) included only TSH and BMI. The models for two other SF36 subscales –bodily pain and health perception included only T4, while the model for role limitations due to emotional problems (SF36_re) included only TSH (**Table 11**).

5. Discussion

In the current study, we found that there is an association between CFS status and sex, so that sex hormones might influence the risk of CFS. Because the means of levels of dehydroepiandrosterone sulfate, follicle stimulating hormone, lluteinizing hormone,

prolactin, sex hormone-binding globulin, and testosterone were statistically different by sex, we considered those hormones are influenced by sex. In addition to sex hormones, our finding also suggests that the level of cortisol, DHEA_S, and testosterone may explain some of the differences between persons with and without CFS. Although cortisol is not related to sex, like the previous studies, our study also found lower mean level of cortisol in CFS persons compared to Non-CFS controls. In addition to hormones, BMI has been one of potential risk factors for CFS since the means of BMI was significantly higher in the CFS group than in the non-CFS group. However, the higher BMI found in the CFS group may be a consequence of the illness as CFS persons have limited physical activity due to the nature of their illness.

Through logistic regression analyses, we conclude that prolactin and BMI were the two most important predictors of CFS. Our study indicated that persons with CFS are more likely to have higher prolactin and higher BMI compared to non-CFS persons..

For the SF-36 analyses, progesterone and BMI were related to each of the functional subscales' scores when all the study participants were included, regardless of CFS status. However, when we only included CFS persons in the logistic regression analyses, hormones did not associate with the SF-36 subscale scores except for sf36_re (Role limitations due to emotional problems) and sf36_rp (Role limitations due to physical health problems). CFS persons who have lower scores on role limitations due to emotional problems are more likely to have higher TSH, and CFS persons who have lower scores on role limitations due to physical health problems are more likely to have higher FSH, LH, and older age.

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7. Appendix

A: Tables

Table 1. Chisq-test by gender

Table of Wagner_Clean_T1 by SEX				
	SEX(SEX)			
Frequency Row Pct	Women	Men	Total	Pr* >= F
CFS	64	6	70	2.486E-05
	91.43	8.57		
Non-CFS	143	69	212	
	67.45	32.55		
Total	207	75	282	

* Fisher's Exact Test

Table 2. Chisq-test by race

Table of Wagner_Clean_T1 by RACE				
	RACE(RACE)			
Frequency Row Pct	Non-White	White	Total	Pr* >= F
CFS	14	56	70	0.5139
	20.00	80.00		
Non-CFS	41	171	212	
	19.34	80.66		
Total	55	227	282	

* Fisher's Exact Test

Table 3. Distribution of hormones and demographic factors by the status of CFS

Variable	CFS			Non-CFS			P*
	N	Mean	Std Error	N	Mean	Std Error	
aldosterone	69	4.86	0.45	212	7.30	1.33	0.2247
cortisol	69	11.48	0.58	212	12.90	0.31	0.0163
DHEAS	69	88.36	8.01	212	112.33	4.62	0.0030
estradiol	68	62.91	12.41	212	55.74	4.66	0.8349
fsh	68	28.79	3.72	210	21.55	1.95	0.0550
lh	69	16.65	2.08	212	13.12	1.02	0.0744
progesterone	64	2.09	0.44	204	1.41	0.20	0.6571
prolactin	69	9.91	0.86	212	8.47	0.35	0.3867
shbg	69	49.26	4.98	212	46.72	2.52	0.7259
t4	70	1.15	0.03	212	1.15	0.01	0.6694
testosterone	65	62.35	12.78	204	152.86	13.23	<.0001
tsh	69	1.69	0.12	212	1.84	0.08	0.2021
AGE	70	48.04	1.19	212	47.67	0.65	0.7415
BMI	70	28.90	0.62	212	26.96	0.35	0.0082

* P values of Wilcoxon's non-parametric two-sample test

Table 4. Distribution of hormones and demographic factors by gender

Variable	Women			Men			P*
	N	Mean	Std Error	N	Mean	Std Error	
aldosterone	206	7.17	1.37	75	5.39	0.48	0.8882
cortisol	206	12.67	0.35	75	12.22	0.41	0.8415
DHEAS	206	89.91	3.91	75	151.85	8.79	<.0001
estradiol	205	67.05	6.18	75	31.31	1.39	0.4474
fsh	203	30.12	2.19	75	4.94	0.45	<.0001
lh	206	17.72	1.16	75	3.75	0.23	<.0001
progesterone	196	1.89	0.25	72	0.71	0.03	0.7296
prolactin	206	9.64	0.44	75	6.57	0.31	<.0001
shbg	206	55.57	2.84	75	24.73	1.20	<.0001
t4	207	1.15	0.01	75	1.15	0.02	0.9122
testosterone	197	36.42	2.17	72	389.76	17.52	<.0001
tsh	206	1.83	0.09	75	1.73	0.10	0.9049
AGE	207	47.33	0.68	75	48.96	1.04	0.2133
BMI	207	26.90	0.38	75	28.95	0.51	<.0001

* P values of Wilcoxon's non-parametric two-sample test

Table 5. Distribution of hormones and demographic factors by race

Variable	Non-White			White			P*
	N	Mean	Std Error	N	Mean	Std Error	
aldosterone	55	4.96	0.72	226	7.12	1.25	0.0228
cortisol	55	13.09	0.69	226	12.42	0.30	0.3137
DHEAS	55	113.44	10.44	226	104.74	4.34	0.8322
estradiol	54	75.94	11.43	226	53.07	5.02	0.0311
fsh	55	17.46	2.99	223	24.77	2.03	0.0537
lh	55	11.62	2.02	226	14.56	1.04	0.0186
progesterone	50	2.21	0.56	218	1.43	0.19	0.1590
prolactin	55	10.20	1.01	226	8.48	0.34	0.0221
shbg	55	48.51	5.80	226	47.06	2.43	0.6102
t4	55	1.13	0.02	227	1.16	0.01	0.4360
testosterone	51	117.39	25.02	218	134.17	11.93	0.4721
tsh	55	1.60	0.11	226	1.85	0.08	0.1413
AGE	55	44.89	1.31	227	48.46	0.63	0.0131
BMI	55	28.18	0.71	227	27.26	0.35	0.1719

* P values of Wilcoxon's non-parametric two-sample test

Table 6. Logistic regression model comparing CFS and Non-CFS

Parameter	Estimate	95% Wald Confidence Limits		Pr > ChiSq
Intercept	2.6810			0.0104
aldosterone	0.0784	0.993	1.178	0.0729
cortisol	0.0596	0.986	1.142	0.1127
progesterone	-0.0989	0.822	0.998	0.0446
prolactin	-0.0681	0.889	0.981	0.0069
BMI	-0.0668	0.883	0.991	0.0224

Table 7. Logistic regression model comparing CFS and Non-CFS women

Parameter	Estimate	95% Wald Confidence Limits		Pr > ChiSq
Intercept	1.7042			0.1698
aldosterone	0.0644	0.974	1.168	0.1658
cortisol	0.0774	0.999	1.169	0.0529
progesterone	-0.0797	0.834	1.022	0.1242
prolactin	-0.0624	0.890	0.992	0.0232
testosterone	0.0221	0.996	1.049	0.0991
tsh	0.2229	0.911	1.714	0.1669
BMI	-0.0924	0.854	0.973	0.0054

Table 8. Logistic regression model comparing CFS and Non-CFS men

Parameter	Estimate	95% Wald Confidence Limits		Pr > ChiSq
Intercept	7.3440			0.0103
lh	-0.2596	0.519	1.147	0.2000
progesterone	-2.9933	0.001	2.405	0.1296
tsh	-0.8864	0.135	1.262	0.1206

Table9. Sf-36 scores for each group (mean and standard error)

Variable	CFS			NF			P*
	N	Mean	Std Error	N	Mean	Std Error	
sf36_bp	64	38.53	2.13	143	84.16	1.23	<.0001
sf36_hp	64	45.67	2.37	143	85.92	1.01	<.0001
sf36_mh	64	60.31	2.65	143	88.62	0.66	<.0001
sf36_pf	64	59.45	3.12	143	96.15	0.47	<.0001
sf36_re	64	54.17	5.48	143	100.00	0.00	<.0001
sf36_rp	64	34.38	4.96	143	99.48	0.30	<.0001
sf36_sf	64	48.83	2.55	143	98.78	0.31	<.0001
sfF36_vef	64	23.13	1.89	143	77.62	1.05	<.0001

Table 10. SF-36 logistic regression model with women from both groups

	Parameter	Gr*	Catg**	Estimate	Pr > ChiSq
Sf36_bp	Intercept	4	>=100	0.3941	0.5190
	Intercept	3	<100	1.5962	0.0097
	Intercept	2	<84	2.6916	<.0001
	Intercept	1	<61		
	tsh			0.2850	0.0058
	progesterone			-0.0731	0.0506
	BMI			-0.0693	0.0013
Sf36_hp	Intercept	4	>=92	0.3842	0.5324
	Intercept	3	<92	2.2379	0.0004
	Intercept	2	<82	2.9046	<.0001
	Intercept	1	<67		
	tsh			0.2027	0.0357
	progesterone			-0.0463	0.2134
	BMI			-0.0777	0.0004

Sf36_mh	Intercept	4	>=92	-0.4770	0.0415
	Intercept	3	<92	0.2785	0.2319
	Intercept	2	<88	1.0343	<.0001
	Intercept	1	<76		
	tsh			0.1860	0.0824
	progesterone			-0.0540	0.1437
sf36_pf	Intercept	4	=100	4.7012	<.0001
	Intercept	3	<100	5.5187	<.0001
	Intercept	2	<95	6.5529	<.0001
	Intercept	1	<85		
	lh			-0.0296	0.0003
	progesterone			-0.1248	0.0017
	AGE			-0.0338	0.0146
	BMI			-0.1014	<.0001
sf36_re	Intercept	4	>=67	3.8228	0.0001
	Intercept	3	<67	3.9960	<.0001
	Intercept	2	<34	4.4876	<.0001
	Intercept	1	<1		
	progesterone			-0.0463	0.3726
	BMI			-0.0673	0.0453
sf36_rp	Intercept	5	100	4.6054	<.0001
	Intercept	4	75	4.7591	<.0001
	Intercept	3	50	4.9887	<.0001
	Intercept	2	25	5.4527	<.0001
	Intercept	1			
	fsh			-0.0134	0.0103
	progesterone			-0.1004	0.0395
	BMI			-0.1013	0.0007
sf36_sf	Intercept	8	100	3.0483	<.0001
	Intercept	7	87.5	3.4872	<.0001
	Intercept	6	75	3.6716	<.0001
	Intercept	5	62.5	3.9583	<.0001
	Intercept	4	50	4.6828	<.0001
	Intercept	3	37.5	5.1479	<.0001
	Intercept	2	25	5.9459	<.0001
	Intercept	1	12.5	7.2185	<.0001
	Intercept				
	progesterone			-0.0723	0.0627
	BMI			-0.0769	0.0021
sfF36_vef	Intercept	4	>=85	-1.0270	0.2000
	Intercept	3	<85	0.0618	0.9384
	Intercept	2	<75	1.2070	0.1330
	Intercept	1	<45		
	tsh			0.1980	0.0475
	lh			-0.0222	0.0063
	progesterone			-0.0683	0.0808
	AGE			0.0322	0.0144
	BMI			-0.0497	0.0232

* Gr : group1 is reference group

**Catg: Gr was categorized by Catg

Table 11. SF-36 logistic regression model for women with CFS

	Parameter	Gr	Freq*	Estimate	Pr > ChiSq
Sf36_bp	Intercept	4	1	-2.8583	0.1314
	Intercept	3	1	-2.1502	0.2217
	Intercept	2	7	-0.5191	0.7549
	Intercept	1	61		
	t4			-1.2351	0.3985
Sf36_hp	Intercept	3	3	0.6864	0.8003
	Intercept	2	5	1.7779	0.5091
	Intercept	1	56		
	t4			-3.3218	0.1770
	progesterone			0.0348	0.7603

Sf36_mh	Intercept	4	7	-3.8631	0.0928
	Intercept	3	5	-3.2263	0.1572
	Intercept	2	5	-2.7753	0.2217
	Intercept	1	52		
	tsh			-0.3357	0.2877
	AGE			0.0573	0.2974
	BMI			-3.8631	0.0928
sf36_pf	Intercept	3	6	1.1518	0.5556
	Intercept	2	13	2.5974	0.1857
	Intercept	1	50		
	lh			-0.0154	0.3906
	AGE			-0.0345	0.2357
	BMI			-0.0589	0.2729
sf36_re	Intercept	4	30	0.6688	0.1551
	Intercept	3	5	0.9746	0.0412
	Intercept	2	13	1.8294	0.0004
	Intercept	1	21		
	tsh			-0.5840	0.0176
sf36_rp	Intercept	100	14	3.6442	0.0925
	Intercept	75	3	3.9565	0.0687
	Intercept	50	8	4.6405	0.0346
	Intercept	25	13	5.6119	0.0119
	Intercept	0	30		
	t4			-1.6253	0.2475
	fsh			-0.0688	0.0060
	lh			0.1482	0.0032
	AGE			-0.0787	0.0120
sf36_sf	Intercept	100	1	-2.6393	0.1255
	Intercept	87.5	2	-1.5097	0.3214
	Intercept	75	9	0.0373	0.9795
	Intercept	62.5	11	0.9373	0.5177
	Intercept	50	22	2.3529	0.1102
	Intercept	37.5	8	2.9625	0.0466
	Intercept	25	8	3.8669	0.0111
	Intercept	12.5	5	5.1990	0.0015
	Intercept		2		
	t4			-1.2480	0.3142
	fsh			-0.0165	0.1567
	lh			0.0187	0.3672
sfF36_vef	Intercept	2	9	-5.2618	0.0472
	Intercept	1	60		
	tsh			-0.3654	0.3975
	lh			-0.0103	0.7149
	BMI			0.1354	0.0866

*Freq: the number of persons in each group(Gr)

Table 12. SF-36 logistic regression model for NF women

	Parameter		Estimate	Pr > ChiSq
Sf36_bp	Intercept	4	2.2452	0.0202
	Intercept	3	3.7849	0.0001
	Intercept	2	6.2177	<.0001
	tsh		0.3232	0.0159
	progesterone		-0.0975	0.0428
	AGE		-0.0510	0.0008
	BMI		-0.0365	0.1650
Sf36_hp	Intercept	4	0.3387	0.6272
	Intercept	3	2.5551	0.0004
	Intercept	2	3.8858	<.0001
	tsh		0.2014	0.0671
	BMI		-0.0651	0.0108
Sf36_mh	Intercept	4	-1.2345	0.1174
	Intercept	3	-0.2195	0.7797
	Intercept	2	1.4490	0.0774
	tsh		0.2638	0.0667
	tsh		-0.00953	0.3505
	fsh		0.0200	0.3352
	lh		0.0478	0.4341
	progesterone		0.0321	0.2343
	BMI		-1.2345	0.1174
sf36_pf	Intercept	4	6.3298	<.0001
	Intercept	3	7.4414	<.0001
	Intercept	2	9.7920	<.0001
	fsh		0.0229	0.0379
	lh		-0.0591	0.0045
	progesterone		-0.1106	0.0617
	AGE		-0.0802	<.0001
	BMI		-0.0636	0.0295
sf36_rp	Intercept		8.7743	0.0337
	t4free_		-2.6272	0.1728
	tsh3rdge_		2.2490	0.0274
	progesterone		-0.1976	0.2166
	BMI		-0.1384	0.1373
sf36_sf	Intercept		3.2803	0.0104
	fsh		-0.0343	0.1422
	lh		0.0941	0.0843
	BMI		-0.0516	0.2456
sfF36_vef	Intercept	4	-2.7380	0.0003
	Intercept	3	-1.3502	0.0640
	Intercept	2	1.7874	0.0370
	tsh		0.2834	0.0259
	lh		-0.0125	0.1765
	AGE		0.0403	0.0059

B: SF-36 QUESTIONNAIRE ITEMS

1. In general, would you say your health is:

(Circle One Number)

Excellent	1
Very good	2
Good	3
Fair	4
Poor	5

2. **Compared to one year ago**, how would you rate your health in general **now**?

(Circle One Number)

Much better now than one year ago	1
Somewhat better now than one year ago	2
About the same	3
Somewhat worse now than one year ago	4
Much worse now than one year ago	5

The following items are about activities you might do during a typical day.
Does **your health now limit you** in these activities? If so, how much?

(Circle One Number on Each Line)

	Yes, Limited a Lot	Yes, Limited a Little	No, Not Limited at All
3. **Vigorous activities,** such as running, lifting heavy objects, participating in strenuous sports	1	2	3
4. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
5. Lifting or carrying groceries	1	2	3
6. Climbing **several** flights of stairs	1	2	3
7. Climbing **one** flight of stairs	1	2	3
8. Bending, kneeling, or stooping	1	2	3
9. Walking **more than a mile**	1	2	3
10. Walking **several blocks**	1	2	3
11. Walking **one block**	1	2	3
12. Bathing or dressing yourself	1	2	3

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

(Circle One Number on Each Line)

		Yes	No
13.	Cut down the **amount of time** you spent on work or other activities.....	1	2
14.	**Accomplished less** than you would like	1	2
15.	Were limited in the **kind** of work or other activities	1	2
16.	Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

During the **past 4 weeks,** have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

(Circle One Number on Each Line)

		Yes	No
17.	Cut down the **amount of time** you spent on work or other activities	1	2
18.	**Accomplished less** than you would like	1	2
19.	Didn't do work or other activities as **carefully** as usual	1	2

20. During the **past 4 weeks,** to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

(Circle One Number)

Not at all.....	1
Slightly	2
Moderately.....	3
Quite a bit.....	4
Extremely.....	5

21. How much **bodily** pain have you had during the **past 4 weeks**?

(Circle One Number)

None.....	1
Very mild.....	2
Mild.....	3
Moderate.....	4
Severe.....	5
Very severe.....	6

22. During the **past 4 weeks,** how much did **pain** interfere with your normal work (including both work outside the home and housework)?

(Circle One Number)

Not at all	1
A little bit	2
Moderately	3
Quite a bit	4
Extremely	5

These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the **past 4 weeks** .

(Circle One Number on Each Line)

		All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
23.	Did you feel full of pep?	1	2	3	4	5	6
24.	Have you been a very nervous person?	1	2	3	4	5	6
25.	Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
26.	Have you felt calm and peaceful?	1	2	3	4	5	6
27.	Did you have a lot of energy?	1	2	3	4	5	6
28.	Have you felt downhearted and blue?	1	2	3	4	5	6
29.	Did you feel worn out?	1	2	3	4	5	6
30.	Have you been a happy person?	1	2	3	4	5	6
31.	Did you feel tired?	1	2	3	4	5	6

32. During the **past 4 weeks,** how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?

(Circle One Number)

All of the time	1
Most of the time	2
Some of the time	3
A little of the time	4
None of the time	5

How TRUE or FALSE is each of the following statements for you.

(Circle One Number on Each Line)

		Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
33.	I seem to get sick a little easier than other people	1	2	3	4	5
34.	I am as healthy as anybody I know.	1	2	3	4	5
35.	I expect my health to get worse.	1	2	3	4	5
36.	My health is excellent.	1	2	3	4	5