CORRELATION BETWEEN WEIGHT LOSS AND SELECT MOTOR SCORES FROM A RETROSPECTIVE CHART REVIEW OF HUNTINGTON’S DISEASE PATIENTS

A Thesis

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By

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ABSTRACT

Objective. Huntington’s disease (HD) is a neurodegenerative disease that is accompanied by a progressive movement disorder and changes in weight. It is the purpose of this present study to investigate how weight change relates to specific measures of disease characteristics in the OSU HD population over a 5-year period.

Methods. A retrospective chart review of patients attending the OSU HD clinic between 2005 and 2011 was performed. Statistical analysis was used to show correlation between weight change and independent variables, represented as change scores. A two-sided hypothesis test was used to determine if the correlation between weight change and the change in other variables was significant.

Results. A total of 186 patient charts were available for review. Lower body weight was correlated significantly with worsening total motor score, chorea score, and dystonia score (p=0.000, p=0.018, p=0.000). Tongue protrusion score did not correlate with body weight (p>0.05). Class of medication use did not significantly correlate with body weight changes and thus was ruled out as a significant contributing factor to weight change.

Conclusions. Our results show that there is a significant correlation between a decrease in weight and worsening chorea, dystonia, and total motor scores.

Keywords: Huntington’s disease, total motor score, weight loss, chorea, dystonia, CAG repeat length
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Chapter 1: Introduction

Background and Significance of the Problem:

Huntington’s disease (HD) is an autosomal dominant neurodegenerative disease caused by a CAG repeat expansion in exon 1 of the Huntington’s (Htt) gene on chromosome 4 (1). Common physical characteristics of the disease include severe motor impairments such as chorea, dystonia, bradykinesia, and dysphagia. HD is also associated with progressive cognitive impairment and behavioral changes such as depression, irritability, apathy, and inflexibility. Along with these symptoms, significant weight loss has been associated with disease progression, even though affected individuals report an increased appetite and consume more energy than non-affected controls (2). This weight loss tends to lead to general weakness and a decline in the quality of life for patients with HD (3).

While several investigators have attempted to identify the cause of this unintended weight loss, it is thought that the root cause of weight loss may be multifactorial and not due to increases in choriform movement alone. Recently diagnosed patients, who have minimal chorea, also have lower body mass indices (BMI) than sex and age matched control patients (2).

Several retrospective chart reviews have been performed with the goal of identifying which characteristics of HD are most significantly related to weight loss. Djoussé et al (4) sought to test the hypothesis that weight loss is an element of HD
that accompanies the onset of clinical symptoms by reviewing data from 361 patients in the Huntington Study Group (HSG) who were in the early stages of HD. Results suggest that neither disease duration, dystonia, nor chorea were associated with BMI among these participants. However, control subjects had higher BMI than case subjects with HD who were free of chorea and dystonia, and suggests that a lower body weight is less likely to be attributable to involuntary movements. Another study using the HSG data base, by Hamilton et al (2), examined longitudinal weight data to identify rate and correlates of weight change during the course of the disease. This chart review included 927 adults with a definite diagnosis of HD who were followed prospectively for an average of 3.4 years. These results conflict with previous studies involving HD and weight loss because on average, patients gained weight over time (0.11±1.7kg/yr.). However, Hamilton et al did not control for diet or medications that are known to cause weight gain. Although patients with HD tended to gain weight over time, affected individuals in this sample still weighed almost 10 kg less than a community sample of comparably healthy, age-matched adults. The authors found that affected individuals who did lose weight, showed a significant relationship between weight loss and worsening chorea (p<0.001).

Aziz et al (3) aimed to specify the course of weight loss in participants from the European Huntington’s Disease Initiative (EHDI) study, and to determine factors that were associated with weight loss. They also assessed whether CAG repeat length was directly related to the rate of weight loss in HD patients. They found that BMI decreased at a greater rate as CAG length increased, and that CAG length was an independent predictor of weight loss. Additionally, the authors evaluated CAG repeat length and
caloric intake in transgenic mouse (R6/2) models and found that mice, fed *ad libidum*, with higher CAG repeats had lower body weight and consumed more energy per gram of body weight compared to mice with lower CAG repeats.

Marder et al (5) analyzed individual dietary intake of patients in the Prospective Huntington At Risk Observational Study (PHAROS) to determine whether there were differences in macronutrient intake, total caloric intake, and BMI, based on CAG repeat length >37. Caloric intake was significantly higher in affected individuals with expanded CAG repeat length. BMI and estimated physical activity were marginally different, while basal energy expenditure did not differ. Calorie intake was significantly higher in affected individuals, which was due to a significantly greater intake of carbohydrates (p=0.02) than individuals with normal CAG repeat length. Marder estimated that there is a 0.26 CAG unit increase for each unit increase in calorie quartile. (Q1=224.4-1,296.4kcal; Q2=1,296.8-1,730.7kcal; Q3=1,734.7-2,272.1kcal; Q4=2,273.7-7,138.2kcal)

Contrary to the findings from Aziz et al, 2008, Marder et al did not find a significant correlation between BMI and CAG repeat length. However, they did observe that individuals with expanded CAG repeat length reported similar caloric intake, yet had a lower BMI compared to those with normal CAG length. An important difference between these two studies is that PHAROS includes individuals who are mostly pre-symptomatic. Therefore, the difference in findings may be more related to changes that occur with motor symptom onset.

In 2006, Robbins et al was reported that weight gain appears to precede weight loss in a study of 73 HD patients (6). Observations by expert physicians at the OSU HD clinic suggest that there have been more overweight or obese patients attending the clinic over
the past 12 years, similar to findings in the general population in central Ohio.

**Objectives:**

It is important to have a better understanding of the weight changes that occur over the course of disease in HD, to be able to make recommendations for the patient concerning ramifications of weight change and nutritional interventions on. Therefore, the objectives of this retrospective medical record review were to analyze the weight status of the OSU Huntington Disease patient population, and to determine if there was a relationship between weight change and symptom scores, including tongue protrusion scores, motor scores, chorea scores, and dystonia scores between February 2005 and December 2011.

**Research Question:**

Is there a weight change associated with increasing symptoms of HD, specifically as tongue protrusion scores, motor scores, chorea scores, and dystonia scores worsen?

**Research Hypothesis:**

We hypothesize that a dynamic pattern of weight change will correlate with the decline of scores for tongue protrusion, dystonia, motor and chorea.

**Research Approach:**

The research approach for this study will be a retrospective medical record chart review (MRR).
Definition of Terms:

**Adlibidum:** Latin for "at one's pleasure".

**Aatrophy:** the partial or complete wasting away of a part of the body

**Autosomal dominant inheritance:** a pattern of inheritance in which the transmission of a dominant allele on an autosome causes a trait to be expressed.

**Axonal transport:** The movement of organelles and molecules down a nerve cell's axon to its terminals.

**Basal ganglia:** a collection of nuclei found on both sides of the thalamus, outside and above the limbic system, but below the cingulate gyrus and within the temporal lobes.

**Body Composition Tracking System (BODPOD):** uses air displacement to measure body composition.

**Body Mass Index (BMI):** A measurement of the relative percentages of fat and muscle mass in the human body, in which mass in kilograms is divided by height in meters squared

**Bradykinesia:** slow movement or slowness of motion.

**Branched chain amino acid (BCAA):** an amino acid having aliphatic side-chains with a branch (a carbon atom bound to more than two other carbon atoms). Among the proteinogenic amino acids, there are three BCAAs: leucine, isoleucine and valine.

**CAG repeat:** a trinucleotide repeat of cysteine, adenosine, and glutamine.

**Cerebral cortex:** a sheet of neural tissue that is outer most to the cerebrum of the mammalian brain. It plays a key role in memory, attention, perceptual awareness, thought, language, and consciousness.

**Chorea:** an irregular, rapid, uncontrolled, involuntary, excessive movement that seems to move randomly from one part of the body to another.

**C-reactive protein (CRP):** a protein found in the blood, the levels of which rise in response to inflammation.

**Cytoplasm:** part of the cell between the cell membrane and the nuclear envelope. It is the jelly-like substance in a cell that contains the cytosol, organelles, and inclusions, but not including the nucleus.
**Dual-emission X-ray absorptiometry (DXA):** DXA scans are used primarily to evaluate bone mineral density. DXA scans can also be used to measure total body composition and fat content.

**Dystonia:** a neurological movement disorder, in which sustained muscle contractions cause twisting and repetitive movements or abnormal postures.

**Endocytosis:** a process by which cells absorb molecules (such as proteins) by engulfing them.

**Erythrocyte sedimentation rate (ESR):** the rate at which red blood cells sediment in a period of 1 hour.

**Excitotoxicity:** the pathological process by which nerve cells are damaged and killed by excessive stimulation by neurotransmitters such as glutamate and similar substances.

**Full penetrance:** The allele is said to have full or complete penetrance if all individuals who have the disease-causing mutation have clinical symptoms of the disease.

**GABAergic medium spiny projection neurons:** a special type of inhibitory cells representing approximately 90% of the neurons within the corpus striatum of the basal ganglia. They play a key role in initiating and controlling movements of the body, limbs, and eyes.

**Ghrelin:** a 28-amino-acid peptide hormone that is secreted primarily by stomach cells and is stimulated by fat storage and food intake.

**Hereditary:** genetically transmitted or transmittable from parent to offspring.

**Huntington’s disease:** a neurodegenerative genetic disorder that affects muscle coordination and leads to cognitive decline and dementia.

**Hypothalamus:** A region of the forebrain below the thalamus that coordinates both the autonomic nervous system and the activity of the pituitary.

**Interleukin-1 beta (IL1B):** A cytokine that is overexpressed in various inflammatory diseases. IL-1 beta activates glial cells and is responsible for other activities involved in the inflammatory response.

**Interleukin 6 (IL6):** A type of biological response modifier (a substance that can improve the body's natural response to infection and disease).

**Insulin:** a hormone central to regulating carbohydrate and fat metabolism in the body.
**Insulin-like growth factor 1:** IGF-1 is a hormone similar in molecular structure to insulin. It plays an important role in childhood growth and continues to have anabolic effects in adults.

**Krebs cycle:** The sequence of reactions by which most living cells generate energy during the process of aerobic respiration.

**Leptin:** A protein produced by fatty body tissue and believed to regulate fat storage.

**Metabolism:** refers to all the physical and chemical processes in the body that convert or use energy.

**Mini Mental State Examination:** a brief 30-point questionnaire test that is used to screen for cognitive impairment.

**Mitochondria:** the primary energy producers of the cell.

**Neurodegeneration:** the progressive loss of structure or function of neurons, including death of neurons.

**Oxidative phosphorylation:** A metabolic pathway that generates ATP from ADP through phosphorylation that derives the energy from the oxidation of nutrients.

**R6/2 Transgenic Mice:** R6/2 transgenic mice express exon 1 of the human Huntington's disease gene with an increased CAG repeat length.

**Reduced penetrance:** Penetrance is said to be reduced or incomplete when some individuals fail to express the trait, even though they carry the allele.

**Respiratory Quotient (RQ):** The ratio of the volume of carbon dioxide released to the volume of oxygen consumed by a body tissue or an organism in a given period.

**Subcortical white matter:** the portion of your brain that has nerves in it that have a coating on them called myelin

**Tetraiodothyronine:** hormone produced by the thyroid glands to regulate metabolism by controlling the rate of oxidation in cells

**Thalamus:** a large, dual lobed mass of grey matter buried under the cerebral cortex. It is involved in sensory perception and regulation of motor functions.

**Thyroid stimulating hormone (TSH):** anterior pituitary hormone that stimulates the function of the thyroid gland.
**Total Functional Capacity (TFC):** A standardized scale used to assess capacity to work, handle finances, perform domestic chores and self-care tasks, and live independently. The TFC scale ranges from 13 (normal) to 0 (severe disability).

**Unified Huntington’s Disease Rating Scale (UHDRS):** developed as a clinical rating scale to assess four domains of clinical performance and capacity in HD: motor function, cognitive function, behavioral abnormalities, and functional capacity.
Chapter 2: Review of Literature

George Huntington presented the first clear clinical description of Huntington’s disease (HD) in 1872 (7). On April 13, 1872, *The Medical and Surgical Reporter* published Huntington’s report on a hereditary form of chorea (8). In Huntington’s writings, the features identified as essential to hereditary chorea are as follows; “1) It is hereditary in nature, 2) A tendency to insanity and suicide, 3) Its manifesting itself as a grave disease only in adult life”(7). Huntington also observed that hereditary chorea was confined to certain families and, when either or both of the parents showed manifestations of the disease, one or more of the offspring suffered from the disease. But if one of the offspring went through life symptom free, then the “thread is broken” and future generations may be free from the disease (7).

Since Huntington’s groundbreaking observations, modern medicine and technology have localized the HD mutation, identified the mutant Huntington gene (mHtt) responsible for the disease, and created the first generation of transgenic HD mouse models (9). Despite these advances, there are fundamental questions yet to be answered regarding the pathogenesis of HD, and an effective disease modifying therapy is yet to be discovered. In this review of literature, an overview of genetics, pathogenesis, and mechanisms of weight loss in HD will be presented. This review will also discuss current knowledge of HD associated weight loss with the aim of identifying
gaps in research and justification for future studies in this area.

In 1983, the genetic defect causing HD was localized to chromosome 4 (10). In 1993, the Huntington’s Disease Collaborative Research Group identified the gene associated with the disease (9,11). From this study, the HD research group discovered that the Htt gene is located on chromosome 4p16.3, and contains a trinucleotide repeat, CAG, that is expanded and unstable on HD chromosomes. Individuals with a normal Htt gene have less than 35 CAG repeat sequences, whereas individuals with mutated Htt gene have ≥36 CAG repeat sequences. This mutated sequence is transmitted through autosomal dominant inheritance (9).

The mechanism by which mHtt causes HD has been largely attributed to the gain of toxic function of the protein but, it is suspected that a loss of normal Htt may also play an important role as well (12). It is known that the CAG repeat length and age of onset of HD are inversely related, and can be a strong predictor of both neurologic and cognitive function (13). Individuals with CAG repeat expansions of 36-39 are considered to have reduced penetrance, while individuals with CAG expansions greater than 40 are considered full penetrance (9). The average age of onset of observable symptoms is typically from 30-50 years, and the disease progresses for 15-25 years after symptoms present until death. However, about 10% of individuals with HD develop symptoms before the age of 20, and are considered to have juvenile HD. Individuals with juvenile HD have higher CAG repeat length, generally over 60 and occasionally up to 80-100 or more CAG repeats. Individuals affected with juvenile HD present with more parkinsonian symptoms and face a more rapid rate disease progression. (22)

Despite being discovered over 20 years ago, the normal function of Htt remains
poorly understood. It is known that Htt plays a role in gene expression, endocytosis, vesicle trafficking, intracellular signaling, and metabolism. A review article by Mochel et al 2011 discusses the normal and pathophysiological functions of the Htt gene, and discusses the role of mitochondrial dysfunction and altered energy metabolism (14). The sequence of events that take place before neuronal death occurs is unclear. Several mechanisms point to energy defects including transcriptional dysregulation changes in axonal transport, excitotoxicity, signaling dysfunction and neuronal aggregates. The protein is not readily classifiable as being a member of any currently described families of cellular proteins.

A major focus of HD research has been directed at understanding brain energy and metabolism defects (14). There is strong evidence for reduced glucose utilization in the brain of HD patients, particularly in the basal ganglia. This decrease is seen even in pre-symptomatic mutant Htt carriers. There is also an increased lactate concentration in the brain of HD patients. Several mechanisms for this energy deficit in HD brain have been proposed, including impaired oxidative phosphorylation, oxidative stress, impaired mitochondrial calcium handling, and several other possible mechanisms (14).

Altered metabolic function is not only seen in the brain of patients with HD, but also in the periphery (14). It has been suggested that a peripheral mitochondrial defect occurs, based on the observation that the ATP/ADP ratio in HD patients is low. Weight loss in patients with HD is not explained by a decrease in energy intake, higher sedentary energy expenditure, or involuntary movements. There is instead evidence for an early, pre symptomatic hypermetabolic state in HD. The dysregulation of the hypothalamus has been suggested as a contributor to the negative energy balance. In patients with HD,
there are increased levels of ghrelin and decreased levels of leptin, both which promote appetite and food intake, which may reflect an adaptation to the increased metabolism in HD so that increased caloric intake will compensate for the potential decrease in body weight. The brain is dependent on energy substrates from the peripheral organs. It has been suggested that early weight loss is the result of the activation of compensatory mechanisms in peripheral organs in an attempt to provide the appropriate energetic substrates for a chronic brain energy deficit in HD (14).

A review article by Ross et al 2011 discusses the principle pathogenesis of HD (15). The HD gene is mostly found in the cytoplasm, with a nuclear export signal present near the C-terminus. Htt shuttles into the nucleus, plays a role in vesicle transport, and can regulate gene transcription. Htt might also have a role in regulating RNA trafficking. Most evidence on the pathogenesis of HD suggests that the disease arises from an increase in toxicity due to an abnormal conformation of mHtt. Key features of the pathogenesis of HD have been described. First, mHtt forms abnormal conformations. Second, the systems responsible for handling abnormal proteins are impaired. Third, Htt is truncated and forms toxic N-terminal fragments. Fourth, post-translational modifications of Htt influence toxicity. Fifth, nuclear translocation of mHtt enhances its toxic effects. And finally, cellular metabolic pathways are impaired.

In concordance with Mochel, Ross suggests that while most clinical features of HD can be attributed to CNS degeneration, some aspects of the disease can be mediated outside the brain, including weight loss, muscle wasting, metabolic dysfunction, and endocrine disturbances. In the brain, there is massive striatal neuronal cell death, with up to 95% loss of GABAnergic medium spiny projection neurons. There is also atrophy of
the cerebral cortex, subcortical white matter, thalamus, hypothalamic nuclei, and other brain regions. In advanced cases, there is widespread brain atrophy. There are several different ways mHtt could have effects on cellular metabolism. First, the cell must deal with the unfolded and abnormal proteins as mentioned earlier. Second, mHtt may have an indirect or direct effect on mitochondria which compromises energy metabolism and increases oxidative damage. Third, calorie restriction in mouse models has been shown to ameliorate the HD phenotype, indicating that pathways related to cell metabolism could modify the diseases pathogenesis (15).

Mochel et al 2007 investigated the underlying causes and mechanisms of weight loss in HD patients who were pre symptomatic or in the early stages of the disease, by identifying biomarkers and comparing them to healthy controls (16). The study included 32 patients with HD, 15 were pre symptomatic, 10 were mildly affected, 7 were moderately affected, and 21 people served as healthy controls. Inclusion criteria for affected carriers was an abnormal CAG repeat expansion >36 and the control participants had to be unrelated to HD patients. Participants were given an open-ended questionnaire with semi-quantitative recording of regular food and beverage consumption for 3 days previous to the study, and a closed-ended questionnaire of intake over the last 24 hours before the study. The questionnaire also inquired about significant weight changes 5 years prior to the study. Participants were required to fast for a minimum of 12 hours before the study. Additional measures included: UHDRS, height, weight, calorie distribution of fat, carbohydrate, and protein, liver and kidney function, serum insulin growth factor type 1 (IGF1), inflammatory markers (CRP, ESR, IL1-beta, IL6), endocrine markers (fasting serum cortisol, insulin, tetraiodothyronine T4L, TSH, fasting
and fed gherkin levels, fasting leptin levels), intermediary metabolism markers (plasma amino acids, acylcarnitines, urinary organic acids), BMI, fat mass, and free fat mass. Participants arrived the morning of testing, had fasting blood and urine samples collected, then were given a standardized meal (450 calories) over a 10 minute period, after which a second blood sample was collected to determine fed ghrelin levels. Results suggested significant weight loss in patients with HD compared to healthy controls 5 years before the study, and that mean weight loss in people who were early and mildly-affected carriers of HD (n=17) was greater than those who were pre-symptomatic carriers (n=15). Interestingly, affected individuals had similar BMI but higher calorie intake.

Concentration in plasma ion exchange by chromatography was done to confirm that branch chain amino acids (BCAA) are affected in HD. Results found that valine, leucine, and isoleucine levels were significantly lower in the HD group when compared to controls. (p=0.009, p<0.001, p=0.002, respectively.) Levels of each BCAA correlated with the observed weight loss in patients, negatively correlated with UHDRS values, and were significantly lower in early stage vs. pre symptomatic and pre symptomatic vs. controls. IGF1 levels were significantly lower in HD group than in controls and were negatively correlated with UHDRS scores. The ratio between pre and postprandial ghrelin levels were the same in participants with HD and healthy controls. Findings from this study confirm that early weight loss in HD is likely associated with a systemic metabolic defect. Future studies can confirm the BCAA findings, which may be used as a biomarker of disease onset and early progression. Also, decreased levels of BCAA may correspond to a critical need for Krebs cycle energy substrates in the brain, supporting the theory that the periphery is trying to provide energy substrates for the brain. Two current
clinical trials in HD (2CARE HD and CREST-E) are assessing whether high dose Coenzyme Q10 or Creatine, two agents that may supplement mitochondrial energy pathways, can affect the course of HD progression.

Another metabolic study, by Goodman et al 2008, evaluated both human and murine models of this disease (17). Eleven people with early stage HD were assessed at two time points, 2 years apart. Inclusion criteria for participants included genetic confirmation for HD, a modified Mini Mental State Examination score \( \geq 24 \), a UHDRS chorea score \( \leq 14 \), a TFC score \( \geq 8 \), an Independence Score \( \geq 80 \), a normal BMI (18-25), ability to eat independently, and non-smoking or light smoking status. Thirteen healthy people were recruited as controls from close family members with no history of HD. Controls were well matched for age, sex, BMI, percent body fat, and fat free mass. Participants were assessed over a 40-hour period during which 2 complementary measures of body composition was obtained: Air Displacement Plethysmography (BODPOD) and Dual Energy Xray Absorptiometry (DXA). Diets were formulated to maintain energy balance, estimated as predicted basal metabolic rate (BMR) and scaled by a factor of 1.48. Participants cycled on an ergometer at 3 time points for 30 minutes each. Urine and fasting blood samples were assessed for HbA1C, glucose, and TSH. Sleeping metabolic rate (SMR) and BMR were also measured. A 7-day food diary was sent to all participants 2-3 weeks after the study.

The R6/2 transgenic mouse models were broken into 2 groups of 8 and 14 weeks old, having CAG repeat lengths between 253-284. The mice were placed in individual chambers in fasted and water-deprived conditions. Body composition, white and brown adipose tissue, and muscle mass were evaluated, along with respiratory exchange ratio.
In this study, HD patients did not exhibit significant change in any parameter over the 2-year period, and weight declined on average -0.2 kg. Energy balance was significantly different, in that HD patients were in greater negative energy balance compared to controls. This was measured by estimating their food intake from the 7-day food record and comparing that to their estimated energy requirements. There was no correlation between energy balance and motor UHDRS score, no significant difference in BMR or SMR between the groups, and no significant difference in fat free mass between groups. Physical activity level scores were not significantly different, nor were there differences in energy expenditure levels and substrate oxidation during exercise between the groups. Overall, during the two years of this study of relatively early stage HD subjects, there was a non-progressive deficit in energy balance in patients with HD that could not be explained by their movement disorder.

In the murine model of HD, the authors found that the older mice (14 week olds) were more severely affected with lower lean body mass tissue but that there was no significant change in fat tissue compared to the younger mouse (8 weeks). Oxygen consumption was also significantly greater in 14-week-old mice compared to 8-week-old mice. The authors suggest that there is a pro-catabolic state in early HD that may not be related to movement disorder.

Trejo et al 2004 compared the nutrition status of patients with HD to healthy controls by analyzing anthropometric and biochemical data (18). The study involved 25 individuals with confirmed HD and 25 age and sex matched controls. The participants were given a 3-day food diary, of which total calories; carbohydrate, protein, and lipid intake was estimated. Anthropometric measurements included weight, height, BMI,
percent ideal body weight, percent body fat, and arm muscle circumference. Biomarkers evaluated were albumin, hemoglobin, hematocrit, total lymphocyte count, glucose, cholesterol, and HbA1C. UHDRS motor function, cognitive function, behavioral abnormalities, and functional ability scores were also evaluated. Participants filled out a questionnaire and reported whether they experienced weight loss, increased or decreased appetite, chewing or swallowing difficulties, within 6 months of the study. The mean weight, BMI, percent ideal body weight, mid arm circumference, arm muscle circumference, and percent body fat were all significantly decreased in patients with HD patients compared to healthy control participants. All biomarkers were decreased in patients with HD, but did not reach a level of significance when compared to controls. Assessment of the 3-day food records showed that mean energy intake was significantly increased in patients with HD compared to the diets of the healthy controls due to a significantly increased consumption of carbohydrates. Despite this increase in energy intake, none of the patients with HD were overweight. Results from the questionnaire found reported weight loss, increased appetite, and chewing/swallowing problems were significantly more frequent in the HD group than in controls. Solid food dysphagia was significantly associated with weight loss in the HD population, but liquid food dysphagia did not reach a significant level when compared to weight loss. A significant relationship between total motor disability scores was found in the following variables: BMI, arm muscle circumference, and percent body fat. Anthropometric values that were significantly affected by worsening chorea scores were percent body fat and BMI.

A study by Gaba et al 2005 compared the 24 hour energy expenditure (EE) and energy intake in persons with early to mid-stage HD with matched control participants.
investigating how HD affects energy balance (19). The study included 13 people with early stage HD and 9 healthy, age matched control subjects. Inclusion criteria for HD subjects were definite diagnosis of HD, a TFC score ≥6, a limited history of serious choking episodes, the ability to eat without assistance, a modified Mini Mental status of >35, and a nonsmoking or light smoking status. Participants were placed in a human respiratory chamber for 24 hours, where they were provided an ad libitum diet. Dietary intake was measured by weighing all food provided. Energy expenditure was measured via indirect calorimetry and displacement of the center of mass (DP) was also measured to assess energy expenditure due to movement. After 24 hour EE was measured, body composition to determine fat free mass and percentage body fat for each subject was assessed by using BODPOD. Metabolic measurements were 24-hour urine sample, of which protein oxidation was calculated from urinary nitrogen. Lipid and carbohydrate oxidation rates were calculated with the use of the nonprotein respiratory quotient. Non-fasting blood samples were obtained from each subject for measurement of leptin, insulin, and glucose. The CAG repeat length in the IT15 gene was determined for all HD subjects. Linear regression was used for the analysis of 24 hours TEE, SMR, and WMR with 2 independent variables; FFM and chorea score for all 22 subjects. The control subjects were assumed to have chorea and dystonia scores of 0 and a TFC of 13, indicating no functional impairment.

In the 13 participants with HD, age at diagnosis was highly correlated with CAG repeat length. There was also a strong correlation between UHDRS chorea scores and duration of disease, as defined by date of diagnosis. Free fat mass was the primary determinant of total energy expenditure, and chorea scores contributed significantly to
energy expenditure while a person was awake but not while asleep. There were no significant differences between the groups for substrate utilization, RQ, 24-hour nitrogen excretion, nonprotein RQ, or serum values for glucose, insulin, or leptin. The average TEE was approximately 11% higher in people with HD, and their SMR was approximately 9% higher, but neither value was significant compared to people who were healthy controls. There was a significant difference in waking metabolic rate (WMR) between the groups, with WMR being approximately 20% higher in people with HD. The overall average DP was significantly greater in people with HD than in healthy controls due to a greater amount of both voluntary and involuntary physical activity. DP was also significantly correlated with the UHDRS chorea score, suggesting involuntary activity was a significant component of total activity. Measured energy intake, during the 24-hr confinement in the metabolic chamber was not significantly different between the groups and most participants consumed more calories than expended during their metabolic chamber tests. The average of three free-living 24-hour dietary recalls indicated that people with HD reported greater overall dietary intake. (p<0.03)

Pratley et al 2000 extended the understanding of energy expenditure by using doubly labeled water methodology in comparison to a metabolic chamber (20). Their intent was to determine whether HD was associated with increased rates of energy expenditure or physical activity by comparing the SMR, 24 hour sedentary EE, and spontaneous physical activity (SPA) in a metabolic chamber, and across a 7 day free-living period where EE was measured by doubly labeled water methodology. A 7-day food record was also collected. Seventeen patients with HD and seventeen age, sex, and BMI matched healthy people, as controls were included in the study. Inclusion required
that patients with HD were independent in basic activities of daily living. The mean age, body weight, fat mass and free fatty mass were not significantly different between groups. On average, the mean 24-hour EE was 14% higher in patients with HD compared to controls and was thought to be the result of an increase in EE attributable to higher SPA levels in patients with HD. TEE measured in free-living conditions, by doubly labeled water, was not significantly higher in patients with HD compared to those in the control group. There was no significant difference in dietary intake between the two groups, however only 11 pairs of patient and control records could be assessed. Among the HD group, 24 hour EE/SMR correlated with severity of chorea, as did 24 hour EE, SPA, and PAEE. In contrast, SMR and TEE did not relate to disease severity when measured in the 24-hour metabolic chamber. In this study, the absence of a significant difference in SMR challenges the theory that there is an intrinsic defect in energy metabolism in patients with HD.

Djousse et al 2002 used a retrospective chart review of participants from the Huntington Study Group (HSG) data base to test the hypothesis that weight loss is a systemic component of HD that accompanies the onset of clinical symptoms (4). The chart review included 361 case subjects, over a 6 year time period, who were in the early stages of the disease. For each case, five matching controls were selected. Neither disease duration, dystonia, nor chorea was associated with BMI among case subjects with HD. However, control subjects had higher BMI than case subjects with HD who were free of chorea and dystonia, suggesting that weight loss may not be attributable to involuntary movements.

Hamilton et al 2004 used the HSG longitudinal dataset to identify rate and
correlates of weight change during the course of the disease (2). This chart review included 927 adults with a definite diagnosis of HD who were followed prospectively for an average of 3.4 years. The results from this study conflict with results found by previous studies on HD and weight loss because on average, patients gained weight over time. However, there was no control for diet or medications that are known to cause weight gain. Although the participants tended to gain weight over time, affected individuals in this sample still weighed almost 10 kg less than a community sample of comparably age-matched adults. Of the affected individuals who did lose weight, a significant relationship existed between weight loss and worsening chorea (r=-0.13; p<0.001).

The Huntington Study Group is an international, non-profit group of physicians and other health care providers from medical centers in the United States, Canada, and Australia. The HSG was formed in 1993 with the recognition that clinical research in HD requires the participation of large numbers of subjects. The aims of the HSG are to advance knowledge about the causes of the disease, disease progression, and treatment of HD and related disorders. Limitations for using this database for the previous two studies include limited data on lifestyle factors such as diet and physical activity. Also, the assessment of the independence scale, TFC, and determination of age of onset of HD rely heavily on clinical assessment, and is based on the subjective opinion of physicians. These studies did not have access to BMI before HD diagnosis to estimate the magnitude of weight loss over time. Furthermore, these studies varied in length, size, and disease progression. (23)

Aziz et al 2008 (1) aimed to specify the course of weight loss and factors
associated with it in participants from the European Huntington’s Disease Initiative (EHDI). They also assessed whether CAG repeat length was directly related to the rate of weight loss in patients with HD. This chart review included 517 patients with early stage HD who were followed over a 3-year period. The authors found that BMI decreased at a greater rate as CAG length increased, and CAG length was an independent predictor of weight loss. In other work involving murine models, they also found that transgenic mice (R6/2) with higher CAG repeats had lower body weight and consumed more energy per gram of body weight compared to mice with lower CAG repeats.

Marder et al 2009 (5) analyzed data from patients with HD participating in the Prospective Huntington At Risk Observational Study (PHAROS). Their intent was to compare participants with and without expanded CAG repeat length to determine whether differences existed in macronutrient intake, total caloric intake, and BMI, and to understand aspects of the relationship between CAG repeat length, BMI, and caloric intake. A total of 435 participants with normal CAG repeat length and 217 participants with abnormal CAG repeat lengths were included in the study. All research participants were enrolled in PHAROS between July 1999 and January 2004. The authors found that caloric intake was significantly higher in affected individuals, BMI and estimated physical activity were marginally different, and basal energy expenditure did not differ between the groups. Carbohydrate intake was significantly higher in affected individuals and accounted for the significantly higher caloric intake. Marder et al estimated that there was a 0.26 CAG unit increase for each unit increase in calorie quartile (Q1=224.4-1,296.4kcal; Q2=1,296.8-1,730.7kcal; Q3=1,734.7-2,272.1kcal; Q4=2,273.7-7,138.2kcal). Contrary to the findings by Aziz et al, 2008, this group did not find a
significant correlation between BMI and CAG repeat length. However, individuals with expanded CAG repeat length reported similar caloric intake, yet had a lower BMI compared to those with normal CAG length.

**Summary**

From these studies, it is apparent that further research is needed in the area of HD and nutrition and change in weight status over time. To date, no study has identified a specific change in weight status that occurs before physical symptoms worsen. It has been suggested that weight gain occurs before weight loss in the HD population. In a letter to the editor in the European Journal of Neurology, Robbins et al 2006 reported that weight gain appears to precede weight loss in a study of 73 HD patients (6). It has also been the observation of clinical physicians at the OSU HD clinic that patients have been steadily increasing in weight over the past 12 years. Therefore, it is the purpose of this study to identify the pattern of weight change in the OSU HD population by performing a retrospective chart review of HD patients who have attended the clinic between February 2005 and December 2011.
Chapter 3: Methodology

Research Design:

Huntington’s disease is a neurodegenerative disease that is often accompanied by changes in weight. The purpose of this study was to investigate weight changes in the OSU HD population over a 5-year period, and to investigate weight changes related to specific measurable disease outcomes. This was a retrospective longitudinal medical record review of HD patients in the OSU population, and was submitted to and approved by the OSU International Review Board (IRB).

Hypotheses

We hypothesized that the dynamic pattern of weight change would correlate with the decline of scores for tongue protrusion, dystonia, motor and chorea. Dependent variables measured were weight at each clinical visit. Independent variables measured were tongue protrusion scores, dystonia scores, motor scores, and chorea scores at each clinical visit. Also, daily medications and amounts prescribed at each clinical visit were collected.

Sample

This study reviewed medical records of all HD patients attending the OSUMC movement disorder clinic, from February 2005 to December 2011. There were approximately 250 patient medical records available for review. Exclusion criteria for this study include: individuals less than 18 years of age, prisoners, nursing home
population, individuals with one office visit, and individuals who came for genetic
counseling and tested negative (n=64). The final number of patient medical records
included in this study is 186. Patients were generally seen at 6 month intervals.

Data collected included the components of the Unified Huntington’s Disease
Rating Scale (UHDRS). The UHDRS is a tool used to measure and evaluate disease
progression, and is divided into four components assessing cognition, motor
performance, behavior, and functional capacity (21). The motor impairment component
consists of 31 questions rated on a 0 to 4 point scale, with a score of 4 indicating the most
severe impairment. The five-item cognitive component consists of a verbal fluency test,
the Symbol Digit Modalities Test, and the Stroop test. The behavioral assessment
consists of 28 items assessing severity and frequency of mood, anxiety, aggression,
psychosis, and other behavioral abnormalities. The functional component is comprised
of three subunits, which are a checklist of 25 yes/no questions, the Independence Scale,
and the Total Functional Capacity Scale. All components of the UHDRS were not
performed at every visit. The motor portion was completed at each visit. The cognitive
tests were preformed approximately every year. A simplified version of the behavioral
assessment was performed at most visits. We specifically collected motor score, tongue
protrusion score, chorea score, and dystonia scores from the UHDRS data. Body weight,
gender, age, and medications were also collected.

Instrumentation

Data was entered into an excel spreadsheet that was used to track each patients
dependent and independent variables. Patient information was accessed on electronic
medical record database from a computer in the Neurological Clinic at OSUMC and from
the Principal Investigator’s hard drive on the 7th floor of 395 W. 12th Avenue. The data collected were stored on a password protected excel file stored on a USB thumb drive. This thumb drive was kept in a locked drawer in the Principal Investigator’s desk on the 7th floor of 395 W. 12th Avenue when not in use by key personal.

A medical record number was used to identify each participant. As soon as the medical record review was completed, the list that identifies participant ID with medical record was destroyed before the data were analyzed. Data from the medical record review forms utilizing the patient medical records was entered into an excel spreadsheet on a computer located in the principal investigator’s locked office for data analysis purposes. The computer and files were password protected.

**Statistical Procedures**

The correlation between weight change and independent variables was represented as change scores. The change score was the last value minus the first value, standardized by the amount of time (years) between the first and last value. The change score represents the average weight gained or lost by subjects per year during the time of observation. A two-sample, two-tailed t-test was run to determine if medication use had an impact on weight change. Statistical analyses were run using SPSS for Windows. Level of significance was p<0.05.
Chapter 4: Results and Discussion

The purpose of this study was to investigate weight change in the OSU HD population over a 5 year period, and also investigate how weight change related to specific measurable outcomes of the disease. There were approximately 250 patient medical records available for review. Exclusion criteria for this study include: individuals less than 18 years of age, prisoners, nursing home population, individuals with one office visit, and individuals who came for genetic counseling and tested negative. A total of 186 patient medical record charts are included in this study, dating from February 2005 to December 2011. Demographic characteristics of these patients are summarized in Table 4.1.

To better understand our patient population, we categorized patients by the number of years they were followed in the clinic, as shown in Table 4.2. Table 4.3 represents demographic characteristics for first and last visit measurements for body weight, total motor score, tongue protrusion score, chorea score, and dystonia score.
<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Number of Patient Charts</td>
<td>186</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Female</td>
<td>95</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Patients who lost weight</td>
<td>86</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Patients who gained weight</td>
<td>60</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Patients with 10% or more weight loss**</td>
<td>34</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Body Weight (kg)</td>
<td>156</td>
<td>44.5</td>
<td>170.0</td>
<td>77.90</td>
<td>20.617</td>
</tr>
<tr>
<td>CAG repeat length</td>
<td>188</td>
<td>37</td>
<td>72</td>
<td>42.84</td>
<td>6.573</td>
</tr>
<tr>
<td>Total Motor Score</td>
<td>181</td>
<td>2</td>
<td>82</td>
<td>41.40</td>
<td>18.887</td>
</tr>
<tr>
<td>Tongue Protrusion Score</td>
<td>181</td>
<td>0</td>
<td>4</td>
<td>1.45</td>
<td>0.997</td>
</tr>
<tr>
<td>Chorea Score</td>
<td>182</td>
<td>0</td>
<td>24</td>
<td>9.55</td>
<td>5.196</td>
</tr>
<tr>
<td>Dystonia Score</td>
<td>182</td>
<td>0</td>
<td>43</td>
<td>3.79</td>
<td>4.544</td>
</tr>
</tbody>
</table>

**Percent weight loss was calculated as: (baseline weight-last visit weight)/baseline weight * 100
N/A=not applicable
Table 4.1. Baseline Characteristics of the OSU HD patient population.

<table>
<thead>
<tr>
<th>Years Followed</th>
<th>n</th>
<th>Percent of Population</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>56</td>
<td>30.80%</td>
<td>22</td>
<td>34</td>
</tr>
<tr>
<td>4</td>
<td>24</td>
<td>12.70%</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>39</td>
<td>20.70%</td>
<td>16</td>
<td>23</td>
</tr>
<tr>
<td>2</td>
<td>52</td>
<td>27.60%</td>
<td>30</td>
<td>22</td>
</tr>
<tr>
<td>1</td>
<td>15</td>
<td>7.90%</td>
<td>9</td>
<td>6</td>
</tr>
</tbody>
</table>

Table 4.2. Patient population categorized into number of years followed at clinic.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Visit</th>
<th>N*</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body Weight (kg)</td>
<td>First Visit</td>
<td>156</td>
<td>44.5</td>
<td>170</td>
<td>77.9</td>
<td>20.6</td>
</tr>
<tr>
<td></td>
<td>Last Visit</td>
<td>148</td>
<td>33.5</td>
<td>166.8</td>
<td>75.5</td>
<td>19.8</td>
</tr>
<tr>
<td>Total Motor Score</td>
<td>First Visit</td>
<td>181</td>
<td>2</td>
<td>82</td>
<td>41.4</td>
<td>18.9</td>
</tr>
<tr>
<td></td>
<td>Last Visit</td>
<td>184</td>
<td>1</td>
<td>101</td>
<td>54.9</td>
<td>21.7</td>
</tr>
<tr>
<td>Tongue Protrusion Score</td>
<td>First Visit</td>
<td>181</td>
<td>0</td>
<td>4</td>
<td>1.5</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Last Visit</td>
<td>184</td>
<td>0</td>
<td>4</td>
<td>2.1</td>
<td>1.1</td>
</tr>
<tr>
<td>Chore Score</td>
<td>First Visit</td>
<td>182</td>
<td>0</td>
<td>24</td>
<td>9.6</td>
<td>5.2</td>
</tr>
<tr>
<td></td>
<td>Last Visit</td>
<td>185</td>
<td>0</td>
<td>27</td>
<td>9.7</td>
<td>5.7</td>
</tr>
<tr>
<td>Dystonia Score</td>
<td>First Visit</td>
<td>182</td>
<td>0</td>
<td>4</td>
<td>3.8</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td>Last Visit</td>
<td>184</td>
<td>0</td>
<td>18</td>
<td>5.9</td>
<td>4.1</td>
</tr>
</tbody>
</table>

*From sample of 186 patient medical records.

Table 4.3. Summary of first and last visit demographic characteristics.

Total motor score is broken up into three subclasses. A score of 1-42 is mild, a score of 43-84 is moderate, and a score of 85-124 is severe. Tongue protrusion score ranges from 0 to 4. A score of 0 indicates that a patient can protrude their tongue for 10 seconds or more, and a score of 4 indicates that a patient can not protrude their tongue past their lips. Chorea score ranges from 0 to 7. A score of 0 means there are visible symptoms, and a score of 7 indicates there are severe chorea symptoms. Dystonia score ranges from 0 to 5. A score of 0 indicates there are no visible symptoms, where as a score of 5 indicates severe dystonia symptoms are present (4).

The correlation between weight change and motor scores is shown as the change between the first visit and last visit, standardized by the amount of time between first and last visits. There was a significant negative correlation between weight and motor scores. This correlation between body weight and motor scores is shown in Table 4.4.

Worsening total motor shift, dystonia shift, and chorea shift are significantly correlated to
weight shift ($r=-0.337, p<0.05; r=-0.541, p<0.05$, $r=-0.210$, $p<0.05$). Tongue protrusion shift does not have a significant relationship with weight shift ($r=-0.042$, $p=0.641$).

Patients with HD are often times on medications that can alter weight. A two-sided hypothesis test was computed to determine if the correlation between weight change and medication use was significant. Group statistics for medications is shown in Table 4.5. The four most commonly prescribed medication drug classes were antidepressants (74%), benzodiazepines (50%), antipsychotics (42%), and anticonvulsants (27%). None of these medications had a significant impact on weight shift when compared to patients who were not taking these medications. However, the dosage of these drugs was not recorded for this review. Instead, patients were assigned a value of 1 if they were marked as being prescribed the above medications, and were assigned a value of 0 if they were marked as not taking medication.

<table>
<thead>
<tr>
<th>Weight Shift</th>
<th>Pearson Correlation</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Motor Shift</td>
<td>-0.337</td>
<td>0.000</td>
</tr>
<tr>
<td>Tongue Protrusion Shift</td>
<td>-0.042</td>
<td>0.641</td>
</tr>
<tr>
<td>Chorea Shift</td>
<td>-0.210</td>
<td>0.018</td>
</tr>
<tr>
<td>Dystonia Shift</td>
<td>-0.541</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Table 4.4. Correlation between weight shift and motor score shift
<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benzodiazepines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 (p=0.997)</td>
<td>67</td>
<td>0.6504</td>
<td>10.50276</td>
<td>1.28312</td>
</tr>
<tr>
<td>1 (p=0.997)</td>
<td>64</td>
<td>0.6442</td>
<td>7.76639</td>
<td>0.97080</td>
</tr>
<tr>
<td><strong>Antidepressants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 (p=0.699)</td>
<td>24</td>
<td>-0.0371</td>
<td>6.70122</td>
<td>1.36788</td>
</tr>
<tr>
<td>1 (p=0.627)</td>
<td>106</td>
<td>0.7762</td>
<td>9.77204</td>
<td>0.94914</td>
</tr>
<tr>
<td><strong>Anticonvulsants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 (p=0.427)</td>
<td>95</td>
<td>0.9598</td>
<td>10.58150</td>
<td>1.08564</td>
</tr>
<tr>
<td>1 (p=0.240)</td>
<td>33</td>
<td>-0.5442</td>
<td>3.82374</td>
<td>0.66563</td>
</tr>
<tr>
<td><strong>Antipsychotics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 (p=0.319)</td>
<td>76</td>
<td>-0.1104</td>
<td>7.01456</td>
<td>0.80463</td>
</tr>
<tr>
<td>1 (p=0.364)</td>
<td>52</td>
<td>1.5695</td>
<td>11.94009</td>
<td>1.65579</td>
</tr>
</tbody>
</table>

Table 4.5. Relationship between weight shift and group medications.

Table 4.6 represents demographic characteristics based on total motor scores. It is generally recognized amongst HD clinicians that total motor score is broken up into three subclasses. The expert clinicians at the OSU HD clinic use the following guidelines for mild, moderate, and severe total motor score classifications: a score of 1-42 is mild, a score of 43-84 is moderate, and a score of 85-124 is severe. There was not a significant relationship between total motor score and weight loss in patients who were followed for five years. However, it is important to note that there is limited weight data available in patient charts on patients that were followed for five years. This is especially true for patients who had a severe total motor score. All patients attending the OSU HD clinic are requested to stop taking their medications 24 hours before their clinic visit. This is done to allow the clinician to fully assess the severity of disease, thus making it difficult to collect an accurate weight.
### Table 4.6. Relationship between group total motor score and weight loss over a 5 years.

<table>
<thead>
<tr>
<th>Total Motor Score</th>
<th>Total Sample**</th>
<th>5 Year Follow Up**</th>
<th>Total Sample Who Lost Weight*</th>
<th>Significance between weight loss and TMS for patients followed 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1-42</strong></td>
<td>51</td>
<td>13</td>
<td>28</td>
<td><strong>P=0.586</strong></td>
</tr>
<tr>
<td><strong>43-84</strong></td>
<td>123</td>
<td>21</td>
<td>53</td>
<td><strong>P=0.601</strong></td>
</tr>
<tr>
<td><strong>85-124</strong></td>
<td>12</td>
<td>1</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

*Weight loss is calculated as the difference between first visit and last visit weight.  
**Represents totals for last visit data.

Figure 4.1. Relationship between weight shift and CAG repeat length.
The relationship between total weight shift and CAG repeat length is represented in Figure 4.1. Although there is not a significant relationship between the two (p=0.267), there appears to be a trend in weight shift as it relates to CAG repeat length. To investigate this relationship further, we looked specifically at individuals who lost weight and what relationship, if any, there was to CAG repeat length. Figure 4.2 represents the correlation between CAG repeat length and body weight for individuals who had a net weight loss from their first to last visit. Because the total number of visits each patient had varies, we normalized their weights by plotting their average body weight. The total number of patients whose net weight change was negative equals 86, however not all patients who lost weight had a recorded CAG. The total number of patients who lost weight and had a recorded CAG equals 57. A two sample equal variance test showed that a negative correlation exists between CAG repeat length and body weight (p<0.05, r=-0.148). However, this correlation is only present for individuals whose net body weight change was negative. It is important to recognize that other factors, both external and internal, may have a greater effect on weight loss than CAG repeat length alone.
Figure 4.2. Relationship between patients with a net weight loss and CAG repeat length.

As indicated by the data, we found that lower body weight was significantly correlated with worsening chorea scores, dystonia scores, and total motor scores. Weight was not significantly correlated with worsening tongue protrusion scores. We were also able to rule out medications as a significant contributing factor to weight change in the population as a whole.

Other larger scale studies have investigated the impact of weight change on various clinical symptoms of HD. Djousse et al 2002 performed a retrospective chart review of participants from the Huntington’s Study Group to test if weight loss is a systemic component of HD that accompanies the onset of clinical symptoms. Although results did not show a significant relationship between BMI and worsening symptoms, control subjects had a higher BMI than case subjects with HD. Hamilton et al 2004 also
used the HSG longitudinal dataset to identify rate and correlates of weight change during the course of the disease. This study followed 927 patients for 3 years. Results from this study of subjects with recent onset, found that patients gained weight over time, however, they weighed 10kg less than a community sample of comparably age-matched adults. These two studies used HD patients who were in early stages of the disease, whereas our database consists of patients across a wide spectrum of disease and include a range of subjects with recent onset of disease to nursing home residents in last stages of disease.

Marder et al 2009 analyzed data from PHAROS, and investigated specifically calorie intake in HD patients. They found that calorie intake was significantly greater in HD patients when compared to controls, however BMI was not significantly different. Calorie intake is important when looking at body weight in the HD population. However, our study did not collect data on calorie intake.

Our study was the first to characterize changes in weight and motor symptoms in a single regional clinic population of HD patients over time, and to include medications as a possible contributing factor to weight change. Subjects ranged from early onset of symptoms through late stage disease demonstrating that over an extended period, weight is significantly correlated with worsening motor scores, specifically chorea, dystonia, and total motor scores. Two smaller scale studies have shown a similar correlation. (Trejo 2004, n=25 varying stages of HD; Mochel 2007, n=17 mild and moderate symptomatic HD subjects).

There are several limitations to our study. Due to available information in clinic charts, we were unable to reliably determine age of onset of HD or determine the number of years since diagnosis. We did not have information on diet history or physical
activity. Patients attending the OSU HD clinic have access to a nutritionist and physical therapist, however no information is available on whether patients follow advice of these professionals. The nutritionist has been assessing patients for approximately 6 months, and the physical therapists have been on staff for approximately 3 years. The number of visits each patient had at the clinic varies, yet this was controlled through statistics. We cannot comment on whether weight loss is due to increased involuntary movement, however other studies suggest that weight loss is present before physical symptoms, such as involuntary movements, occur (4,2). It is important to note that although weight was found to be significantly correlated with worsening motor scores, there are other factors, both external and internal, that could potentially have a greater contribution to disease severity than weight loss alone. A recent study by van der Burg et al, investigated gastrointestinal dysfunction as a contributing factor to weight loss in HD mice(24). Mutant Huntington was not only expressed in the brain, but also along the GI tract. This study demonstrated that the GI tract of HD mice was affected, causing impaired gut motility, diarrhea, and malabsorption of food. The degree of malabsorption of food was inversely associated with body weight (24).

Future studies that are potentially warranted in this area are further investigating GI dysfunction, and key nutrients that have an impact on disease progression. A recent study by Ruskin et al investigated the effects of a ketogenic diet on weight loss and motor function in HD mice. Findings from this study are encouraging, as the reduction in body weight of treated HD mice was delayed (25). There is also potential to study branch chain amino acids, specifically valine, leucine, and isoleucine, in the HD population. A previous study on HD affected individuals showed that these BCAA levels were
significantly lower in HD population, and levels of BCAA were correlated with weight loss and UHDRS values (16).

**Conclusion.** Our study investigated the dynamic pattern of weight change in relation to worsening motor scores. Our results show that there was a significant correlation between a decrease in weight and worsening chorea, dystonia, and total motor scores. To our knowledge, this is the first study to assess all patients within one community’s HD referral center over time. Future studies to replicate these results, and to determine a rate of weight change that occurs before physical symptoms worsen, could be beneficial for practicing clinicians and their HD patients. This information is beneficial to the HD community, to acknowledge that weight change is correlated to disease progression, and warrants future studies in this area.
Chapter 5: Correlation Between Weight Loss And Select Motor Scores From A Retrospective Chart Review Of Huntington’s Disease Patients.

Abstract

Objective. Huntington’s disease (HD) is a neurodegenerative disease that is accompanied by a progressive movement disorder and changes in weight. It is the purpose of this present study to investigate how weight change relates to specific measures of disease characteristics in the OSU HD population over a 5-year period.

Methods. A retrospective chart review of patients attending the OSU HD clinic between 2005 and 2011 was performed. Statistical analysis was used to show correlation between weight change and independent variables, represented as change scores. A two-sided hypothesis test was used to determine if the correlation between weight change and the change in other variables was significant.

Results. A total of 186 patient charts were available for review. Lower body weight was correlated significantly with worsening total motor score, chorea score, and dystonia score (p=0.000, p=0.018, p=0.000). Tongue protrusion score did not correlate with body weight (p>0.05). Class of medication use did not significantly correlate with body weight changes and thus was ruled out as a significant contributing factor to weight change.

Conclusions. Our results show that there is a significant correlation between a decrease in weight and worsening chorea, dystonia, and total motor scores.
Keywords: Huntington’s disease, total motor score, weight loss, chorea, dystonia, CAG repeat length

Introduction

Huntington’s disease is an autosomal dominant neurodegenerative disease caused by a CAG repeat expansion in the exon 1 of the Huntington’s (Htt) gene (1). Common physical characteristics of the disease include severe motor impairment such as chorea, dystonia, and bradykinesia. HD is also accompanied by cognitive impairment and behavioral changes such as depression, irritability, apathy, and inflexibility. Along with these symptoms, significant weight loss has been associated with the disease, even though affected individuals report an increased appetite and consume more energy than non-affected controls (2). This weight loss tends to contribute to general weakness and a decline in the quality of life for patients with HD (3). While several investigators have attempted to identify the cause of this unintended weight loss, it is thought that the root cause of weight loss may be multifactorial and not due to choreiform movement alone. Recently diagnosed patients, who have minimal chorea, also have lower body mass indices (BMI) than sex and age matched control patients (2).

Several retrospective chart reviews have been performed with the goal of identifying which characteristics of HD are most significantly related to weight loss. Djousse et al (4) sought to test the hypothesis that weight loss is an element of HD that accompanies the onset of clinical symptoms by reviewing 361 patients who were in the early stages of HD from the Huntington Study Group (HSG). Results suggest that neither disease duration, dystonia, nor chorea were associated with BMI among
participants with HD. However, control subjects had higher BMI than case subjects with HD who were free of chorea and dystonia, and suggests that weight loss is less likely to be attributable to involuntary movements. Another study using the HSG, by Hamilton et al (2), examined longitudinal weight data to identify rate and correlates of weight change during the course of the disease. This chart review included 927 adults with a definite diagnosis of HD who were followed prospectively for an average of 3.4 years. These results conflict with previous studies involving HD and weight loss because on average, patients gained weight over time (0.11±1.7kg/yr.). However, Hamilton et al did not control for diet or medications that are known to cause weight gain. Although patients with HD tended to gain weight over time, affected individuals in this sample still weighed almost 10 kg less than a community sample of comparably healthy, age-matched adults. The authors found that affected individuals who did lose weight, showed a significant relationship between weight loss and worsening chorea (p<0.001).

Aziz et al (3) aimed to specify the course of weight loss in participants from the European Huntington’s Disease Initiative (EHDI) study, and to determine factors that were associated with weight loss. They also assessed whether CAG repeat length was directly related to the rate of weight loss in HD patients. They found that BMI decreased at a greater rate as CAG length increased, and that CAG length was an independent predictor of weight loss. Additionally, the authors evaluated CAG repeat length and caloric intake in transgenic mouse (R6/2) models and found that mice, fed ad libidum, with higher CAG repeats had lower body weight and consumed more energy per gram of body weight compared to mice with lower CAG repeats.
Marder et al (5) analyzed individual dietary intake of patients in the Prospective Huntington At Risk Observational Study (PHAROS) to determine whether there were differences in macronutrient intake, total caloric intake, and BMI, based on CAG repeat length $\geq 37$. Caloric intake was significantly higher in affected individuals with expanded CAG repeat length. BMI and estimated physical activity were marginally different, while basal energy expenditure did not differ. Calorie intake was significantly higher in affected individuals, which was due to a significantly greater intake of carbohydrates ($p=0.02$) than individuals with normal CAG repeat length. Marder estimated that there is a 0.26 CAG unit increase for each unit increase in calorie quartile. (Q1=224.4-1,296.4 kcal; Q2=1,296.8-1,730.7 kcal; Q3=1,734.7-2,272.1 kcal; Q4=2,273.7-7,138.2 kcal)

Contrary to the findings from Aziz et al, 2008, Marder et al did not find a significant correlation between BMI and CAG repeat length. However, they did observe that individuals with expanded CAG repeat length reported similar caloric intake, yet had a lower BMI compared to those with normal CAG length.

Interestingly, in a 2006 letter to the editor by Robbins et al, it was reported that weight gain appears to precede weight loss in a study of 73 HD patients (6). It has also been the anecdotal observation of the HD clinicians at the OSU HD clinic that, as a whole, there have been increasingly more overweight or obese patients attending the clinic over the past 12 years.

It is important to be aware of the weight changes that occur in HD, and the ramifications weight change can have on health outcomes in this population. Therefore, the objectives of this retrospective medical record review were to analyze the weight status of the OSU Huntington Disease patient population, and to determine if there is a
relationship between weight change and symptom scores, including tongue protrusion scores, motor scores, chorea scores, and dystonia scores between February 2005 and December 2011.

Methods

Sample. This study is a review of medical records of HD patients attending The Ohio State University Huntington’s Clinic, from February 2005 to December 2011. There were approximately 250 patient medical records available for review. Exclusion criteria for this study include: individuals less than 18 years of age, prisoners, nursing home population, individuals with one office visit, and individuals who came for genetic counseling and tested negative (n=64). The final number of patient medical records included in this study is 186.

Data collected include the components of the Unified Huntington’s Disease Rating Scale (UHDRS). The UHDRS is a tool used to measure and evaluate disease progression, and is divided into four components assessing cognition, motor performance, behavior, and functional capacity (21). The motor impairment component consists of 31 questions rated on a 0 to 4 point scale, with a score of 4 indicating the most severe impairment. The five-item cognitive component consists of a verbal fluency test, the Symbol Digit Modalities Test, and the Stroop test. The behavioral assessment consists of 28 items assessing severity and frequency of mood, anxiety, aggression, psychosis, and other behavioral abnormalities. The functional component is comprised of three subunits, which are a checklist of 25 yes/no questions, the Independence Scale, and the Total Functional Capacity Scale. This study specifically collected motor score,
tongue protrusion score, chorea score, and dystonia scores from the UHDRS data. We also collected body weight, gender, age, and medications.

**Instrumentation.** Data was entered into an excel spreadsheet that was used to track each patients dependent and independent variables. Patient information was accessed from the hospitals integrated healthcare information system, from a computer in the Neurological Clinic at OSUMC and from the PI’s hard drive on the 7th floor of 395 W. 12th Avenue. The data collected was stored on a password protected excel file stored on a USB thumb drive. This thumb drive was kept in a locked drawer in the Principal Investigator’s desk on the 7th floor of 395 W. 12th Avenue when not in use by key personal.

A medical record number (MRR) was used to identify each participant. As soon as the MRR review was completed, the list that identifies participant ID with medical record was destroyed before the data was analyzed.

**Statistical Procedures.** The correlation between weight change and independent variables are represented as change scores. The change score is the last value minus the first value, standardized by the amount of time between the first and last value. Time in this case is measured in years. The change score represents the average weight gained or lost by subjects per year during the time of observation. A two-sided hypothesis test was computed to determine if the correlation between weight change and the change in other variables was significant. All data was analyzed in SPSS for Windows, Version 19.0. Level of significance was p<0.05.
Results

The purpose of this study was to investigate weight change in the OSU HD population over a 5 year period, and also investigate how weight change related to specific measurable outcomes of the disease. There were approximately 250 patient medical records available for review. Exclusion criteria for this study include: individuals less than 18 years of age, prisoners, nursing home population, individuals with one office visit, and individuals who came for genetic counseling and tested negative (n=64). A total of 186 patient medical record charts are included in this study, dating from February 2005 to December 2011. Demographic characteristics of these patients are summarized in Table 5.1.

To better understand our patient population, we categorized patients by the number of years they were followed in the clinic, as shown in Table 5.2. Table 5.3 represents demographic characteristics for first and last visit measurements for body weight, total motor score, tongue protrusion score, chorea score, and dystonia score.
<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Number of Patient</td>
<td>186</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Charts</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>95</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Patients who lost weight</td>
<td>86</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Patients who gained weight</td>
<td>60</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Patients with 10% or more</td>
<td>34</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>weight loss**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body Weight (kg)</td>
<td>156</td>
<td>44.5</td>
<td>170.0</td>
<td>77.90</td>
<td>20.617</td>
</tr>
<tr>
<td>CAG repeat length</td>
<td>186</td>
<td>37</td>
<td>72</td>
<td>42.84</td>
<td>6.573</td>
</tr>
<tr>
<td>Total Motor Score</td>
<td>181</td>
<td>2</td>
<td>82</td>
<td>41.40</td>
<td>18.887</td>
</tr>
<tr>
<td>Tongue Protrusion Score</td>
<td>181</td>
<td>0</td>
<td>4</td>
<td>1.45</td>
<td>0.997</td>
</tr>
<tr>
<td>Chorea Score</td>
<td>182</td>
<td>0</td>
<td>24</td>
<td>9.55</td>
<td>5.196</td>
</tr>
<tr>
<td>Dystonia Score</td>
<td>182</td>
<td>0</td>
<td>43</td>
<td>3.79</td>
<td>4.544</td>
</tr>
</tbody>
</table>

**Percent weight loss was calculated as: (baseline weight - last visit weight)/baseline weight * 100
N/A=not applicable

Table 5.1. Baseline Characteristics of the OSU HD patient population.

<table>
<thead>
<tr>
<th>Years Followed</th>
<th>n</th>
<th>Percent of Population</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>56</td>
<td>30.80%</td>
<td>22</td>
<td>34</td>
</tr>
<tr>
<td>4</td>
<td>24</td>
<td>12.70%</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>39</td>
<td>20.70%</td>
<td>16</td>
<td>23</td>
</tr>
<tr>
<td>2</td>
<td>52</td>
<td>27.60%</td>
<td>30</td>
<td>22</td>
</tr>
<tr>
<td>1</td>
<td>15</td>
<td>7.90%</td>
<td>9</td>
<td>6</td>
</tr>
</tbody>
</table>

Table 5.2. Patient population categorized into number of years followed at clinic.
Table 5.3. Summary of first and last visit demographic characteristics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Visit</th>
<th>N*</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body Weight (kg)</td>
<td>First Visit</td>
<td>156</td>
<td>44.5</td>
<td>170</td>
<td>77.9</td>
<td>20.6</td>
</tr>
<tr>
<td></td>
<td>Last Visit</td>
<td>148</td>
<td>33.5</td>
<td>166.8</td>
<td>75.5</td>
<td>19.8</td>
</tr>
<tr>
<td>Total Motor Score</td>
<td>First Visit</td>
<td>181</td>
<td>2</td>
<td>82</td>
<td>41.4</td>
<td>18.9</td>
</tr>
<tr>
<td></td>
<td>Last Visit</td>
<td>184</td>
<td>1</td>
<td>101</td>
<td>54.9</td>
<td>21.7</td>
</tr>
<tr>
<td>Tongue Protrusion Score</td>
<td>First Visit</td>
<td>181</td>
<td>0</td>
<td>4</td>
<td>1.5</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Last Visit</td>
<td>184</td>
<td>0</td>
<td>4</td>
<td>2.1</td>
<td>1.1</td>
</tr>
<tr>
<td>Chore Score</td>
<td>First Visit</td>
<td>182</td>
<td>0</td>
<td>24</td>
<td>9.6</td>
<td>5.2</td>
</tr>
<tr>
<td></td>
<td>Last Visit</td>
<td>185</td>
<td>0</td>
<td>27</td>
<td>9.7</td>
<td>5.7</td>
</tr>
<tr>
<td>Dystonia Score</td>
<td>First Visit</td>
<td>182</td>
<td>0</td>
<td>4</td>
<td>3.8</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td>Last Visit</td>
<td>184</td>
<td>0</td>
<td>18</td>
<td>5.9</td>
<td>4.1</td>
</tr>
</tbody>
</table>

*From sample of 186 patient medical records.

Total motor score is broken up into three subclasses. A score of 1-42 is mild, a score of 43-84 is moderate, and a score of 95-124 is severe. Tongue protrusion score ranges from 0 to 4. A score of 0 means that a patient can protrude their tongue for 10 seconds or more, and a score of 4 means that a patient can not protrude their tongue past their lips. Chorea score ranges from 0 to 7. A score of 0 means there are visible symptoms, and a score of 7 indicates there are severe chorea symptoms. Dystonia score ranges from 0 to 5. A score of 0 indicates there are no visible symptoms, whereas a score of 5 indicates severe dystonia symptoms are present. (Djousse et al, 2002)

The correlation between weight change and motor scores is shown as the change between the first visit and last visit, standardized by the amount of time between first and last visits. There was a significant negative correlation between weight and motor scores. This correlation between body weight and motor scores is shown in Table 5.4. Total motor shift dystonia shift, and chorea shift are significantly correlated to weight shift (r=-
0.337, p<0.05; r=-0.541, p=<0.05, r=-0.210, p<0.05). Tongue protrusion shift does not have a significant relationship with weight shift (r=-0.042, p=0.641).

<table>
<thead>
<tr>
<th>Weight Shift</th>
<th>Pearson Correlation Coefficient</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Motor Shift</strong></td>
<td>-0.337</td>
<td>0.000</td>
</tr>
<tr>
<td><strong>Tongue Protrusion Shift</strong></td>
<td>-0.042</td>
<td>0.641</td>
</tr>
<tr>
<td><strong>Chorea Shift</strong></td>
<td>-0.210</td>
<td>0.018</td>
</tr>
<tr>
<td><strong>Dystonia Shift</strong></td>
<td>-0.541</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Table 5.4. Correlation between weight shift and motor score shift.

Patients with HD are often times on medications that can alter weight. A two-sided hypothesis test was computed to determine if the correlation between weight change and medication use was significant. Group statistics for medications is shown in Table 5.5. The four most commonly prescribed medication drug classes were antidepressants (74%), benzodiazepines (50%), antipsychotics (42%), and anticonvulsants (27%). None of these medications had a significant impact on weight shift when compared to patients who were not taking these medications. However, the dosage of these drugs was not recorded for this review. Instead, patients were assigned a
value of 1 if they were marked as being prescribed the above medications, and were assigned a value of 0 if they were marked as not taking medication.

<table>
<thead>
<tr>
<th>Benzodiazepines</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (p=0.997)</td>
<td>67</td>
<td>0.6504</td>
<td>10.50276</td>
<td>1.28312</td>
</tr>
<tr>
<td>1 (p=0.997)</td>
<td>64</td>
<td>0.6442</td>
<td>7.76639</td>
<td>0.97080</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antidepressants</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (p=0.699)</td>
<td>24</td>
<td>-0.0371</td>
<td>6.70122</td>
<td>1.36788</td>
</tr>
<tr>
<td>1 (p=0.627)</td>
<td>106</td>
<td>0.7762</td>
<td>9.77204</td>
<td>0.94914</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anticonvulsants</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (p=0.427)</td>
<td>95</td>
<td>0.9598</td>
<td>10.58150</td>
<td>1.08564</td>
</tr>
<tr>
<td>1 (p=0.240)</td>
<td>33</td>
<td>-0.5442</td>
<td>3.82374</td>
<td>0.66563</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antipsychotics</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (p=0.319)</td>
<td>76</td>
<td>-0.1104</td>
<td>7.01456</td>
<td>0.80463</td>
</tr>
<tr>
<td>1 (p=0.364)</td>
<td>52</td>
<td>1.5695</td>
<td>11.94009</td>
<td>1.65579</td>
</tr>
</tbody>
</table>

Table 5.5. Relationship between weight shift and group medications.

Table 5.6 represents demographic characteristics based on total motor scores. It is generally recognized amongst HD clinicians that total motor score is broken up into three subclasses. The expert clinicians at the OSU HD clinic use the following guidelines for mild, moderate, and severe total motor score classifications: a score of 1-42 is mild, a score of 43-84 is moderate, and a score of 85-124 is severe. There was not a significant relationship between total motor score and weight loss in patients who were followed for five years. However, it is important to note that there is limited weight data available in patient charts on patients that were followed for five years. This is especially true for patients who had a severe total motor score. All patients attending the OSU HD clinic
are requested to stop taking their medications 24 hours before their clinic visit. This is done to allow the clinician to fully assess the severity of disease, thus making it difficult to collect an accurate weight.

<table>
<thead>
<tr>
<th>Total Motor Score</th>
<th>Total Sample**</th>
<th>5 Year Follow Up**</th>
<th>Total Sample Who Lost Weight*</th>
<th>Significance between weight loss and TMS for patients followed 5 years.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-42</td>
<td>51</td>
<td>13</td>
<td>28</td>
<td>P=0.586</td>
</tr>
<tr>
<td>43-84</td>
<td>123</td>
<td>21</td>
<td>53</td>
<td>P=0.601</td>
</tr>
<tr>
<td>85-124</td>
<td>12</td>
<td>1</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

*Weight loss is calculated as the difference between first visit and last visit weight.
**Represents totals for last visit data.

Table 5.6. Relationship between group total motor score and weight loss over a 5 years period.
Figure 5.1. Relationship between weight shift and CAG repeat length.

The relationship between total weight shift and CAG repeat length is represented in Figure 5.1. Although there is not a significant relationship between the two (p=0.267), there appears to be a trend in weight shift as it relates to CAG repeat length. To investigate this relationship further, we looked specifically at individuals who lost weight and what relationship, if any, there was to CAG repeat length. Figure 5.2 represents the correlation between CAG repeat length and body weight for individuals who had a net weight loss from their first to last visit. Because the total number of visits each patient had varies, we normalized their weights by plotting their average body weight. The total
number of patients whose net weight change was negative equals 86, however not all patients who lost weight had a recorded CAG. The total number of patients who lost weight and had a recorded CAG equals 57. A two sample equal variance test showed that a negative correlation exists between CAG repeat length and body weight (p<0.05, r=-0.148). However, this correlation is only present for individuals whose net body weight change was negative. It is important to recognize that other factors, both external and internal, may have a greater effect on weight loss than CAG repeat length alone.

Figure 5.2. Relationship between patients with a net weight loss and CAG repeat length.
Discussion

As indicated by the data, we found that lower body weight is significantly correlated with worsening chorea scores, dystonia scores, and total motor scores. Weight was not significantly correlated with worsening tongue protrusion scores. We were also able to rule out medications as a significant contributing factor to weight change in the population as a whole.

Other larger scale studies have investigated the impact of weight change on various clinical symptoms of HD. Djousse et al 2002 performed a retrospective chart review of participants from the Huntington’s Study Group to test if weight loss is a systemic component of HD that accompanies the onset of clinical symptoms. Although results did not show a significant relationship between BMI and worsening symptoms, control subjects had a higher BMI than case subjects with HD. Hamilton et al 2004 also used the HSG longitudinal dataset to identify rate and correlates of weight change during the course of the disease. This study followed 927 patients for 3 years. Results from this study of subjects with recent onset found that patients gained weight over time, however, they weighed 10kg less than a community sample of comparably age-matched adults. These two studies used HD patients who were in early stages of the disease, whereas our database consists of patients across a wide spectrum of the disease and include a range of subjects with recent diagnosis to nursing home residents in last stages of disease.

Marder et al 2009 analyzed data from PHAROS, and investigated specifically calorie intake in HD patients. They found that calorie intake was significantly greater in HD patients when compared to controls, however BMI was not significantly different.
Calorie intake is important when looking at body weight in the HD population, however, our study did not collect data on calorie intake.

Our study was the first to characterize changes in weight and motor symptoms in a single regional clinic population of HD patients over time, and to include medications as a possible contributing factor to weight change. Subjects ranged from early onset of symptoms through late stage disease demonstrating that over an extended period, weight is significantly correlated worsening with motor scores, specifically chorea, dystonia, and total motor scores. Two smaller scale studies have shown a similar correlation. (Trejo 2004, n=25 varying stages of HD; Mochel 2007, n=17 mild and moderate symptomatic HD subjects).

There are several limitations to our study. Due to available information in clinic charts, we were unable to reliably determine age of onset of HD or determine the number of years since diagnosis. We did not have information on diet history or physical activity. Patients attending the OSU HD clinic have access to a nutritionist and physical therapist, however no information is available on whether patients follow advice of these professionals. The nutritionist has been working with patients for 6 months, since Fall 2011, and the physical therapists have been on staff for approximately 3 years. The number of visits each patient had at the clinic varies, yet this was controlled through statistics. We cannot comment on whether weight loss is due to increased involuntary movement, however other studies suggest that weight loss is present before physical symptoms, such as involuntary movements, occur (4,2). It is important to note that although weight was found to be significantly correlated with worsening motor scores, there are other factors, both external and internal, that could potentially have a greater
contribution to disease severity than weight loss alone. A recent study by van der Burg et al, investigated gastrointestinal dysfunction as a contributing factor to weight loss in HD mice(24). Mutant Huntington is not only expressed in the brain, but also along the GI tract. This study demonstrated that the GI tract of HD mice is affected, causing impaired gut motility, diarrhea, and malabsorption of food. The degree of malabsorption of food was inversely associated with body weight. (24)

Future studies that are potentially warranted in this area are further investigating GI dysfunction, and investigating key nutrients that have an impact on disease progression. A recent study by Ruskin DN et al investigated the effects of a ketogenic diet on weight loss and motor function in HD mice. Findings from this study are encouraging, as the reduction in body weight of treated HD mice was delayed. (25). There is also potential to study branch chain amino acids, specifically valine, leucine, and isoleucine, in the HD population. A previous study on HD affected individuals showed that these BCAA levels were significantly lower in HD population, and levels of BCAA was correlated with weight loss and UHDRS values (16).

**Conclusion.** Our study investigated the dynamic pattern of weight change in relation to worsening motor scores. Our results show that there is a significant correlation between a decrease in weight and worsening chorea, dystonia, and total motor scores. To our knowledge, this is the first study to assess all patients within one community’s HD referral center over time. Future studies to replicate these results, and to determine a rate of weight change that occurs before physical symptoms worsen, could be beneficial for practicing clinicians and their HD patients. This information is beneficial to the HD
community, to acknowledge that weight change is correlated to disease progression, and warrants future studies in this area.
References:


