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Delineating Psychological and Biomedical Profiles in a Heterogeneous Fibromyalgia Population Using Cluster Analysis

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Abstract

The heterogeneity of patients meeting American College of Rheumatology (ACR) criteria for a diagnosis of fibromyalgia (FM) challenges our ability to understand the underlying pathogenesis and to optimize treatment of this enigmatic disorder. Our goal was to discern clinically relevant subgroups across multiple psychological and biomedical domains to better characterize the phenomenology of FM. Women meeting 1990 ACR criteria for FM (N=107) underwent psychological (childhood trauma, mood, anxiety, and stress) and biomedical (neuroendocrine, immune, metabolic) testing. Cluster analysis identified four distinct subgroups. Subgroups I, II and III exhibited profiles that included high psychological distress. Subgroup I was further distinguished by a history of childhood maltreatment and hypocortisolism, and these women reported the most pain and disability. Subgroup II evinced more physiological dysregulation and also reported high levels of pain, fatigue, and disability. Subgroup III was characterized by normal biomarkers and reported intermediate pain severity with higher global functioning. Subgroup IV was distinguished by their psychological wellbeing, reporting less disability and pain. Our findings underscore the heterogeneity of both psychological and physiological features among FM patients presenting with nearly identical TP counts. This subgroup categorization is compatible with hypothesized pathogenetic mechanisms of early trauma, stress system dysregulation, and pro-inflammatory bias, each prominent in some but not all FM patients. Appreciation of distinct FM subgroup features is invaluable for selecting the most appropriate treatment modalities.

Keywords

Fibromyalgia; Pain; Distress; Maltreatment; Immune; Metabolic; neuroendocrine [6 MeSH terms]

Introduction

Although the term fibromyalgia (FM) is widely used, it remains a controversial and enigmatic diagnosis. In 1990, the American College of Rheumatology (ACR) established diagnostic criteria requiring a history of chronic widespread musculoskeletal pain with pain

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on digital palpation of at least 11 of 18 possible tender points [1]. However, individuals meeting these FM criteria present with widely divergent degrees of FM-associated emotional distress, fatigue, and disability, and many have other comorbid medical and psychiatric disorders [2, 3]. For at least some FM patients, childhood trauma and/or contemporaneous life stress may contribute to symptom etiology and progression [4]. Although the underlying pathogenesis remains elusive, a process of central sensitization appears to contribute to pain symptomatology [5]. The extant research has also documented neuroendocrine and immune alterations in FM patients, but these findings are not universally found [6].

This variation in presentation contributes to a lack of agreement about how best to treat FM. While many pharmacologic and psychosocial interventions have been evaluated, none benefit a majority of patients. Increasingly, there is a growing consensus that FM is not one discrete entity but a spectrum of somatic pain and psychic distress, which overlaps other conditions [3]. Recently, this view led the ACR to introduce alternative diagnostic criteria based on additional clinical features of FM, including fatigue, cognitive, and somatic symptoms [7]. The purpose of our project was to examine the delineation of subgroups based on the diverse psychological and physiological phenomena seen in clinical settings and also identified in prior research.

Recognizing the importance of a better nosology for FM, Turk et al. [8] argued for an empirical delineation of more homogeneous subgroups and they were the first to apply the statistical technique of cluster analysis to this population. Cluster analysis generates distinctive subgroups, or clusters of individuals, with similar attributes. Applying cluster analysis to the Multidimensional Pain Inventory in FM patients yielded three psychosocial profiles with varying levels of emotional distress described as Dysfunctional, Interpersonally Distressed, and Adaptive Copers [9]. Subgroup membership predicted degrees of pain, perceived disability [9], pain behavior [10] and response to a multidisciplinary treatment program [11]. Categorizing FM patient profiles based on mood, coping style, and evoked pain responses, Giesecke et al. [12] identified three clusters. High catastrophizers with mood disturbances were highly tender, while those with moderate levels of catastrophizing and mood disturbance had relatively low tenderness, and a third, small subgroup with normal mood and coping were somewhat surprisingly the most tender. A recent study based on symptoms from the Fibromyalgia Impact Questionnaire (FIQ), identified two subgroups, one with high levels of psychological distress and self-reported pain and the other free from depression and anxiety [13]. Both FM subgroups exhibited similar hyperalgesia and allodynia to induced pain. Thus, it appears that FM patients fall into distinct subgroups based on the level of emotional distress and pain-related behaviors. We extended this approach by including a history of childhood maltreatment and additional biological features associated with FM in our analyses.

A history of childhood maltreatment has been hypothesized to play an important role in the development and/or maintenance of FM [4], and may help to explain discrepancies in the literature on hypothalamic-pituitary-adrenal axis (HPA) activity in FM. These reports include findings of hypocortisolism as well as normal [14] and elevated cortisol secretion [15]. Childhood abuse and familial dysfunction has been reported in up to 64% of FM patients [16] and can be associated with a flattening of the diurnal cortisol rhythm [17]. Failure to separate FM patients into groups with and without childhood maltreatment could result in the inconsistent cortisol findings that obscure conclusions about abuse-related sequelae. Therefore, we determined whether there was a history of childhood emotional, physical and/or sexual maltreatment, and incorporated this information into our cluster analyses.

Beyond dysregulation of HPA activity, many other biologic abnormalities have been identified in some, but not all, FM patients. Consistent with a contributing role for neuroendocrine dysfunction in FM pathogenesis, many FM patients have mildly deficient growth hormone (GH) levels [18] and low testosterone [19]. In a prior analysis, we found that women with FM have a 5-fold increased risk of meeting criteria for metabolic syndrome even when young to middle-aged [20]. Yet only a subgroup of about 20% of the assessed women actually met full criteria. Dysregulated immune and inflammatory responses are also evident in some FM patients, including impaired natural killer (NK) cell activity [21], elevated levels of antinuclear antibodies (ANA) and Westergren sedimentation rates (ESR) [22]. Therefore, we included biomedical measures of stress and neuroendocrine activity (cortisol, GH, testosterone), metabolic functioning (BMI, Hemoglobin A_{1C} (HA_{1C}), cholesterol, creatinine clearance), and immune/inflammatory status (ANA and NK cell levels, ESR) in our cluster analyses. Each biomarker had been reported to be abnormal in at least a subset of FM patients. Yet it is not known if the abnormalities cohere in particular individuals or with the psychological dysregulation in a way that contributes to pathogenesis or severity of FM symptoms.

The primary aim was to discern homogeneous subgroups with distinctive psychological and biomedical profiles. We also assessed how these empirically derived FM subgroups differed in their experiences of pain, fatigue, and inability to perform daily tasks, which impact quality of life.

Methods

Study sample and design

Data for the 14 cluster variables were available for 107 women with FM who had participated in 2 phases of the University of Wisconsin Mind/Body Center's study of FM. Phase 1 was designed to assess the psychological and physiological phenomenology of FM [23]. The same phenomenological assessments were attained for Phase 2 participants at baseline prior to a later trial of training in mindfulness-based stress reduction. Only their baseline data were included to preclude potential effects of the intervention. To be eligible, women between 21 and 49 years of age must have been diagnosed with FM by a rheumatologist or primary care physician and met the 1990 ACR diagnostic criteria for FM at our evaluation, which re-confirmed the diagnosis by examination of the 18 specified tender points (TP) [20]. The 2010 ACR criteria were not applied because the study was conducted prior to their publication. Demographic information and TP counts from our examination information are shown in Table 1. This study was limited to females because FM may manifest differently in men [24]. Phase 1 data had found no differences in TP counts or other FM-related pain, including dolorimetry and pain diaries, across the menstrual cycle and thus menstrual timing was not included in the current analyses [23]. Exclusion criteria included having any other pain-inducing illness, uncontrolled endocrine disorders (e.g., diabetes, polycystic ovary syndrome), autoimmune or other rheumatologic conditions, malignancy, substance abuse, severe psychiatric disorders (e.g., psychotic disorders or active suicidality), severe physical impairment (i.e., unable to maintain employment or education) and use of steroid, narcotic, or antipsychotic medications. All participants were recruited from the community by advertisements in a local newspaper. Written informed consent was obtained from all participants, as approved by the Institutional Review Board.

Cluster Variable Measures

Psychological Measures—Childhood maltreatment was assessed with *The Childhood Trauma Questionnaire* (CTQ), a 28-item self-report inventory of childhood emotional and

physical abuse and neglect, and sexual abuse [25]. The CTQ is well validated and has been shown repeatedly to perform well with community and clinical adult samples [26, 27]. The total maltreatment score, a summary score reflecting both frequency and severity of emotional, physical, and sexual maltreatment, was used in this analysis. The *Perceived Stress Scale* (PSS), a brief scale with substantial reliability and validity, was self-administered, and used as a global measure of distress during the prior week [28]. The General Distress from Anxiety Symptoms subscale of the *Mood and Anxiety Symptom Questionnaire-Short Form* (MASQ) was employed as a measure of anxiety over the last week [29]. The *Positive and Negative Affect Schedule* (PANAS), a well validated instrument consisting of two 10-item scales, provided two dimensions of mood, Positive and Negative Affect [29]. We used the ratio of Positive-to-Negative affect as a reflection of the balance of mood states over the previous week.

Biomedical Measures—Anthropomorphic measurements were performed by nurses at our General Clinical Research Center. Body Mass Index (BMI) was calculated as: weight (kg.)/(height (m))². Phlebotomy for blood analyses was performed between 0700–0900. An overnight urine collection began 12 h prior to the participants' wake-up time, thereby minimizing the effects of differential levels of physical activity. Urinary free cortisol concentrations (mg) were determined by high-pressure liquid chromatography (HPLC) and adjusted by creatinine (g) for body size and partial voids, providing an integrated measure of nighttime HPA axis activity. Creatinine clearance was calculated based on 24 h values: (urinary creatinine × volume of urine) / (plasma creatinine × time (24 h)). Assays for hemoglobin A_{1C} (HA_{1C}), ANA, ESR, serum cholesterol, and creatinine were performed by the University Hospital's clinical laboratories. NK cell counts were determined by immunophenotyping, using monoclonal antibodies to enumerate the number of CD16+/CD56+ cells. GH and testosterone levels were determined by radioimmunoassay (RIA).

FM Experiential Measures

Pain—A Visual Analogue Scale (VAS) was used to assess subjective perception of global pain based on a 10-cm line (0, no pain to 10, pain as bad as it could be). **Fatigue**. A subset of items from the *Piper Fatigue Scale* a reliable and valid measure of fatigue, were used to assess the extent to which fatigue was felt to be abnormal, destructive, and unpleasant on a scale of 0-to-10 [30]. Low scores reflected higher levels of fatigue. This measure was administered to a subgroup of participants (N = 42) as it was added after the study was ongoing. **Global Functioning** was determined during a Structured Clinical Interview for DSM-IV (SCID) with the interviewer rating occupational, social, and psychological functioning from 1 to 100 on the Global Assessment of Functioning (GAF) scale [31]. **Functional Ability**. The *Fibromyalgia Impact Questionnaire* (FIQ) is the standard instrument used to gauge impairment of functional abilities. We used the 10 FIQ items that assess how FM symptoms impact the ability to complete tasks of daily living during the prior week (e.g., interfere with shopping, laundry, visiting friends, etc.) [32].

Statistical Analysis

Our goal was to delineate homogenous and maximally distinct subgroups. Therefore, a cluster analytical procedure that formed subgroups of individuals with similar psychobiological profiles was used. The SLEIPNER 2.1 program was employed because it generates reliable clusters. It was conducted with Ward's method, standardized scores, and the squared Euclidean distance to determine similarities among individuals. Ward's method, a hierarchical agglomerative technique, was chosen because it maximizes the differences between clusters and minimizes the differences between individuals within each cluster. The final analysis was conducted on 93 participants because 14 were identified by the residue procedure as multivariate outliers, meaning that each could not be readily categorized with

other individuals (squared Euclidean distance threshold of .90) and so did not fit into the emergent cluster solution. The residue procedure minimizes the influence of outliers and multivariate outliers generating the most stable cluster solutions [33].

Subgroup differences for each of the 14 cluster variables and for the measures of FM severity (pain, fatigue, GAF, and functional ability) were evaluated with post hoc univariate analyses of variance (ANOVA). To minimize the potentially large number of secondary post hoc comparisons, planned orthogonal t-test contrasts were used to determine which subgroups differed from the other three. Post hoc analyses were conducted using SPSS 10, with a two-tailed alpha = 0.05. Cortisol and growth hormone values were log-transformed and ANA titers were rank-ordered to normalize the distributions.

Results

A 4-cluster solution proved to be the best fit for these data because it generated the most interpretable profiles and also achieved a smaller error sum of squares (4.35%) compared to the 3- and 2-cluster solutions (5.34% and 13.07%, respectively). Expanding from a 4- to a 5-cluster solution did not substantially reduce the error sum of squares (which would indicate a reduction in unexplained variance). A statistical Relocate procedure was used to transfer individuals between clusters to achieve a better fit and more reliable cluster solution. This last refinement resulted in a reassignment of 28 individuals to attain the most homogenous clusters and a further reduction in the error sum of squares (3.86%). The final solution contained 4 relatively homogenous clusters with homogeneity coefficients ranging from 1.37 to 1.86 (illustrated in Figure 1).

A series of univariate ANOVA's confirmed that the 4 subgroups differed significantly from each other on 13 out of 14 cluster variables, P s < .03, with the single exception being HA_{1c} (Table 2). Differences between the 4 clusters were not attributable to demographic characteristics (Table 1). The only significant demographic difference was that individuals in Cluster III were slightly younger (by an average of 5 years, $t = 2.97$, $P < .005$).

As can be seen in Table 2, individuals in Cluster I were most likely to have reported childhood maltreatment ($t = 10.54$, $P < .001$), had the highest perceived stress ($t = 5.61$, $P < .001$), and lowest ratio of positive-to-negative affect ($t = 4.75$, $P < .001$). They also had lower testosterone ($t = 1.98$, $P = .05$) and low ANA titers ($t = 2.27$, $P < .03$). These patients were designated as the *Maltreated* subgroup.

Women in Cluster II had the highest ANA titers ($t = 4.06$, $P = .001$) and total cholesterol levels ($t = 3.96$, $p < .001$), larger BMI values ($t = 2.21$, $P < .04$), with trends toward the highest ESR ($t = 2.02$, $P = .056$) and lowest creatinine clearance ($t = 1.85$, $P = .067$). These patients also had the lowest NK cell numbers ($t = 3.95$, $P < .001$), cortisol ($t = 2.78$, $P < .007$), growth hormone ($t = 3.20$, $P < .002$), and testosterone levels ($t = 3.80$, $P < .001$). Given that they were distinctive on nearly every biological index measured, Cluster II was designated as having Dysregulated Biology. This group reported the highest levels of anxiety ($t = 2.92$, $P = .005$) with high perceived stress ($t = 2.91$, $P < .007$), and negative-to-positive affect ($t = 3.28$, $P < .003$).

In contrast, Cluster III was distinguished from the others by normal BMI ($t = 4.70$, $P < .001$), cholesterol ($t = 4.78$, $P < .001$), ESR ($t = 3.86$, $P < .001$), and HA_{1c} levels ($t = 2.33$, $P = .02$). These women had the highest GH ($t = 2.68$, $P < .009$) and testosterone levels ($t = 4.18$, $P < .001$) with a trend for higher cortisol ($t = 1.91$, $P = .06$). Because their metabolic and neuroendocrine measures appeared to be better regulated without indications of inflammation, this cluster was named Normal Biology. Normal Biology patients had

experienced little childhood maltreatment ($t = 4.34$, $P < .001$), yet reported high anxiety levels ($t = 2.01$, $P = .047$).

Cluster IV reported the most positive relative to negative affect ($t = 7.40$, $P < .001$) along with the lowest levels of perceived stress ($t = 8.95$, $P < .001$) and anxiety ($t = 11.01$, $P < .001$). Because of their more optimal psychological profile, this group was labeled Positive Outlook. They also tended to excrete the highest levels of cortisol, without evidence of hypocortisolemia ($t = 1.90$, $P = .06$).

Univariate ANOVA indicated that there were no differences in TP counts between the 4 clusters ($F(3,89) = .21$, NS). All women met ACR diagnostic criteria of having 11 or more TP. Nonetheless, discerning these four subgroups proved to have statistically predictive value for understanding variation in patients' subjective experience of pain and ability to function in daily life. There were significant differences in self-reported pain intensity on the VAS across the four subgroups, ($F(3,89) = 3.23$, $P = .026$). As illustrated in Figure 2, the Maltreated group reported the most pain ($t = 2.01$, $P < .05$), while the Positive Outlook cluster reported the least ($t = 2.78$, $P < .007$). There were also group differences in GAF ($F(3,87) = 3.29$, $P = .024$), with the Normal Biology cluster reporting relatively high global functioning ($t = 2.10$, $P = .04$). The Positive Outlook cluster functioned at a similarly high level, but because of the smaller number of subjects, the difference was significant only when compared directly with the Maltreated ($P < .05$) or Dysregulated Biology groups ($P < .05$). There were also tendencies for the clusters to differ in fatigue and ability to complete tasks. While an overall ANOVA did not reach significance across the four subgroups, when the Dysregulated Biology cluster was specifically targeted in post hoc analyses, these women were the most fatigued ($t = 2.34$, $P = .024$) and the least able to complete tasks ($t = 2.07$, $P = .042$).

Discussion

In keeping with prior studies and clinical experience, this community sample of women with FM, which was both physician-diagnosed and verified by our research team, proved to be highly heterogeneous, yet could be organized into distinct and coherent subgroups. To our knowledge, this study is the first to characterize FM subgroups based on profiles integrating current psychological status with both a history of childhood maltreatment and physiological functioning. The 4 subgroups that emerged in the cluster analyses had distinctive psychobiologic profiles characterized by: (1) a history of childhood maltreatment and hypocortisolism; (2) evidence of immunologic, metabolic and neuroendocrine dysregulation; (3) healthy biomedical profiles despite typical FM psychological distress; and (4) more resilient psychological profiles and less disability despite pain sensitivity. Interestingly, all clusters had nearly identical TP counts and intolerance for dolorimetry pressure upon exam [23]. However, they could be clearly differentiated on the basis of their ability to function in daily life (GAF) and self-reported pain on the VAS. This diversity in phenomenology among patients meeting ACR diagnostic criteria for FM may help to explain inconsistencies across previous investigations that utilized statistical methodologies focusing on average group differences in unselected FM populations. In addition, the diversity likely contributes to the finding that most treatments for FM are effective for only a subset of patients.

A history of childhood abuse and/or neglect was reported by a distinct subgroup and this background cohered with more current psychological distress and cortisol levels below the norm for healthy adult women ($20.3 - 27.5 \mu\text{g/g creatinine}$) [20], as well as low testosterone (of significance because higher testosterone has been reported to be associated with subjective well-being in women [19]). This finding gives credence to childhood trauma as one etiopathogenic pathway leading to hypocortisolism in a significant subset of FM

patients. Although their TP counts were not higher, women in the Maltreated group reported the most subjective pain and poorest global functioning, which would be consistent with the high prevalence of psychological disturbance following early adversity. This subgroup would likely overlap previously published descriptions of: (a) Dysfunctional Copers in whom pain behaviors were predicted by lower cortisol [10], and (b) high catastrophizers with greater emotional distress whose VAS scores of 6.5 were nearly identical to the mean of 6.3 in our Maltreated group [12].

Women in the Dysregulated Biology subgroup were distinguished most by several immune and inflammatory markers (ANA seropositivity, ESR, and NK cell numbers), which were not as abnormal in the other clusters. The reported occurrence of ANA+ tests in FM patients has ranged from 8–30%, but the consensus has been that prevalence of ANA positivity is not greater than in healthy individuals, nor does it reliably predict future development of autoimmune conditions or connective tissue disease [34]. Nevertheless, the co-occurrence of higher ANA titers with higher ESR concurs with prior reports that some FM patients show signs of a proinflammatory bias [22], which may facilitate development of central sensitization to pain [35]. It is likely that immunological dysregulation plays a pathogenetic role in only a subgroup of FM patients and the extant literature suggesting an immune explanation for FM has likely been over-generalized from this subset. These women were further characterized by evidence of dysregulation of neuroendocrine systems that are frequently associated with chronic life stress: hypocortisolism, the lowest GH and testosterone, and warning signs of metabolic syndrome.

Many FM patients show signs of hyporeactivity in their stress-responsive physiology, which may be due to early adversity, the persistent strain of pain and fatigue or other stress in adulthood, and/or genetic vulnerability [4]. However this stress-diathesis model appears to be most applicable to a subset of patients: women similar to those in the Maltreated and Dysregulated Biology subgroups. Indeed, women in both subgroups perceived themselves to be the most stressed and reported high levels of pain, fatigue, and disability.

Despite also experiencing pain, anxiety and psychic distress, another subgroup emerged with a healthier panel of immune, hormone and metabolic biomarkers. These women appeared to be more biologically resilient and, therefore, might be more likely to respond better to non-pharmacologic treatments, such as cognitive-behavioral or affective regulation therapies [36]. This subgroup was, on average, about 5 years younger than the other three, so it is possible they were still at an earlier stage of disease progression, prior to developing further biologic dysregulation. If so, these women may be especially important to target because early treatment intervention has been shown to improve outcomes in FM [37].

Although affective state is often negatively valenced in FM [38], the fourth subgroup was characterized by a more positive skew, and reported the lowest levels of stress and anxiety. Given the prevailing view of FM patients as frequently psychologically disturbed, it is important to recognize this well-adjusted subset [39]. The biomedical evaluation of these Positive Outlook patients was distinctive primarily in revealing that they had the highest cortisol values. These women reported higher functioning and energy and the mildest subjective pain despite comparable TP counts. This seeming discrepancy in pain reporting is consistent with the important distinction between tenderness and the more protracted experience of pain-suffering, in which emotional processes play a pivotal role [40]. Our conclusions about this more resilient subgroup appear similar to prior reports on: Adaptive Copers [10] and low catastrophizers, who reported nearly identical pain scores on VAS (3.9 vs. our 4.1) [12], as well as a subtype based on the FIQ who appeared to be relatively free of psychological distress [13].

Despite the clear emergence of 4 distinct subgroups, which concurs with the extant literature, it is important to acknowledge that this study was cross-sectional and therefore causality cannot be inferred. It is possible, for example, that the Positive Outlook cluster was able to maintain a healthier psychological profile because these women were experiencing less disability and fatigue. A further limitation is that when subdivided, our sample size is relatively small. Subgroup prevalence in other settings or the general population cannot be predicted. In addition, our statistical modeling captured the variance evinced by approximately 90% of participants, still leaving some more idiosyncratic features of this complex disorder to be explained. Thus, the results warrant replication in a larger population-based study incorporating other variables, such as sleep quality, for which we did not have data.

Treatment of FM will likely become more successful only when it is more specifically tailored to this type of more personalized classification [41]. Our results suggest that some FM patients will likely benefit more from pharmacologic treatments, whereas others might achieve greater improvement with psychotherapeutic interventions or exercise. Upon replication of this subgroup breakdown, the nosology could provide the basis for patient-tailored interventions. In conclusion, the findings validate the view of FM as heterogeneous, but show that clinically relevant taxonomies can be generated to advance our investigation and understanding of the pathogenetic pathways as well as for refining specific treatment approaches.

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Fig. 1.

Psychological and biomedical profiles of FM subgroups. Cluster I (N = 19) was named Maltreated; Cluster II (N = 20), Dysregulated Biology; Cluster III (N = 36), Normal Biology; Cluster IV (N = 18), Positive Outlook. CTQ = Childhood Maltreatment Questionnaire; PSS = Perceived Stress Scale; Anx = General Distress from Anxiety Symptoms; PA/NA = the ratio of positive-to-negative affect; Chol = total cholesterol (mg/dL); HA_{1c} = Hemoglobin A_{1c}; CrCl = creatinine clearance; cort = cortisol; GH = growth hormone; Testo = testosterone; NK = natural killer cell counts; ESR = erythrocyte sedimentation rate (mm/hr); ANA = antinuclear antibody titers.

Fig. 2. Subgroup differences in the FM symptoms of subjective pain, measured by the Visual Analogue Scale, and Global Assessment of Functioning, assessed with a Structured Clinical Interview for DSM-IV.

Table 1

Demographic and clinical characteristics of the FM participants aggregated into 4 subgroups via cluster analysis.

Clusters:	I	II	III	IV
	Dysregulated	Normal	Positive	
	Maltreated	Biology	Biology	Outlook
	(n = 19)	(n = 20)	(n = 36)	(n = 18)
Mean Age (SD) *	39.0 (7.6)	39.5 (7.2)	34.1 (8.5)	39.0 (5.5)
Partner Status				
Married/Living w/partner	57.9	50.0	45.7	58.8
Single, Divorced/Separated	42.1	50.0	54.3	41.2
Employment Status, %				
Employed or Student	99.7	78.9	75.0	94.4
Unemployed	5.3	21.1	25.0	5.6
Education, %				
High School Degree	10.5	25.0	13.9	11.1
Some College	52.6	35.0	36.1	27.8
College Degree	26.3	20.0	30.6	38.1
Graduate Studies	10.5	20.0	19.4	22.2
Income, %				
<\$30,000	21.1	45.0	52.8	38.9
\$30,000–69,999	57.9	30.0	36.1	38.9
>\$70,000	21.1	25.0	11.1	22.2
Ethnicity, %				
Caucasian	94.7	95.0	97.2	100
Non-Caucasian	5.3	5.0	2.8	0
Tender Point, No. (SD)	14.8 (2.4)	15.0 (2.5)	14.5 (2.2)	14.7 (2.5)

* $P < .05$, group difference by univariate ANOVA.

† All other comparisons were non-significant.

Table 2

Mean values (standard deviation) of untransformed cluster variables by subgroup.

	Cluster I: Maltreated (n=19)	Cluster II: Dysregulated Biology (n = 20)	Cluster III: Normal Biology (n = 36)	Cluster IV: Positive Outlook (n=18)	P-value (between all clusters)
Childhood	77.2(13.3) *	45.4(12.2)	41.3 (12.2) *	44.4(13.0)	<.001
Trauma					
Questionnaire					
Perceived	26.6 (4.2) *	24.3 (5.0) *	21.2(5.0)	11.3(4.5) *	<.001
Stress					
(PSS)					
Anxiety	28.1(5.9)	29.1(3.2) *	28.3 (5.6) *	19.7 (2.3) *	<.001
(MASQ)					
Positive to	0.93 (.27) *	1.0 (.38) *	1.2(.37) †	2.4 (.75) *	<.001
Negative Affect					
(PANAS)					
Body Mass	28.9 (4.3)	30.9 (8.7) *	23.8(4.7) *	28.9 (5.4)	<.001
Index, kg/m ²					
Cholesterol, mg/dL	204.4(33.0)	224.1(27.9) *	177.5(29.3) *	202.0 (39.1)	<.001
Hemoglobin	5.0 (.3)	5.0 (.4)	4.9 (.3) *	5.1 (.2)	.144
A _{1c} , %					
Creatinine	112.6(28.5) †	91.1 (28.3) †	96.3 (23.7)	111.2(7.7) †	.028
Clearance					
mL/min					
ANA titer	29.5(49.6) *	308.1(434.5) *	40.0 (70.3) *	42.2(80.6)	<.001
Sedimentation	14.0(10.8)	17.7(13.5) †	8.6 (5.6) *	13.8 (6.6)	.005
Rate, mm/hr					

	Cluster I: Maltreated (n=19)	Cluster II: Dysregulated Biology (n = 20)	Cluster III: Normal Biology (n = 36)	Cluster IV: Positive Outlook (n=18)	P-value (between all clusters)
NK cells, /uL	225.7(97.4)	142.5 (52.7) *	218.6 (96.5)	208.8 (69.8)	.007
Urinary Cortisol, µg/g	17.4 (9.7)	15.8 (8.6) *	22.9(12.1) †	26.8(22.1) †	.005
Creatinine Growth Hormone, ng/mL	1.71 (2.34)	0.69(1.13) *	2.29(3.10) *	0.96(1.26)	.005
Testosterone, ng/mL	16.2 (7.9) †	12.9 (5.9) *	26.2(12.1) *	21.7(7.3)	<.001

* t-test contrasts indicate significant difference (p<.05) from the other 3 clusters.

† t-test contrasts show a trend (p .07) to be different from the other 3 clusters.