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Data Mining: Comparing the Empiric CFS to the Canadian ME/CFS Case Definition

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Abstract

This article contrasts two case definitions for Myalgic Encephalomyelitis/chronic fatigue syndrome (ME/CFS). We compared the empiric CFS case definition (Reeves et al., 2005) and the Canadian ME/CFS Clinical case definition (Carruthers et al., 2003) with a sample of individuals with CFS versus those without. Data mining with decision trees was used to identify the best items to identify patients with CFS. Data mining is a statistical technique that was used to help determine which of the survey questions were most effective for accurately classifying cases. The empiric criteria identified about 79% of patients with CFS and the Canadian criteria identified 87% of patients. Items identified by the Canadian criteria had more construct validity. The implications of these findings are discussed.

Chronic fatigue syndrome (CFS), sometimes referred to as Myalgic Encephalomyelitis (ME), has frequently been defined by the Fukuda et al. (1994) criteria, which state that a person needs to experience six or more months of chronic fatigue of a new or definite onset, that is not substantially alleviated by rest, not the result of ongoing exertion, and results in substantial reductions in occupational, social, and personal activities. The Fukuda et al. case definition uses polythetic criteria: a set of symptoms in which not all need to be present to make a diagnosis. For example, because the Fukuda et al. criteria only requires four symptoms out of a possible eight, critical CFS symptoms such as post-exertional malaise, and memory and concentration problems are not required of all patients.

This case definition for CFS (Fukuda et al., 1994) was characterized by vaguely worded criteria that are lacking operational definitions and guidelines to assist health care professionals in their interpretation and application of the diagnostic tool (Jason, King, et al., 1999; Reeves et al., 2003). In order to provide more guidelines and specific criteria for this

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case definition, the Centers for Disease Control and Prevention (CDC) developed an empiric case definition for CFS that involved assessment of symptoms, disability, and fatigue using standardized scales (Reeves et al., 2005). Jason, Evans, et al. (in press) used Receiver Operating Characteristics to examine the use of the Multidimensional Fatigue Inventory (MFI) fatigue scale (Smets, Garssen, Bonke, & DeHaes, 1995), which was used to identify whether participants meet the fatigue criterion for the CFS empiric case definition. Jason, Evans, et al. found that the MFI did identify all CFS cases, but these scales were not able to successfully identify those who did not have CFS. In addition, Jason, Brown, et al. (in press) examined Reeves et al.'s recommended use of selected subscales from the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) to measure disability. Notably, Jason, Brown, et al. found that the recommended cutoff of less than or equal to 66.7 on the SF-36 Role-Emotional subscale would select the majority of those with chronic fatigue explained by psychiatric reasons as meeting the CFS disability criterion. Furthermore, the area under the curve (AUC) for the Role-Emotional subscale was the worst among the eight SF-36 subscales for discriminating patients with CFS from controls (Jason, Brown, et al., in press). Using the CFS empiric criteria, the estimated rates of CFS has increased to 2.54% (Reeves et al., 2007), which is ten times higher than prior CDC (Reyes et al., 2003) and other investigator prevalence estimates (Jason, Richman, et al., 1999). Jason et al. (2009) also found that 38% of those with a diagnosis of a Major Depressive Disorder were misclassified as having CFS using the new, more broadly based CDC empiric case definition.

To further highlight the challenge of identifying patients with this poorly understood illness, a third case definition was developed for use by clinicians treating patients with ME/CFS, which is referred to as the Canadian clinical case definition for ME/CFS (Carruthers et al., 2003). In contrast to the polythetic method of the Fukuda et al. (1994) criteria, the Canadian clinical case definition requires the presence of symptoms often considered to be hallmarks of this illness such as post-exertional malaise, neurocognitive symptoms, and unrefreshing sleep. Some research suggests the Canadian criteria select a more specific group of patients with this illness. For example, Jason, Torres-Harding, Jurgens, and Helgerson (2004) compared persons meeting the Canadian clinical case definition, the Fukuda et al. criteria, and people experiencing chronic fatigue explained by psychiatric reasons. The Canadian criteria in contrast to the Fukuda et al. criteria selected cases with less psychiatric co-morbidity, more physical functional impairment, and more fatigue/weakness, neuropsychiatric, and neurology symptoms. The differences in symptomatology and prevalence rates across various case definitions of ME/CFS suggest that additional research is needed to determine a diagnostic approach with optimal sensitivity and specificity.

Data mining, often also referred to as machine learning, might help determine the types of symptoms that may be most useful in accurately diagnosing chronic fatigue syndrome. In particular, data mining is a technique to explore large sets of data and either 1) replicate human decisions, especially when the process by which these decisions are made are not well-understood or 2) uncover patterns in the data that would not be evident to humans because of the size and complexity of the data. In the particular case of diagnosing CFS, both goals are desirable; using machine learning to augment physicians' diagnoses could result in more uniform diagnoses, while understanding what symptoms are important in the diagnosis process could allow researchers to focus attention on the evaluation of those symptoms.

This study explored the use of decision trees to implement the data mining. Decision trees attempt to predict a classification (diagnosis) for each patient based on successive binary choices: at each branch point of the tree, all the symptoms are examined with respect to their effect on the entropy of the diagnoses. Symptoms with high entropy are deemed important

and used to split all the cases into two parts. Successive analysis of symptoms contributing less entropy leads to further branching of the tree, until such branchings produce groupings with homogenous labels. In particular, this study used two sets of symptoms for analysis. One was a subset of the larger set of symptoms that focused on the empirical definition of CFS, while the other was a subset that focused on the Canadian definition. In both cases, the trees attempted to predict the medical diagnosis based on the Fukuda criteria.

While the ultimate ability of the tree to predict diagnoses is important, the choice of which symptoms are deemed important, and the values of the symptoms upon which the split is determined also provide useful insight: if the decision tree determines that a symptom is important in the classification, then this symptom can be considered an important contributor to CFS. In addition, the sequence of the symptoms chosen for splitting indicates their relative importance to diagnosis. The study attempted to use a series of questions to differentiate those with CFS from Idiopathic Chronic Fatigue, chronic fatigue explained by psychiatric or medical reasons, and controls. The empirical CFS (Reeves et al.) and Canadian ME/CFS case definitions (Carruthers et al., 2003) were contrasted.

Method

Participants

Participants for this study were derived from a 10-year natural history study of CFS consisting of two waves. Wave 1 refers to a group of 213 individuals who were medically and psychiatrically evaluated from 1995–1997 as part of an epidemiological study (Jason, Jordan, et al., 1999). The Wave 1 sample is a stratified random sample of several neighborhoods in Chicago, Illinois, specifically selected to contain individuals from different ethnic and socioeconomic profiles. As a whole, Chicago is an ethnically and socioeconomically diverse city. We sampled in eight Chicago community locations, including low socioeconomic areas such as West Garfield Park, middle-socioeconomic areas such as Bridgeport and Armour Park, gentrifying areas such as the near West Side, and high socioeconomic areas such as the Loop and the near North Side. The telephone numbers comprising the stratified random sample were obtained from Survey Sampling, Incorporated. This company generated random telephone numbers using valid Chicago exchanges, resulting in a sample of both listed and unlisted numbers (as well as business and non-working numbers). In the first stage of data collection in the original Wave 1 study, procedures developed by Kish (1965) were used to select one adult from each household for subsequent screening for CFS-like illness. Birth dates for each adult were gathered and the person with the most recent birthday was selected to be interviewed. The final sample of respondents consisted of 18,675 households. Racial data indicate that the sample consisted of 20.0% African-Americans, 52.6% Caucasians, 18.7% Latinos, 0.5% Native Americans, 5.5% Asian Americans, 1.4% multiracial individuals, and 1.3% individuals of other races (Jason, Jordan, et al., 1999).

For Wave 1, after a medical and psychiatric evaluation, we had physician consensus on diagnoses for the following conditions: 32 participants with CFS, 45 with idiopathic chronic fatigue (ICF), 89 were Exclusionary for CFS due to medically/psychiatrically explained chronic fatigue, and 47 Controls. Those with ICF had at least six months duration of fatigue, but with insufficient symptoms to meet the case definition of CFS. The Exclusionary group had chronic fatigue for at least six months duration, but with medical explanations of the fatigue including active medical conditions that explain chronic fatigue (e.g., untreated hypothyroidism), previously diagnosed medical disorders whose resolution has not been documented beyond reasonable clinical doubt, and whose continued activity may explain the chronic fatiguing illness (e.g., unresolved cases of hepatitis C). The Exclusionary group also included those with chronic fatigue for at least six months duration, but with psychiatric

explanations of the fatigue (e.g., delusional disorders, schizophrenia, etc). Controls had less than 6 months of fatigue. Wave 2 refers to a follow-up of the Wave 1 sample collected approximately 10 years later, and it is the data used in the current study (for more details, see Jason, Porter, Hunnell, Rademaker, & Richman, in press). The Wave 2 follow-up was carried out in two stages. In Stage 1, we attempted to re-contact the 213 adults who had been previously medically and psychiatrically evaluated. Stage 2 of the study encompassed a structured psychiatric assessment and a complete physical examination and a structured medical history.

Stage 1—The *CFS Screening Questionnaire* consists of two parts and was administered to all participants during Wave 2. It assesses participants' sociodemographic characteristics and fatigue characteristics to determine whether any changes have occurred since the first wave of data collection in the original study. Basic demographic data included age, ethnicity, socioeconomic status, work status, marital status, parental status (including number of children) and gender.

The CFS Screening Questionnaire also contains questions measuring more specific aspects of fatigue and health status. The questionnaire included questions assessing the degree to which participants are experiencing each of the eight CFS symptoms as defined by the Fukuda et al. (1994) criteria. In addition, questions assessed the level of impairment that fatigue and illness cause to daily activities, as well as the frequency and duration of the fatigue. Respondents were also asked if they have ever been diagnosed with any other medical or psychiatric conditions associated with chronic fatigue and what current treatments they were receiving. A version of the screening scale used in the present study was evaluated by Jason et al. (1997). They recruited four groups of participants (i.e., those diagnosed with CFS, Lupus, and Multiple Sclerosis, and a healthy control group). All participants were interviewed with a screening instrument twice over a two-week period of time. The screening scale exhibited high discriminant validity and excellent test-retest and inter-rater reliability (Jason et al., 1997). Hawk, Jason, and Torres-Harding (2006) revised this CFS Screening Questionnaire, and administered the questionnaire to three groups (those with CFS, Major Depressive Disorder, and healthy controls). The revised instrument, which was used in the present study, evidences good test-retest reliability and has good sensitivity and specificity.

Stage 2—In Stage 2, the *Structured Clinical Interview for the DSM-IV* (SCID; Spitzer, Williams, Gibbon, & First, 1995) was administered to assess current psychiatric diagnoses as defined on Axis I of the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV; American Psychiatric Association, 1994). The SCID was administered in both Waves 1 and 2. The SCID is a valid and reliable semi-structured interview guide that approximates a traditional psychiatric interview (First, Spitzer, Gibbon, & Williams, 1995). It has been successfully used to assess psychiatric disorders in samples of people with CFS (Taylor & Jason, 1998).

Following the structured psychiatric interview, participants were provided a medical history interview and complete medical examination. These procedures were followed for both Waves 1 and 2. Prior to the physical examination, the interviewer who accompanied participants and provided transportation to the medical examination administered the Medical Questionnaire at the physician's office to assess current and past medical history. The Medical Questionnaire is a modified version of The Chronic Fatigue Questionnaire, a structured instrument developed by Komaroff and Buchwald (1991) and has been used in previous CFS studies (Komaroff et al., 1996). This comprehensive instrument assesses symptoms related to CFS and chronic fatigue, as well as other medical and psychiatric symptoms, in order to help rule out exclusionary conditions such as HIV/AIDS, active

malignancies, iatrogenic conditions resulting from the side effects of medication, unresolved cases of hepatitis, and active substance use. In addition, the Medical Questionnaire measures fatigue severity, fatigue-related social role impairment, psychosocial stressors, job satisfaction, toxic exposures prior to CFS onset, chemical sensitivities, presence of CFS or chronic fatigue in other network members, and family medical history.

The *Medical Outcomes Study 36-Item Short-Form Health Survey* (SF-36; Ware & Sherbourne, 1992), a reliable and valid measure, was administered in Stage 2 to discriminate between gradations of disability. This instrument encompasses multi-item scales to assess Physical Functioning, Social Functioning, Role-Physical functioning, Role-Emotional functioning, Vitality, Bodily Pain, General Health, and Mental Health. Back-translated, Spanish language versions of all measures were administered to individuals choosing to respond in Spanish.

The CDC Symptom Inventory: The CDC Symptom Inventory assesses information about the presence, frequency, and intensity of 19 fatigue related symptoms during the past one month (Wagner et al., 2005). All eight of the critical Fukuda et al. symptoms were included as well as 11 other symptoms (e.g. diarrhea, fever, sleeping problems, nausea etc.). For each of the eight Fukuda et al. (1994) symptoms, participants were asked to report the frequency (1= a little of the time, 2= some of the time, 3= most of the time, 4= all of the time) and severity (the ratings were transformed to the following scale: .08= very mild, 1.6= mild, 2.4=moderate, 3.2= severe, 4= very severe)[1]. The frequency and severity scores were multiplied for each of the eight critical Fukuda et al. symptoms and were then summed.

The Multidimensional Fatigue Inventory: This instrument is a 20-item self-report instrument consisting of five scales: general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue (Smets, Garssen, Bonke, & DeHaes, 1995). Each scale contains four items rated from one to five with the scale score of one meaning completely true and the scale score of five meaning no, not true. Reeves et al. employed the Multidimensional Fatigue Inventory to measure severe fatigue, and to do this, they used only two of the five subscales; general fatigue and reduced activity.

Following the medical history interview, the physician conducted a detailed medical examination. This examination was carried out in order to rule out exclusionary medical conditions and detect evidence of diffuse adenopathy, hepatosplenomegaly, synovitis, neuropathy, myopathy, cardiac or pulmonary dysfunction, or any other medical disorder. An 18-tender-point examination was used to test for Fibromyalgia (Goodnick & Sandoval, 1993). Laboratory tests administered to all participants included a chemistry screen (glucose, calcium, electrolytes, uric acid, liver function tests, and renal function tests), complete blood count with differential and platelet count, T4 and TSH, erythrocyte sedimentation rate, arthritic profile (which includes rheumatoid factor and antinuclear antibody), hepatitis B surface antigen, CPK, HIV screen, and urinalysis. An intra-dermal, intermediate-strength PPD skin test was applied, and a posterior-anterior chest x-ray was completed, if it was not already obtained by the participant within eight months of entering the study. At the time of evaluation, the examining physician was blinded to participants' status with respect to initial classification based upon the Stage 1 screen. Participants were reimbursed $100.00 for the time and effort involved in participation. Participants also signed the Human Participant Consent Form.

Diagnosing CFS—At the end of Stage 2, a team of physicians was responsible for making final diagnoses. Two physicians independently rated each file according to the current U.S. definition of CFS, ICF, Exclusionary for CFS due to medically/psychiatrically explained chronic fatigue (Fukuda et al., 1994), or Control (participants with no exclusionary illness

and less than 6 months of fatigue). Reviewing physicians had access to all information gathered on each participant during each of the phases of the study. Physicians were not blind to Wave 1 status because they needed to be fully appraised of the medical history. The review panel was also provided with all results from the physical exam. If a disagreement occurred regarding whether a participant should receive a diagnosis of CFS, ICF, Exclusionary due to medically/psychiatrically explained chronic fatigue, or Controls during the physician review process, the participant's file was rated by a third physician reviewer, and the diagnosis was determined by majority rule. We used refinements of the Fukuda et al. criteria as recommended by an International Research Group and the CDC (Reeves et al., 2003).

By Wave 2, of the original group of 32 individuals with CFS, 4 had died, and 24 were found and agreed to be re-evaluated (completion rate of 24/28=86%). By Wave 2, among the 45 ICF individuals at Wave 1, 4 had died, and we were able to re-evaluate 21 (completion rate of 51%). By Wave 2 among those 89 with an Exclusionary illnesses at Wave 1, 16 had died and we were able to re-evaluate 41 (completion rate of 56%). Finally, by Wave 2, among the 47 Controls at Wave 1, 5 had died, and we were able to re-evaluate 22 (completion rate of 53%). In this study of Wave 2 participants, we had 24 individuals with a CFS diagnosis compared to 80 without a CFS diagnosis.

Empiric Case Definition

A case of the chronic fatigue syndrome is defined by the presence of the following: clinically evaluated, unexplained, persistent or relapsing chronic fatigue that is of new or definite onset (has not been lifelong); is not the result of ongoing exertion; is not substantially alleviated by rest and results in substantial reduction in previous levels of occupational, educational, social, or personal activities. The CDC's empiric CFS case definition (Reeves et al., 2005) assesses fatigue using the MFI (Smets et al., 1995). Reeves et al. define severe fatigue as a score of greater than or equal to 13 on the MFI general fatigue subscale or greater than or equal to 10 on the MFI reduced activity subscale. To meet criterion, an individual also has to score below the 25^{th} percentile on any one of the following four SF-36 subscales to measure disability: Physical Functioning (less than or equal to 70), Role-Physical (less than or equal to 50), Social Functioning (less than or equal to 75), or Role-Emotional (less than or equal to 66.7). The Symptom Inventory (SI; Wagner et al., 2005) is used to assess symptoms. The frequency and severity scores were multiplied for each of the eight critical Fukuda et al. (1994) symptoms and were then summed. To meet the Reeves et al. symptom criteria, a person needed to have four or more symptoms and a total score greater or equal to 25 on the SI.

Canadian ME/CFS Case Definition

The Canadian clinical case definition (Carruthers et al., 2003) specifies that post-exertional malaise must occur with a loss of physical or mental stamina, rapid muscle or cognitive fatigability, usually taking 24 or longer to recover. In addition, there need to be two or more neurological/cognitive manifestations (e.g., confusion, impairment of concentration and short term-memory). There also needs to be unrefreshing sleep or poor sleep quantity or rhythm disturbance, as well as a significant degree of arthralgia and/or myalgia (there are a small number of patients with no pain or sleep dysfunction and a diagnosis can only be given when these individuals have a classical case with an infectious illness onset). Finally, there needs to be at least one symptom from two of the following categories: autonomic manifestations (neurally mediated hypotension, light headedness), neuroendocrine manifestations (e.g., recurrent feelings of feverishness and cold extremities) and immune manifestations (e.g., recurrent sore throats).

Statistical Analyses—We used decision trees to help distinguish among individuals with CFS and other conditions (ICF, Exclusions, and Controls) provided their responses to survey questions. For the empiric CFS case definition (Reeves et al., 2005), there were altogether 14 different SI symptoms, SF-36 sub-scales, and MFI questions that were used as features for the decision tree classification. There were altogether 43 questions that were used as features for the decision tree for the analysis to tap the Canadian clinical criteria. These items have recently been described in an article by Jason et al. (2010). SPSS Answer Tree software was used to build our decision tree models. In order to build the models, we used a Classification and Regression Tree (CART) algorithm with a 10-fold cross validation. The value of the model was measured with risk estimates (risk statistic and cross validation) which give an estimate of how many unknown cases will be misclassified, allowing this technique the ability to be generalized to new data.

Results

For the empiric CFS criteria, the risk statistic was .21 indicating that 79% of the cases were identified correctly. The cross validation statistic was .32, which is the average risk of the 10 trees created during the 10-fold cross validation. This indicates the generalizability of the classification: one can expect that 68% of new cases will be identified correctly. The 6 items that loaded (were the most significant for the classification) were sore throat, lymph node pain, MFI reduced activity, SF-36 social functioning, joint pain, and SF-36 role physical.

For the Canadian criteria, the risk statistic was .13 indicating that 87% of the cases were identified correctly, and the cross validation statistic was .27, indicating that 73% of new cases would be identified correctly. The 6 items that loaded were sore throat, lymph node pain, inability to concentrate, presence of multiple chemical sensitivities, post-exertional malaise, and unfreshing sleep.

Discussion

The study's overall findings were that the Reeves et al. (2005) criteria were not as capable of identifying cases from non-cases as the Canadian criteria (Carruthers et al., 2003). As mentioned in the introduction, the Reeves criteria have been criticized as being more general and broader than the Fukuda et al. (1994) criteria, and the results of this study suggest that these criteria are only able to discriminate 79% of cases from others, whereas the Canadian criteria were able to 87% of cases. Also, the Canadian criteria appears to generalize better to new cases. In addition, when examining the items selected in both analyses, it is apparent that the Canadian criteria appear to select cardinal and central features of the illness.

ME/CFS is often thought to include post-exertional malaise and neurocognitive disorders, and both did emerge as predictive factors in the Canadian criteria, but not within the Reeves et al. (2005) empiric case criteria. In addition, sleeping disorders and pain symptoms, other key symptoms of ME/CFS did emerge from the Canadian criteria. Even within the other category of the Canadian criteria, two symptoms emerged in the immune areas (i.e., sore throat and multiple chemical sensitivities), and this supports evidence for the Canadian criteria. In contrast, the empiric criteria tended to identify more general areas, including less activity, social and role functioning problems, and some pain issues. However, critical symptoms such as post-exertional malaise, neurocognitive symptoms and sleep disorders were not identified as discriminating symptoms.

Data mining may be a useful tool in aiding in the diagnosis of ME/CFS. There are many challenges in diagnosing ME/CFS because it is a very heterogenous disease, some symptoms associated with it are common of other illnesses, and, as we have outlined, there

are competing definitions that investigators may use. More work with data mining in ME/CFS research could aid in further identification of cardinal symptoms, leading to better diagnostic ability. This would also combine an objective, computer driven decision with a physician's medically influenced decision to come up with a better and more reliable way to diagnose and treat ME/CFS. This technique has been used in other medical diagnoses, like breast cancer. Kuo et al. (2001) found that using data mining with decision trees in diagnosing malignant breast tumors increased diagnostic accuracy to 95% from just 87% with a physician alone.

There were several limitations in the study. The sample size was relatively small, and there clearly is need to replicate this study with larger samples. In addition, the Fukuda et al. (1994) criteria were used to select cases, and this might have biased the study toward having the empiric case definition do better, as it is based upon the Fukuda et al. criteria. However, this was not the case as the Canadian criteria was better able to classify cases and non-cases. There were more items in the Canadian criteria than the empiric case definition, but if we were to compare the two sets of criteria, we needed to use what is specified in both criteria, and to select fewer items for the Canadian criteria would have not been a fair test of these criteria. Note further that despite the disparity in the number of features, both definitions produced the same number of significant items.

In conclusion, the present study examined items that could discriminate two criteria for identifying cases versus non-cases. The Canadian criteria appeared to have a better risk statistic, and this indicates that it was better able to separate cases from non-cases than the empiric case definition. In addition, when examining items selected, the Canadian criteria appeared to have more items that are central to a ME/CFS case definition, and this provides some construct validity to this criteria.

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