Body Composition and Health of Children with Hemophilia

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A Thesis

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This is to certify I have read the Master's thesis of

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List of Abbreviations and Acronyms

BMI	Body Mass Index
CDC	Centers for Disease Control
CDRC	Child Development and Rehabilitation Center
CwH	Children with Hemophilia
FM	Fat Mass
LM	Lean Mass
OHSU	Oregon Health & Science University
PWH	Persons with Hemophilia
UDC	Universal Database Collection
USDA	United States Department of Agriculture

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Specific Aims and Hypotheses:

Children with hemophilia (CwH) are advised to take special precautions when engaging in physical activity due to the risk of bleeding from an injury. The obesity epidemic we currently face in the general population is evident in CwH as well. Research suggests those with a body mass index (BMI) in the overweight and obese ranges have an increased risk of experiencing joint mobility limitations (1).

Despite the risks associated with physical activity, participation in exercise is highly encouraged. Treatment for hemophilia includes a complex multidisciplinary care network to provide education and support needed for patients to lead a healthy and active life. CwH work closely with physical therapists who can recommend exercise regimens that are safe. However, children in the general pediatric population are typically more sedentary than past generations making overweight and obesity an increasing problem (2). Recently, research has shown that managing weight, including decreasing caloric intake and increasing physical activity, is advantageous to the overall health of CwH (3). However, BMI calculations alone may not consistently predict indicators of health status, such as weight and body composition (4). Body composition measurements involving the ratio of fat mass to lean body mass have yet to be reported in the hemophilia pediatric population.

For this research project, we hypothesize that the majority of CwH will have more fat mass and lower lean body mass compared to age-, sex- and BMI- matched unaffected control children. Furthermore, we hypothesize that those CwH who engage in regular physical activity and have a higher lean body mass composition will have better health outcomes. To test these hypotheses, we will:

Specific Aim #1: Analyze the body composition of CwH using bioelectrical impedance analysis (BIA) and compare to a control group. *Hypothesis*- CwH have a lower lean body mass and higher fat mass than children with a similar age, gender and BMI in the unaffected group.

Specific Aim #2: Measure the effects of lean body mass versus fat mass on health outcomes in children with hemophilia. *Hypothesis*- Children's percent fat is inversely correlated with physical activity and positively correlated with food insecurity and dietary intake.

Background

Overview

Hemophilia is a rare bleeding disorder that is characterized by a lack of or insufficient clotting factor in the blood. Clotting factors are proteins found in plasma which aid in blood coagulation. Lack of clotting factor impairs the coagulation of blood leading to a prolonged hemorrhage due to an inability to properly clot when a blood vessel is ruptured. The amount of clotting factor present in the blood is used to classify the severity of hemophilia as being mild, moderate, or severe. A person with a severe diagnosis has less than 1% of the normal clotting factor activity and is at a higher risk for hemorrhage than a person with a mild or moderate diagnosis. There are two types of hemophilia - A and B. Hemophilia occurs in 1 in 5,000 live male births, with hemophilia A being 4 times as common than hemophilia B. Persons with hemophilia A have a deficiency of clotting factor VIII. Meanwhile, hemophilia B is associated with a deficiency in clotting factor IX (5).

Inheritance of Hemophilia

Hemophilia is a genetic disorder inherited in an X-linked recessive pattern. A male child receives an X-chromosome from his mother and a Y-chromosome from his father. If the X-chromosome carries the gene associated with hemophilia, he will have hemophilia. A female child receives an X-chromosome from each parent. If the child receives one X-chromosome that carries the hemophilia trait from the mother, a carrier, she could have bleeding complications related to her carrier status. Hemophilia is extremely rare among females (5). Although Hemophilia is passed down from the mother to children, in some cases, hemophilia occurs as the result of a spontaneous mutation. This occurs in approximately 30% of cases (6). A mutation of the F8 and F9 genes are responsible for Hemophilia A and B respectively. These mutations cause

the clotting factor proteins produced from the F8 or F9 genes to either not work or to be missing entirely (5, 7).

Diagnosis

Screening tests and clotting tests are used to diagnose hemophilia. A screening test involves the collection of a blood sample and is used to analyze the blood's ability to clot. If impaired, the clotting test is then used to determine the type and severity of hemophilia. If a family history of hemophilia is known, screening and clotting tests are bypassed and a test to determine if clotting factor is present is conducted. One third of babies with hemophilia are diagnosed without having a previous family history. In these cases, a screening test may be warranted if a newborn experiences unusual bleeding after circumcision, heel sticks, or unusual bruises. According to the CDC, approximately 400 babies in the U.S. are diagnosed with severe hemophilia each year (7, 8).

Symptoms of Hemophilia

Signs and symptoms of hemophilia aren't always clear since bleeding can occur both externally and internally. While an external bleeding episode is easily visible, an internal episode can go unnoticed. Signs of an internal bleeding episode include bruising, redness, or tenderness in a designated area. Internal bleeding episodes in hemophilia typically occur in the joints such as the knees or elbows. Persons with hemophilia usually report feelings of tightness and swelling in the injured joint when an internal bleed has transpired. Other signs of internal bleeding may include blood in the urine, feces, or vomit. Internal bleeding episodes in the brain can lead to significant adverse side effects ranging from headaches to seizures to death (9).

Complications of Hemophilia

Repeated bleeding episodes can stimulate a number of complications such as joint disease, infection, and psychological distress. Bleeding in the joints can cause chronic swelling, discomfort, pain, and limited mobility. Associated swelling can increase pressure placed on nerves and potentially lead to permanent nerve damage and pain. Repeated bleeding episodes can also damage the lining of joints causing synovitis, a condition of chronic inflammation in the joints.[15] Synovitis can result in degeneration of the joints which can cause extreme pain. Hemorrhages located in the head and brain can cause seizures, paralysis, and death (10). Goals of treatment should aim to prevent and treat complications associated with hemophilia.

Hemophilia Treatments

Factor Replacement Therapy

Factor replacement therapy is the preferred method of treatment for moderate and severe hemophilia (11). It involves injecting the missing clotting factor into a peripheral vein. The clotting factor is then immediately available for use in the bloodstream promoting proper clotting of the blood. A catheter can also be implanted under the skin and inserted into a central vein for infusion of factor replacement. The severity of an individual's disorder dictates the frequency of factor replacement (12). Treatment can be provided prophylactically or on-demand.

Prophylaxis

Prophylaxis is considered the optimal treatment for children with moderate to severe hemophilia (12). This treatment method involves the infusion of clotting factor on a regular basis to prevent bleeds from occurring. There are two types of prophylaxis - primary and secondary.

Primary prophylaxis is typically continued for a long period of time beginning infusions at an early age. Secondary prophylaxis involves regular infusion of treatment on a short-term basis (13).

Advantages and Disadvantages

The advantages of prophylaxis include reduced risk of joint damage, ability to participate in physical activity, and decreased risk of bleeding (12). The main disadvantage of factor replacement therapy is that it is a very expensive treatment costing anywhere from $500 to $10,000 per dose (depending on the person's weight, inhibitor status, factor type, and insurance coverage). Prophylaxis has served as a hallmark treatment for individuals with hemophilia. It has mitigated the effects and disabilities associated with the disease due to the individualized regimens that are currently available. Prophylaxis has aided in the improvement of quality of life and life expectancy of persons with hemophilia. Adherence to treatments is essential for successful management (14). A 2017 literature review concluded individuals using prophylaxis had significantly better average health related quality of life than those who received on demand factor (15).

Other Treatment Types

On-Demand is another treatment option for individuals with hemophilia. Patients can inject clotting factor on an as needed basis to treat specific bleeding episodes. Factor replacement is injected following an injury to provide clotting factor and promote normal healing (12).

Lifestyle Recommendations

Regular exercise can help strengthen the muscle tone and decrease risk of bleeding episodes, as well as improve quality of life (16). Physical activity recommendations should reflect the interests and functional capacity of the individual. Since some physical activity can

lead to injury, a great deal of caution is involved for CwH. This can potentially encourage a more sedentary lifestyle for the child. Regardless of the risk of bleeding episodes, physical exercise is one of the basic foundations in the hemophilia treatment plan (17).

Obesity and Body Mass Index

Obesity in Hemophilia

Childhood obesity has more than doubled in the past thirty years. The prevalence of obesity in CwH is similar to that of the general U.S. population (8). A 2005 CDC report stated that 16.4% of CwH were overweight compared to 13.7% in the general population in the United States (18). According to a 2011 study, more than 23% of patients with hemophilia were found to be obese in the United States (18). It's imperative that CwH maintain a healthy weight since excess weight has an adverse impact on weight-bearing joints. Added stress to the joints can increase risk of bleeding and joint disease (19). Trends among studies suggest as BMI increases, a patient's range of motion decreases in their lower extremities (18).

In 2011, a study recruited 15 obese adults with hemophilia and 15 age-matched control subjects of normal weight. Joint limitations were compared between groups. It was concluded that the obese group experienced heightened pain and joint limitations compared to those of normal weight. Furthermore, one-third of obese hemophilia patients had osteoarthritis compared to 20% of the normal-weight patients (20). Obesity is a preventable disease and interventions can be made to help the hemophilia population lead healthy, active lives. Maintenance of a healthy weight and BMI can be established through regular physical activity and a healthy diet. Such lifestyle modifications can diminish pain, a severe co-morbidity, experienced in hemophilia (21).

Physical Activity and Joint Limitations

The World Federation of Hemophilia and the National Hemophilia Foundation both encourage CwH to participate in regular physical activity due to its extensive benefits. Evidence suggests physical activity promotes a healthy body weight, enhances muscle strength, physical functioning, and increases self-esteem (22). Engagement in physical activity has also been shown to decrease frequency of bleeding episodes and thus limit joint pain and dysfunction. Due to the strong body of evidence, physical activity is always recommended and encouraged to significantly promote enhanced quality of life for CwH. However, previous studies have identified lower physical activity levels among children and adolescents with hemophilia. A 2017 study found that CwH tend to be less fit, have a lower aerobic exercise tolerance, and are more overweight compared to the general pediatric population (23).

Physical Activity Levels in CwH

Several studies have reported the physical activity levels among children with hemophilia. However, the results are inconclusive as to whether they vary between CwH and the general pediatric population. A 2014 study revealed 79% of participants between the ages of 5 to 14 years participated in physical activity at least 4 days per week. Additionally, 62% of participants ages 15-64 years reported a high level of physical activity (24). Therefore, the majority of participants met the 2008 Physical Activity Guidelines for Americans. A pilot study investigated the physical activity patterns of boys with hemophilia including type, frequency, intensity, and duration.[5] The study found boys with severe hemophilia reported more time in sedentary activities compared to those with mild and moderate forms. The researchers attributed the increase in sedentary activity among the severe population to previously existing arthropathy.

Until the development of prophylaxis treatment for hemophilia, CwH were instructed to abstain from physical activity to reduce their risk of injury and bleeding. CwH who are primarily sedentary, may experience some fear around participation in physical activity due to their perceived risk. Behavior change approaches to increase their understanding of the benefits of exercise can be used to inspire participation (25).

Joint Limitation

Recurrent joint bleeding episodes can create pain, muscle atrophy, and restricted movement in CwH. Soucie et al. (2004) analyzed the effect of disease severity on joint limitation. Limitations in joint mobility were positively associated with number of bleeding episodes, older age, nonwhite race, and increased BMI (26). The goal of hemophilia care is to minimize incidences of bleeding. As established earlier, maintaining a healthy BMI can reduce the frequency of bleeding and consequently joint limitations. A cross-sectional study conducted by Gringeri et al. (2004) found 11.3% of children aged 4 to 16 years with a diagnosis of severe hemophilia experienced functional joint impairments (27). Many studies are in agreement that severe hemophilia is associated with the escalation of joint limitations. Boadas et al (2015) evaluated the effect of swimming exercises on musculoskeletal pain in eight youth participants (mean age 18.8 years) with severe hemophilia (28). After participating in regular swimming, the children and adolescents reported a decrease in elbow pain, as well as, an increase of muscle strength in the ankles. This study suggested physical activity can improve joint mobility and relieve symptoms of pain in the hemophilia population. Exercise programs should be modified to reduce risk of harm to those with hemophilia while providing the same physical, psychological, and social benefits that are associated with engaging in physical activity (28).

Physical Activity Recommendations

Physical activity and exercise are fundamental components of the hemophilia treatment care plan. Niu (2014) concluded in a recent literature review a detailed exercise regimen that includes aerobic activity of 150 minutes at a moderate level per week combined with resistance training 2-3 times per week should be encouraged at hemophilia treatment centers (24). Additional leisure activities should be encouraged as well. This study presents the ability for CwH to participate in physical activities rated at a moderate intensity. Recommendations for CwH participating in organized sports include supervision by an adult, adherence to prophylaxis regimen, and avoidance of high contact sports (17).

There is a risk of injury with sports participation. However, there are limited records to support a relationship between injuries and high contact sports in populations of CwH. A retrospective, cohort study assessed participation of CwH in sports and risk for injury in 30 males 10-18 years old. Of the study sample with hemophilia, 20.8% were overweight and 16.7% were obese. Forty percent of the subjects participated in basketball which is considered a moderately dangerous sport based on the National Hemophilia Foundation guidelines. The results showed 75% of subjects experienced an injury, but did not require additional factor to treat. The number of injuries experienced were the same among participants who participated in sports as among those who did not. Therefore, McGee et al. concluded that the benefits of physical activity far outweigh the risks (29). Those who are concerned about CwH participating in sports can make appropriate preparations to maximize their safety.

A 2017 study by Sholzberg investigated coagulation activity in response to physical activity in persons with hemophilia. Twenty-two adults with hemophilia A and B were recruited to participate. After engaging in 5 minutes of moderate intensity exercise, participants

experienced a 3% increase of clotting factor which was found to be statistically significant (30). This topic of research is currently in its infancy and the mechanism of action pertaining to the increase in clotting factor is unknown. However, the evidence is consistent in that recommendations should support exercise regimens that are individualized to the child's interests and medical history. It's recommended that hemophilia care providers consider the child's bleeding history when making physical activity recommendations.

Treatment Implications and Cost

Obesity and Prophylaxis

Recent studies have investigated the complications of obesity related to factor replacement therapy. Increased adipose tissue, or increased adiposity can limit venous visibility and access when administering prophylaxis. According to the Universal Data Collection (UDC) database, individuals with obesity had significantly lower infusion rates compared to those of normal weight. This discrepancy may be attributed to challenges in visualizing veins due to excessive adiposity. A lack of adherence to factor replacement therapy can increase risk of bleeding episodes. Especially in cases of children using on-demand treatment, it is critical to be able to easily access treatment sites in order to receive clotting factor immediately (31).

Additional complications related to treatment include a decrease in dosing accuracy for those who are obese since dosing of factor replacement is based on patient's weight. Since fat tissue contains less blood than lean tissue, dosing based on body weight has the potential to overestimate total blood volume. A 2013 study reported a 1.4-fold increase in the use of clotting factor in obese patients compared to non-obese patients with hemophilia (32). While there are no adverse effects related to higher doses of factor replacement, there is a direct correlation to cost.

Studies have suggested, moderate weight loss could result in pharmacoeconomic benefits, as well as, routine dosing adherence (33). Kidwell et al., (2016) has suggested to dose clotting factor based on ideal body weight (IBW) rather than actual body weight (ABW) for CwH who fall within obesity ranges (34).

Cost of Prophylaxis

The cost of treatment for hemophilia is extremely high and can cause financial stress for patients and caregivers (35). A retrospective, cross-sectional study including a cohort of adult patients analyzed the economic and psychosocial burden of severe hemophilia in five European countries. Total one-year costs of severe hemophilia among all five countries was estimated to be 1.55 billion dollars. Per patient costs were estimated to be $199,541. Furthermore, 97% of costs were directly related to clotting factor replacement therapy (36). Since prophylaxis is a lifelong treatment for CwH, the economic costs are substantial. A retrospective study conducted in the U.S. analyzed patient out-of-pocket (OOP) expenses. Annual costs from a total of 762 male patients with hemophilia were calculated. The mean per patient OOP cost averaged $2,672/year for hemophilia A and $1,838/year for hemophilia B (37).

Another study compared healthcare costs of children utilizing prophylaxis treatment compared to children who were not. The results showed that children receiving prophylaxis had significantly lower hemophilia-related non-pharmacy costs than their counterpart. They also had fewer hemophilia-related emergency room visits. Although pharmaceutical costs are high, other expenses are saved when utilizing prophylaxis (38).

Food Security

According to the USDA, food security refers to a household's physical, social, and economic access to sufficient, safe, and nutritious food that provides for an active and healthy

life (39). Currently, there are no published studies revealing poverty or food insecurity within the hemophilia population. According to the U.S. Census, the median household income in 2015 was $56,516 (40). With prophylaxis costs estimated at $199,541 per year and out-of-pocket costs averaged at $2,672 per year, it is probable that many families experience food insecurity (36). It is also important to consider other factors that could impact a family's financial state before drawing conclusions, such as reduced parental employment due to child health needs.

Study Objectives

As previously stated, managing a healthy weight and BMI is important for decreasing the occurrence of bleeding episodes in hemophilia. By maintaining a normal BMI, there is less pressure placed on the joints preventing damage and decreasing joint limitations. A child's ability to engage in activities is critical for their quality of life. Appropriate treatment and care plans should be developed to support normal functioning and activity (21). Currently, there is no published literature analyzing the effect of body composition on health outcomes including physical activity and quality of life in children with hemophilia. Our study aims to analyze the differences in body composition including fat mass and lean body mass in children with hemophilia. Since BMI is not an indicator of fat mass, it can falsely identify an individual as obese. The results from our study may provide preliminary data for appropriately making weight-based recommendations for improved health outcomes for children with hemophilia.

Methods and Procedures

Each participant visited Doernbecher Children's Hospital clinics or outreach sites one time to collect measurements. The procedures that were performed are listed in table 1 (below). Anthropometric measurements, dietary intake assessment, and physical activity questionnaire were obtained from subjects at their time of visit. Measurement of weight and height are part of routine clinical care for hemophilia and pediatric patients. Anthropometric measurements were obtained from the patient's medical records via EPIC, OHSU's electronic medical record system. The consent and authorization form, food security survey, 24-hour diet recall, physical activity survey, 6-minute walk test and BIA measurement used for this study took approximately 20 minutes to complete. Study surveys and data collection forms are in appendix.

Table 1. Study Visit Procedures
Informed Consent/Assent/HIPAA Authorization
Medical Release Form Completion
Inclusion/Exclusion Assessment
Measurement of Height
Measurement of Weight
BIA Measurement
24 Hour Recall
Physical Activity Questionnaire
Six Minute Walking Test
Food Insecurity Questionnaire

General Study Design

This study represents an observational prospective study carried out at Oregon Health and Science University's Child Development and Rehabilitation Center (CDRC). We worked with families who receive care at the Hemophilia Center at OHSU and Doernbecher Children's Hospital general pediatrics clinic. We compared body composition between children with hemophilia and age-sex- BMI- matched controls in the general pediatric population. We also examined the relationship between body composition, physical activity, dietary intake and food security in children with hemophilia aged 5 through 18 years. Anthropometric measurements, 24-hour dietary intake, physical activity questionnaire, and food security questionnaire were

obtained at the study visit. Written informed parental consent and child assent for children over the age of 7 was obtained.

Study Population and Recruitment

Subjects aged 5 years through 18 years with an established diagnosis of hemophilia A or B were recruited from the Hemophilia Center at OHSU. Ten age, gender and BMI matched controls aged 5 years through 18 years were recruited from the General Pediatric Clinic at Doernbecher Children's Hospital who were in overall good health and did not have hemophilia. Eligible children with hemophilia and children for the control group without hemophilia were identified by chart review or provider referral. Families of children from 5 through 18 years old were provided a handout about the study at the time of a clinic visit or at a Pediatric- or Hemophilia Center-affiliated outreach event. Inclusion and exclusion criteria are summarized in Table 2a. Children recruited for the study were required to stand for anthropometric measurements including weight and height. They were also required to complete a dietary recall from the prior day with help from a parent or guardian. Children with the following characteristics were excluded from this study: one or more missing limbs, altered fluid balance, implanted defibrillators, diagnosis of failure to thrive, abnormal weight gain and an eating disorder. Assessments that are part of children's routine clinical care were carried out in keeping with provider recommendations and routine clinical practice.

Table 2a. Inclusion and Exclusion Criteria for Test Subject Recruitment	
Inclusion Criteria	**Exclusion Criteria**
Ages 5 through 18 years	One or more missing limbs
Male	Implanted defibrillator
Diagnosis of Hemophilia A or B	Diagnosis of failure to thrive, abnormal weight gain, or an eating disorder
Willing to participate in the study	Altered fluid balance
	Inability to play

Parents of qualified children under 10 years of age were asked to complete study questionnaires on behalf of their children. Parents of children 10 years or older were asked to assist in the completion of study questionnaires with their child's input. Outcome data (weight and height) assessed as part of routine clinical care was obtained by chart review for each participating child.

Participants did not receive a payment for participation in this study. However, a graph reporting child body composition and dietary intake was provided to the child and their parent. Parental consent and child assent was obtained for all subjects (eIRB #12047).
Non-English-speaking subjects were excluded from this study.

Table 2b. Inclusion and Exclusion Criteria for Control Subject Recruitment	
Inclusion Criteria	**Exclusion Criteria**
Ages 5 through 18 years	One or more missing limbs
Male	Implanted defibrillator
Willing to participate in the study	Diagnosis of failure to thrive, abnormal weight gain, or an eating disorder
	Altered fluid balance
	Inability to play

Anthropometric Measurements and Analysis

After consent and assent were received from study subjects, they were directed into a clinic room where anthropometric measurements were taken. Height was measured in both inches (in) and centimeters (cm) using a stadiometer. For the most accurate measurements, participants were instructed to remove their shoes, socks, and outerwear, as well as stand upright against the wall until their measurements are completed. The CDC growth chart was used to chart height-for-age and then expressed as a percentile and z-score (41).For the purposes of this study, a z-score greater than 1 was considered normal, a z-score -2 or less was be considered low height-for-age, and a z-score greater than 2 will be considered a high height-for-age. Weight was recorded in both kilograms (kg) and pounds (lb). Participants were instructed to remain barefoot, with light clothing, and stand on the scale to obtain measurements. A bioimpedence

analyzer [Biodynamics 450] was used to obtain resistance, body cell mass, lean body mass, fat mass, basal metabolic rate (BMR), body mass index (BMI), intracellular water, extracellular water, and total body water measurements. The bioimpedence analysis works on the basis that lean tissue contains more water than adipose tissue. To complete this test, the participants remained barefoot, with light clothing, and removed any jewelry they were wearing. They then laid in a supine position on the exam table with their arms at their sides, thighs not touching. The participant's right wrist, hand, ankle, and foot were gently cleaned with an alcoholic wipe. Red electrodes were attached to their right wrist and ankle; meanwhile, black electrodes were attached to their right hand and foot. Leads were then attached to each of the four electrodes. Subjects were instructed to refrain from moving during this procedure. The bioimpedence analyzer was then turned on. The patient's age, gender, height and weight was entered and the test was then performed. A printout was generated including their resistance in ohms, body cell mass, extracellular mass, lean body mass, fat mass in pounds, as well as, percent fat mass. BMR was recorded in calories (Kcals) and BMI in kg/m^2. Intracellular water, extracellular water, and total body water were recorded in liters (L) and as a percent of total body water. Following this procedure, weight and BMI was charted on a CDC growth chart according to the participant's age and expressed as a percentage and a z-score. Once anthropometric measurements were completed, study subjects were asked to put their shoes, socks, and outerwear back on.

Dietary Intake Analysis

Dietary intake was acquired using a 24-hour multi-pass technique. The study subject or the subject's parent or guardian provided the interviewer with a list of foods the subject had eaten in the past 24 hours, as well as the time and occasion of intake. The interviewer probed the

subject for details including brands of food consumed, preparation methods, and amounts. Dietary assessment software (Food Processor, ESHA Research, 2006) was used to analyze the child's diet to determine calories, carbohydrate (g), fat (g), and protein (g).

Physical Activity Questionnaire

A validated physical activity questionnaire (PAQ-C/A) was used to assess each subject's physical activity level over the previous 7-day period (42). The subject completed the questionnaire with the help of their parent or guardian. The questionnaire asked about activities participated in, number of days participated Monday through Sunday, as well as total minutes or hours of involvement. An activity score 1-5 was calculated for each item, 1 indicating low physical activity and 5 indicating high physical activity. A mean of all scores was then computed to assign one composite physical activity score for each participant.

Six Minute Walking Test

A six-minute walking test was performed at the Hemophilia or Pediatric Clinic (43). Participants were asked to wear comfortable clothing and appropriate shoes for walking. In addition, participants were asked to avoid vigorous activity two hours prior to the test. Each participant was assessed for any contraindications before beginning the test. The participant was then asked to stand in preparation for the exam. A lap counter was set to zero and a timer was set to 6 minutes. The participant was then instructed to walk as far as possible without running, back and forth, in a hallway for a total of six minutes. Rest periods were optional at any time. The number of laps and distance were recorded in meters at the completion of the six-minute walk.

Food Insecurity

Food insecurity status was assessed using the USDA's "U.S. Household Food Security Survey Module, 2012." Participants were asked with the help of their parent or guardian to answer the 18 multiple choice questions related to their access to food, ability to afford food, types of food, and food eaten in their household over the last year (44). Once completed, responses were scored to assess their food security level – high, marginal, low and very low food security. Two or more affirmative responses – "yes," "often," "sometimes," "almost every month," "some months," and "1-2 months" – were required for a classification of very low food security (39).

Outcome Variables

Body composition outcome variables included height, weight, BMI, percent lean body mass (%LBM), and percent fat mass (%FM). Outcome measures such as height, weight, and BMI were normalized as a percentile and as a z-score. BMI was categorized into underweight, normal weight, overweight, and obese (45). Dietary intake variables included calories, protein (g), fat (g), and carbohydrates (g). These were also expressed as g/kg of body weight. Outcome measures were normalized as a percentage of total dietary intake. Physical activity variables included physical activity questionnaire scores and distance in the 6-minute walk test. Data from each study procedure were collected and written on the study data collection sheet, "Nutrient Intake and Body Composition in Children with Hemophilia."

Data Analysis:

Descriptive statistics included means and standard deviations as measures of central tendency and variance for all primary outcome variables: height, weight, BMI, % LBM, % FM, calories, protein (g/kg and % of calories), fat (% of calories), carbohydrates (% of calories), and physical activity level. Percentiles and z-scores were taken from recordings in patients charts through EPIC, OHSU's electronic health record system; or from Medcalc, an online clinical calculator database. A paired t-test was used to determine the significance of differences in body composition between variables in the hemophilia pediatric population and the general pediatric population. A p value <0.05 was considered statistically significant. Analyses were carried out using PRISM (Graphpad, La Jolla, CA Version 7).

Results

Specific Aim #1: Analyze the body composition of CwH using bioelectrical impedance analysis (BIA) and compare to a control group. Hypothesis- CwH have a lower lean body mass and higher fat mass than children with a similar age, gender and BMI in the unaffected group.

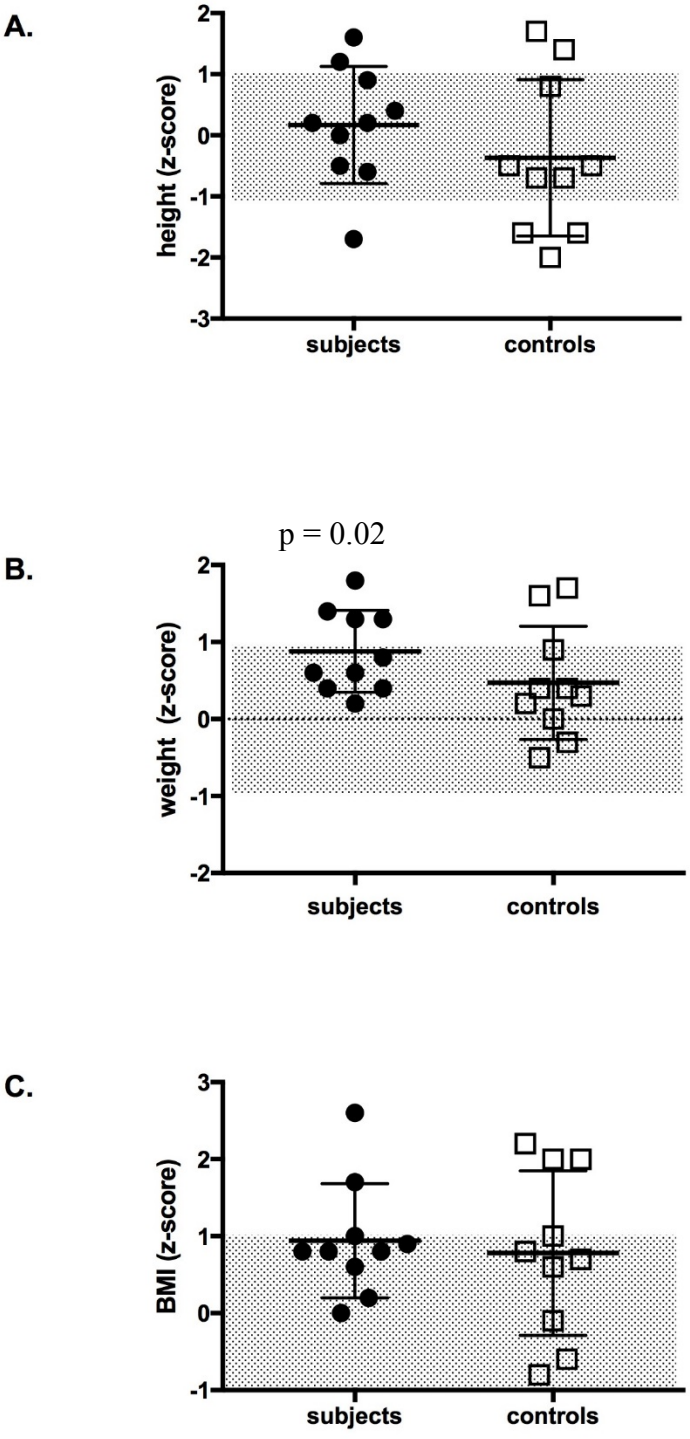
Anthropometrics and body composition measurements were completed in 10 study participants with hemophilia and 10 age- gender- and BMI-matched controls. Characteristics of the study participants are given in Table 1. There was no difference in fat mass % ($p = 0.9$) or lean mass % ($p = 0.67$) between CwH and the control group

There were no differences between groups for height or weight. Height, weight, and BMI z-scores are shown in Figure 1 A, B, C respectively. Height, weight, and BMI percentiles are shown in Figure 2A, B and C respectively. We observed a statistically significance difference in weight percentiles (-20.59 ± 28.51), as well as, weight z-scores (-0.41 ± 0.463). The control group had lower weight percentiles and weight z-scores compared to CwH.

Table 3. Body Composition Variables for Study Participants (n=20)				
	Subjects (n=10)	**Range**	**Controls (n=10)**	**Range**
Mean Age (years)	12.2 ± 4.7	(5, 18)	12.6 ± 5.0	(5, 19)
Mean Wt (kg)	51.5 ± 20.8	(20.0, 78.3)	49.3 ± 19.4	(17.3, 69.1)
Mean Ht (in)	59.9 ± 10.9	(43.3, 71.7)	59.0 ± 11.7	(40.0, 72.0)
Mean BMI	25.1 ± 3.0	(16,25)	21.0 ± 2.9	(16.6, 23.8)
% FM	11.1 ± 8.1	(3.0, 19.3)	11.0 ± 3.7	(5.6, 17.0)
% LM	87.7 ± 8.5	(70.3, 97.0)	89.0 ± 3.7	(83.0, 94.2)

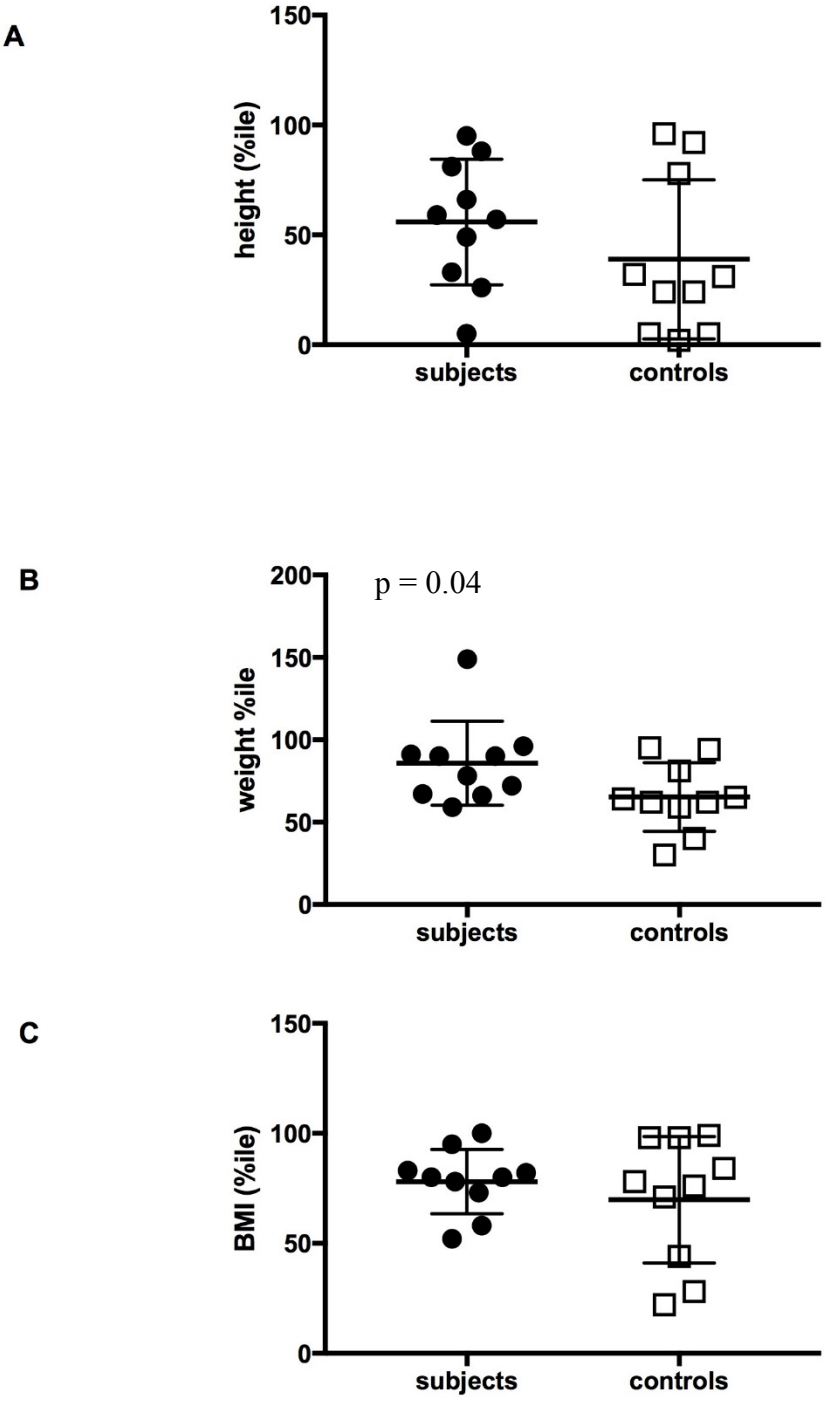
Data presented as means, standard deviations, and ranges.

Figure 1.



Box plots represent mean (middle horizontal line) and 95% confidence intervals of the data. Individual data points are illustrated. Black dots represent CwH and open squares represent controls.

Figure 2.



Box plots represent mean (middle horizontal line) and 95% confidence intervals of the data. Individual data points are illustrated. The black dots represent CwH and open squares represent controls.

Specific Aim #2: *Measure the effects of lean body mass versus fat mass on health outcomes in children with hemophilia. Hypothesis- Children's percent fat is inversely correlated with physical activity and positively correlated with food insecurity, and dietary intake.*

All 10 subjects and 10 controls completed the six-minute walk test without any complications. Distances were recorded in meters (see Figure 3A). There were no significant differences found between the subject and control groups. The mean distance for CwH was 655 ± 110 meters compared to 648 ± 72 meters in the control group ($p = 0.85$).

In addition to the six-minute walk test, all 10 subjects and 10 controls completed the Physical Activity Questionnaire for Children (PAQ-C) or Adolescents (PAQ-A). The questionnaire used was determined based on their school grade. The questionnaire assessed participation in different physical activities over a 7-day period. There were no significant differences found between the subject and control groups. The mean activity score for CwH (2.8 ± 1) was not statistically significant different than the mean for controls (2.5 ± 0.8) ($p = 0.85$). See Figure 3B.

Both groups completed the 18-item USDA Household Food Security Survey Module. This tool assessed access and availability to nutritionally adequate foods. Subjects received a score between 0 and 8; 0 being high or marginal food security and 8 being very low food security. Households for one out of ten of the CwH responded affirmatively to one or more of the food security questions. The household with affirmative response received a score of 8 reflecting a household with very low food security. None of the control subjects responded affirmatively to the questionnaire and were all deemed food secure. A chi square analysis was performed to examine the prevalence of food security between groups. The results are given in Table 3. The

test was found to be statistically significant ($p = 0.03$), and therefore indicates increased food insecurity in the CwH group compared to the control group.

Twenty-four-hour diet recalls were completed by 10 of the study subjects with hemophilia, as well as 10 of the controls. Characteristics of the study participants' dietary intake are reported in Table 2. There were no significant differences reported between CwH and controls in regard to total energy, energy per kg of body weight, total grams of carbohydrates, total grams of protein, and total grams of fat.

Table 4. Dietary Intake Variables for Study Participants (n=20)

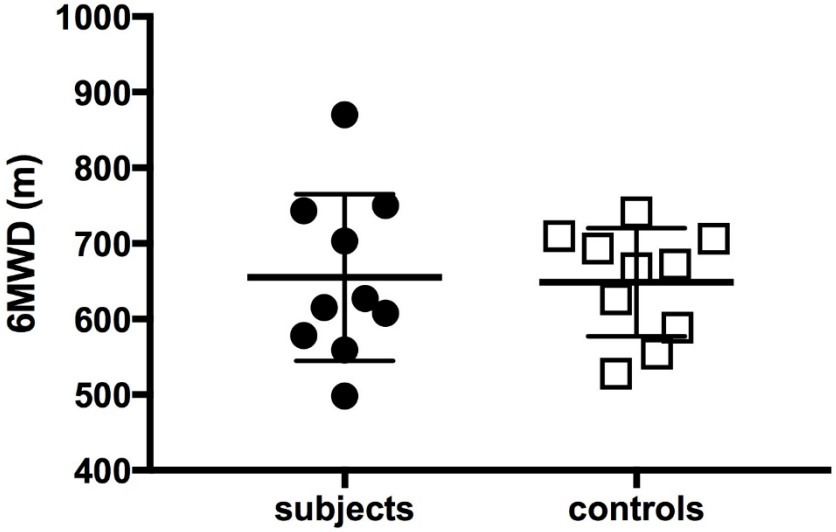
	Subjects (n=10)	Range	Controls (n=10)	Range	P value
Total Energy	1794.3	1036, 3114	1911.5	1052, 2877	0.6625
CHO (grams)	230.4	166, 306	261.5	168, 402	0.2661
CHO (g/kg)	4.5		5.3		
CHO (%kcal)	53.2	34.5, 64.1	54.91	45.1, 63.9	0.5384
PRO (grams)	73.5	36.3,113.3	75.3	39.3, 127.1	0.9005
PRO (g/kg)	1.4		1.5		
PRO (%kcal)	16.1	12.4, 18.9	16.24	9.0, 38.8	0.9617
FAT (grams)	65.6	33.8, 173.6	71.7	30.8, 151	0.7008
FAT (g/kg)	1.3		1.5		
FAT (%kcal)	30.91	22.5, 50.2	32.7	25.7, 47.2	0.5841

Data presented as means and ranges.

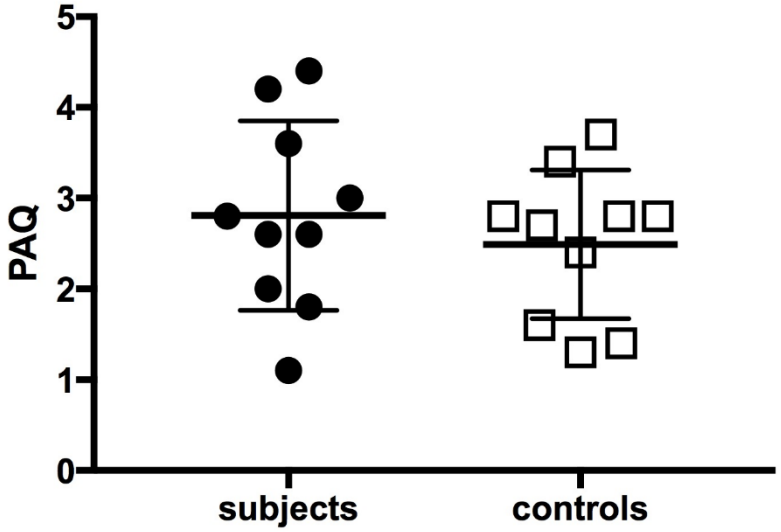
Table 3. Chi Square Analysis of Food Security for Study Participants (n=20)			
	Food Secure	**Food Insecure**	**n**
CwH	9 9.50 (0.03)	1 0.50 (0.50)	10
Controls	10 9.50 (0.03)	0 0.50 (0.50)	10
	19	**1**	**20**

Figure 3.

A.



B.



Box plots represent mean (middle horizontal line) and 95% confidence intervals of the data. Individual data points are illustrated. The black dots represent CwH and open squares represent controls.

6MWD: Six Minute Walk Distance
PAQ: Physical Activity Questionnaire

Discussion

This is the first evaluation to assess the differences in body composition of CwH compared to a control group. Previous studies have analyzed differences in populations in regard to BMI and weight, but not lean mass versus fat mass. It has been concluded from prior research that maintaining a normal BMI enhances the health of CwH, including reduced pain, joint damage, increased mobility and quality of life. In addition, Kidwell (2016) established the importance of body composition in relation to dosing accuracy since dosing is based on body weight (34). Adipose tissue contains less blood volume than muscle, therefore, BMI can overestimate the amount of factor required for a CwH (46). Due to the substantial number of recommendations for PWH based on weight, further research relative to the distribution of lean mass to fat mass, supports the significance of our current study.

In this study, there were no differences in body composition of CwH compared to the pediatric control population. The CwH seen in OHSU's Doernchecher Children's Hospital are scheduled for regular clinic visits and receive care from a multidisciplinary team. In this small cohort, CwH who have the same BMI as a comparable control population have a similar % fat mass and lean body mass. This study did not find differences in BMI between groups in comparison to previous studies which found CwH to have a higher BMI than the general pediatric population.[2] This is shown in the data from the CDC (2005) which found 16.4% of CwH to be overweight compared to 13.7% in the general pediatric population in the U.S (18). The BMI ranges of our CwH in a small population contrast that of the national population.

Results of this study revealed no differences in physical activity levels based on both the physical activity questionnaire and six-minute walk test. Previous studies have not observed consistent results in relation to physical activity levels of CwH. A 2014 study reported 79% of

their participants (CwH) to be active at least 4 days per week (24). However, a 2016 pilot study found CwH to engage in more sedentary activities (47). This study confirms previous findings by Niu (2014) that CwH engage in exercise that meets the 2008 Guidelines for Americans (24). Since physical activity levels were comparable between groups in the current study, this could contribute to the similarities between study groups in body composition including % fat mass and lean mass.

Weight was not different between groups. However, our analysis did find significant differences between groups in weight z-scores and weight percentiles. As a collective, the control group had lower weight z-scores and percentiles compared to CwH. Since we had to adjust our control criteria to match the CwH, the statistical significance found could be attributed to a type one error, the incorrect conclusion that a difference exists when no difference is truly present. The difference between groups could also be attributed to other factors such as inaccuracy in height and weight measurements since they were completed by different nursing staff at clinic visits. The CDC growth charts are used to assess growth percentiles among children 2 through 19 years of age compared to a global population. A z-score is a measure of how much an individual value varies from the population mean. Each individual participant was compared to the normal distribution of weight for that participant's age and sex. In this case, our sample is no longer compared just between the CwH or control group, but to a larger population of children with a broader age and BMI range that made up our control group. There was no difference in body weight by t-test between groups, but the control group did have a slightly lower mean and range compared to the CwH. The conversion of these relatively minor difference in body weight to population percentiles and z-scores appeared to exaggerate the differences of weight z-scores (95% CI: -40.98 to -0.20; -0.74 to -0.08).

With reference to food security, one subject in the CwH group responded affirmatively and deemed to be of "very low food security." There were no cases of food insecurity in the control group. The prevalence of food insecurity among CwH was found to differ significantly ($p>0.05$) compared to the control group. Interpretation is limited due to a small sample size. It would be interesting to distribute the USDA U.S. Household Food Security Survey Module to hemophilia treatment centers on a national level to be completed by families of CwH. Future studies should assess the poverty and food security levels of all patients receiving prophylaxis. The American Academy of Pediatrics recommends pediatricians incorporate a food insecurity screening tool into their practice. Furthermore, they deem the USDA's 18-item survey to be the standard tool for research. However, for ease and decreased patient burden, the two-item tool including a subset of questions from the USDA's Household Food Security Survey Module may be more practical (48). Recommendations for resources available for receiving financial aid and insurance can then be made within hemophilia treatment centers. Such assistance should be made part of the multidisciplinary care approach for CwH.

The main limitation of this study was the small sample size. For this study, we were also limited to recruitment from one hemophilia treatment center. During the recruitment phase, it was also difficult to find age- and BMI- matched controls. As a result, we had to loosen the criteria for matched controls: +/- 1 year of age, +/- 2 kg/m^2 (BMI). If allotted more time for subject recruitment, it would have been beneficial to attend hemophilia-related events or outreach clinics.

Our study used two different types of questionnaires to assess physical activity levels and food security status. Children along with a parent or guardian completed the questions to the best of their ability. With such models, there is always room for bias and inaccuracy in reporting data.

However, both questionnaires used have been previously validated and we observed no differences in physical activity between groups. No differences in physical activity corresponds to our body composition data suggesting a similar body composition between groups.

There have been many strides in the treatment plan and options available for CwH over the past decade. Children and adults with hemophilia are experiencing a longer life expectancy, as well as fewer complications due to effective treatment strategies such as, prophylaxis factor replacement. Increasing evidence to support maintenance of a healthy weight and physical activity schedule have also been critical in the care plan among hemophilia treatment centers worldwide and recent findings related to BMI and physical activity. Future directions should include the analysis of body composition of CwH for a larger population. Physical activity, dietary intake, and food security should be taken into consideration during these endeavors.

This study established methods for evaluating the body composition and health status of CwH. There is a limited body of literature assessing these parameters in the hemophilia population. Future studies using similar methods in a larger population are needed to definitively test these hypotheses. Healthy lifestyle practices including a nutritious diet, physical activity, and adherence to treatment plan are fundamental for providing excellent healthcare. CwH are capable of living long, healthy, and active lives.

Appendix A

U.S. HOUSEHOLD FOOD SECURITY SURVEY MODULE:
THREE-STAGE DESIGN, WITH SCREENERS
Economic Research Service, USDA
September 2012

Revision Notes: The food security questions are essentially unchanged from those in the original module first implemented in 1995 and described previously in this document.
September 2012:

- Corrected skip specifications in AD5
- Added coding specifications for "How many days" for 30-day version of AD1a and AD5a. ***July 2008:***
- Wording of resource constraint in AD2 was corrected to, "…because there wasn't enough money for food" to be consistent with the intention of the September 2006 revision.
- Corrected errors in "Coding Responses" Section ***September 2006:***
- Minor changes were introduced to standardize wording of the resource constraint in most questions to read, "…because there wasn't enough money for food."
- Question order was changed to group the child-referenced questions following the household- and adult-referenced questions. The Committee on National Statistics panel that reviewed the food security measurement methods in 2004-06 recommended this change to reduce cognitive burden on respondents. Conforming changes in screening specifications were also made. NOTE: Question numbers were revised to reflect the new question order.
- Follow up questions to the food sufficiency question (HH1) that were included in earlier versions of the module have been omitted.
- User notes following the questionnaire have been revised to be consistent with current practice and with new labels for ranges of food security and food insecurity introduced by USDA in 2006.

Transition into Module (administered to all households):
These next questions are about the food eaten in your household in the last 12 months, since (current month) of last year and whether you were able to afford the food you need.

Optional USDA Food Sufficiency Question/Screener: Question HH1 (This question is optional. It is not used to calculate any of the food security scales. It may be used in conjunction with income as a preliminary screener to reduce respondent burden for high income households).

HH1. [IF ONE PERSON IN HOUSEHOLD, USE "I" IN PARENTHETICALS, OTHERWISE, USE "WE."]

Which of these statements best describes the food eaten in your household in the last 12 months: —enough of the kinds of food (I/we) want to eat; —enough, but not always the kinds of food (I/we) want; —sometimes not enough to eat; or, —often not enough to eat?

1. Enough of the kinds of food we want to eat
2. Enough but not always the kinds of food we want
3. Sometimes not enough to eat
4. Often not enough to eat

[ ] DK or Refused

Household Stage 1: Questions HH2-HH4 (asked of all households; begin scale items).

[IF SINGLE ADULT IN HOUSEHOLD, USE "I," "MY," AND "YOU" IN PARENTHETICALS; OTHERWISE, USE "WE," "OUR," AND "YOUR HOUSEHOLD."]

HH2. Now I'm going to read you several statements that people have made about their food situation. For these statements, please tell me whether the statement was often true, sometimes true, or never true for (you/your household) in the last 12 months—that is, since last (name of current month).

The first statement is "(I/We) worried whether (my/our) food would run out before (I/we) got money to buy more." Was that often true, sometimes true, or never true for (you/your household) in the last 12 months?

[ ] Often true
[ ] Sometimes true
[ ] Never true
[ ] DK or Refused

HH3. "The food that (I/we) bought just didn't last, and (I/we) didn't have money to get more." Was that often, sometimes, or never true for (you/your household) in the last 12 months?

[ ] Often true
[ ] Sometimes true
[ ] Never true
[ ] DK or Refused

HH4. "(I/we) couldn't afford to eat balanced meals." Was that often, sometimes, or never true for (you/your household) in the last 12 months?

[ ] Often true
[ ] Sometimes true
[ ] Never true
[ ] DK or Refused

Screener for Stage 2 Adult-Referenced Questions: If affirmative response (i.e., "often true" or "sometimes true") to one or more of Questions HH2-HH4, OR, response [3] or [4] to question HH1 (if administered), then continue to ***Adult Stage 2;*** otherwise, if children under age 18 are present in the household, skip to ***Child Stage 1,*** otherwise skip to ***End of Food Security Module.***

NOTE: In a sample similar to that of the general U.S. population, about 20 percent of households (45 percent of households with incomes less than 185 percent of poverty line) will pass this screen and continue to Adult Stage 2.

Adult Stage 2: Questions AD1-AD4 (asked of households passing the screener for Stage 2 adult-referenced questions).

AD1. In the last 12 months, since last (name of current month), did (you/you or other adults in your household) ever cut the size of your meals or skip meals because there wasn't enough money for food?

[ ] Yes
[ ] No (Skip AD1a)
[ ] DK (Skip AD1a)

AD1a. [IF YES ABOVE, ASK] How often did this happen—almost every month, some months but not every month, or in only 1 or 2 months?

[ ] Almost every month
[ ] Some months but not every month
[ ] Only 1 or 2 months
[ ] DK

AD2. In the last 12 months, did you ever eat less than you felt you should because there wasn't enough money for food?

[ ] Yes
[ ] No
[ ] DK

AD3. In the last 12 months, were you every hungry but didn't eat because there wasn't enough money for food?

[ ] Yes
[ ] No
[ ] DK

AD4. In the last 12 months, did you lose weight because there wasn't enough money for food?

[ ] Yes
[ ] No
[ ] DK

Screener for Stage 3 Adult-Referenced Questions: If affirmative response to one or more of questions AD1 through AD4, then continue to ***Adult Stage 3;*** otherwise, if children under age 18 are present in the household, skip to ***Child Stage 1,*** otherwise skip to ***End of Food Security Module.***

NOTE: In a sample similar to that of the general U.S. population, about 8 percent of households (20 percent of households with incomes less than 185 percent of poverty line) will pass this screen and continue to Adult Stage 3.

Adult Stage 3: Questions AD5-AD5a (asked of households passing screener for Stage 3 adult-referenced questions).

AD5. In the last 12 months, did (you/you or other adults in your household) ever not eat for a whole day because there wasn't enough money for food?

[ ] Yes
[ ] No (Skip AD5a)
[ ] DK (Skip AD5a)

AD5a. [IF YES ABOVE, ASK] How often did this happen—almost every month, some months but not every month, or in only 1 or 2 months?

[ ] Almost every month
[ ] Some months but not every month
[ ] Only 1 or 2 months
[ ] DK

Child Stage 1: Questions CH1-CH3 (Transitions and questions CH1 and CH2 are administered to all households with children under age 18) Households with no child under age 18, skip to ***End of Food Security Module.***

SELECT APPROPRIATE FILLS DEPENDING ON NUMBER OF ADULTS AND NUMBER OF CHILDREN IN THE HOUSEHOLD.

Transition into Child-Referenced Questions:
Now I'm going to read you several statements that people have made about the food situation of their children. For these statements, please tell me whether the statement was OFTEN true, SOMETIMES true, or NEVER true in the last 12 months for (your child/children living in the household who are under 18 years old).

CH1. "(I/we) relied on only a few kinds of low-cost food to feed (my/our) child/the children) because (I was/we were) running out of money to buy food." Was that often, sometimes, or never true for (you/your household) in the last 12 months?

[ ] Often true
[ ] Sometimes true
[ ] Never true
[ ] DK or Refused

CH2. "(I/We) couldn't feed (my/our) child/the children) a balanced meal, because (I/we) couldn't afford that." Was that often, sometimes, or never true for (you/your household) in the last 12 months?

[ ] Often true
[ ] Sometimes true
[ ] Never true
[ ] DK or Refused

CH3. "(My/Our child was/The children were) not eating enough because (I/we) just couldn't afford enough food." Was that often, sometimes, or never true for (you/your household) in the last 12 months?

[ ] Often true
[ ] Sometimes true
[ ] Never true
[ ] DK or Refused

Screener for Stage 2 Child Referenced Questions: If affirmative response (i.e., "often true" or "sometimes true") to one or more of questions CH1-CH3, then continue to ***Child Stage 2;*** otherwise skip to ***End of Food Security Module.***

NOTE: In a sample similar to that of the general U.S. population, about 16 percent of households with children (35 percent of households with children with incomes less than 185 percent of poverty line) will pass this screen and continue to Child Stage 2.

Child Stage 2: Questions CH4-CH7 (asked of households passing the screener for stage 2 child-referenced questions).
NOTE: In Current Population Survey Food Security Supplements, question CH6 precedes question CH5.

CH4. In the last 12 months, since (current month) of last year, did you ever cut the size of (your child's/any of the children's) meals because there wasn't enough money for food?

[ ] Yes

[ ] No

[ ] DK

CH5. In the last 12 months, did (CHILD'S NAME/any of the children) ever skip meals because there wasn't enough money for food?

[ ] Yes

[ ] No (Skip CH5a)

[ ] DK (Skip CH5a)

CH5a. [IF YES ABOVE ASK] How often did this happen—almost every month, some months but not every month, or in only 1 or 2 months?

[ ] Almost every month
[ ] Some months but not every month
[ ] Only 1 or 2 months
[ ] DK

CH6. In the last 12 months, (was your child/were the children) ever hungry but you just couldn't afford more food?

[ ] Yes
[ ] No
[ ] DK

CH7. In the last 12 months, did (your child/any of the children) ever not eat for a whole day because there wasn't enough money for food?

[ ] Yes
[ ] No
[ ] DK

Appendix B

Physical Activity Questionnaire (Elementary School)

Name:_____ Age:_____

Sex: M_____ F_____ Grade:_____

Teacher:_____

We are trying to find out about your level of physical activity from ***the last 7 days*** (in the last week). This includes sports or dance that make you sweat or make your legs feel tired, or games that make you breathe hard, like tag, skipping, running, climbing, and others.

Remember:

1. There are no right and wrong answers — this is not a test.
2. Please answer all the questions as honestly and accurately as you can — this is very important.

---

1. Physical activity in your spare time: Have you done any of the following activities in the past 7 days (last week)? If yes, how many times? (Mark only one circle per row.)

	No	1-2	3-4	5-6	7 times or more
Skipping					
Rowing/canoeing					
In-line skating					
Tag					
Walking for exercise					
Bicycling					
Jogging or running					
Aerobics					
Swimming					
Baseball, softball					
Dance					
Football					
Badminton					

Skateboarding .....
Soccer .....
Street hockey .....
Volleyball .....
Floor hockey .....
Basketball .....
Ice skating .....
Cross-country skiing .....
Ice hockey/ringette .....
Other:
_____.....
_____.....

2. In the last 7 days, during your physical education (PE) classes, how often were you very active (playing hard, running, jumping, throwing)? (Check one only.)

I don't do PE .....
Hardly ever .....
Sometimes .....
Quite often .....
Always .....

3. In the last 7 days, what did you do most of the time *at recess*? (Check one only.)

Sat down (talking, reading, doing schoolwork)…… Stood around or walked around .....
Ran or played a little bit .....
Ran around and played quite a bit .....
Ran and played hard most of the time .....

4. In the last 7 days, what did you normally do *at lunch* (besides eating lunch)? (Check one only.)

Sat down (talking, reading, doing schoolwork)…... Stood around or walked around .....
Ran or played a little bit .....
Ran around and played quite a bit .....
Ran and played hard most of the time .....

5. In the last 7 days, on how many days *right after school*, did you do sports, dance, or play games in which you were very active? (Check one only.)

None .....
1 time last week .....
2 or 3 times last week .....
4 times last week .....
5 times last week .....

6. In the last 7 days, on how many *evenings* did you do sports, dance, or play games in which you were very active? (Check one only.)

None .....
1 time last week .....
2 or 3 times last week .....
4 or 5 last week .....
6 or 7 times last week .....

7. *On the last weekend*, how many times did you do sports, dance, or play games in which you were very active? (Check one only.)

None .....
1 time .....
2 — 3 times .....
4 — 5 times .....
6 or more times .....

8. Which *one* of the following describes you best for the last 7 days? Read *all five* statements before deciding on the *one* answer that describes you.

A. All or most of my free time was spent doing things that involve little physical effort .....……

B. I sometimes (1 — 2 times last week) did physical things in my free time (e.g. played sports, went running, swimming, bike riding, did aerobics) .....……

C. I often (3 — 4 times last week) did physical things in my free time .....……..

D. I quite often (5 — 6 times last week) did physical things in my free time ……...

E. I very often (7 or more times last week) did physical things in my free time ……..

⏮▄ Mark how often you did physical activity (like playing sports, games, doing dance, or any other physical activity) for each day last week.

	None	Little bit	Medium	Often	Very often
Monday					
Tuesday					
Wednesday					
Thursday					
Friday					

Saturday .....

Sunday .....

10. Were you sick last week, or did anything prevent you from doing your normal physical activities? (Check one.)

Yes .....……
No .....

If Yes, what prevented you? _____

Appendix C

Physical Activity Questionnaire (High School)

Name:_____ Age:_____

Sex: M_____ F_____ Grade:_____

Teacher:_____

We are trying to find out about your level of physical activity from ***the last 7 days*** (in the last week). This includes sports or dance that make you sweat or make your legs feel tired, or games that make you breathe hard, like tag, skipping, running, climbing, and others.

Remember:

3. There are no right and wrong answers — this is not a test.
4. Please answer all the questions as honestly and accurately as you can — this is very important.

---

1. Physical activity in your spare time: Have you done any of the following activities in the past 7 days (last week)? If yes, how many times? (Mark only one circle per row.)

	No	1-2	3-4	5-6	7 times or more
Skipping					
Rowing/canoeing					
In-line skating					
Tag					
Walking for exercise					
Bicycling					
Jogging or running					
Aerobics					
Swimming					
Baseball, softball					
Dance					
Football					
Badminton					
Skateboarding					

Soccer ..... ……
Street hockey .....
Volleyball .....
Floor hockey .....
Basketball .....
Ice skating .....
Cross-country skiing .....
Ice hockey/ringette .....
Other:
_____.....
_____.....

2. In the last 7 days, during your physical education (PE) classes, how often were you very active (playing hard, running, jumping, throwing)? (Check one only.)

I don't do PE .....
Hardly ever .....
Sometimes .....
Quite often .....
Always .....

3. In the last 7 days, what did you normally do *at lunch* (besides eating lunch)? (Check one only.)

Sat down (talking, reading, doing schoolwork)..... Stood
around or walked around .....
Ran or played a little bit .....
Ran around and played quite a bit .....
Ran and played hard most of the time .....

4. In the last 7 days, on how many days *right after school*, did you do sports, dance, or play games in which you were very active? (Check one only.)

None 1
time last week 2
or 3 times last week 4
times last week .....
5 times last week .....

5. In the last 7 days, on how many *evenings* did you do sports, dance, or play games in which you were very active? (Check one only.)

None 1
time last week 2
or 3 times last week 4
or 5 last week .....
6 or 7 times last week .....

6. *On the last weekend*, how many times did you do sports, dance, or play games in which you were very active? (Check one only.)

None .....
1 time .....
2 — 3 times .....
4 — 5 times .....

6 or more times ....

7. Which *one* of the following describes you best for the last 7 days? Read *all five* statements before deciding on the *one* answer that describes you.

F. All or most of my free time was spent doing things that involve little physical effort .....……

G. I sometimes (1 — 2 times last week) did physical things in my free time (e.g. played sports, went running, swimming, bike riding, did aerobics) .....…….....

H. I often (3 — 4 times last week) did physical things in my free time .....……..

I. I quite often (5 — 6 times last week) did physical things in my free time ……...

J. I very often (7 or more times last week) did physical things in my free time …..

Mark how often you did physical activity (like playing sports, games, doing dance, or any other physical activity) for each day last week.

	None	Little bit	Medium	Often	Very often
Monday					
Tuesday					
Wednesday					
Thursday					
Friday					
Saturday					
Sunday					

9. Were you sick last week, or did anything prevent you from doing your normal physical activities? (Check one.)

Yes ....
No ....

If Yes, what prevented you? ___________________________________

Appendix D

IRB#: 12047

Research Consent Summary

You are being asked to join a research study. You do not have to join the study. Even if you decide to join now, you can change your mind later.

1. The purpose of this study is to learn more about hemophilia and body composition.

2. We want to learn:

    a. If there is a difference in body composition between children with hemophilia and children who do not have hemophilia.

    b. If there is a relationship between body composition in children with hemophilia and physical activity, food insecurity, and frequency of bleeding episodes.

3. If you join the study, you will have a single visit. If you have hemophilia, your medical records will be accessed to record your bleeding episodes which have been documented over the past year.

4. There is a small risk of breach of confidentiality.

5. If you agree, information collected during the study may be saved for future.

OREGON HEALTH&SCIENCE UNIVERSITY

IRB#: 12047

Research Consent and Authorization Form

TITLE: Body Composition in Children with Hemophilia

PRINCIPAL INVESTIGATOR:	Elizabeth Adams, PhD, RD	(503)	494-0981
CO-INVESTIGATORS:		(516)	476-8549
	Jaime Ruisi, BS	(503)	494-1682
	Melanie Gillingham, PhD, RD	(503)	418-
	Michael Recht, MD, PhD	5150	

PURPOSE:

"You" means you or your child in this consent form.
You have been invited to be in this research study because either you have hemophilia or you do not have hemophilia and are willing to participate as part of a comparison group.
The purpose of this study is to learn more about body composition in hemophilia and how it compares to people without hemophilia.
This study requires no additional visits to the clinic. The research visit will be scheduled at the same time as the clinic visit. Research procedures will take about 90 minutes to complete.
We are asking you to provide information for a data bank, also called a repository. This information will be stored indefinitely and may be used and disclosed in the future for research.
There will be a total of 30 children with Hemophilia and 30 of the children's parents or guardians enrolled in this research study at OHSU. There will also be a total of 30 children who are followed by the Doernbecher Children's Hospital Pediatric Clinic and 30 of their parents or guardians enrolled.

PROCEDURES:

The study will compare two groups.

1. Subjects 5 through 18 years of age with hemophilia
2. Subjects 5 through 18 years of age who do not have hemophilia

If you agree to participate in the study, you will have the following procedures:

	Single Study Visit
Consent Discussion and medical history	X
Height Measurement	X
Weight Measurement	X
Bioimpedance Analysis	X
Dietary Intake 24 Hour Recall	X
Physical Activity Questionnaire	X
Six Minute Walking Test	X
Food Insecurity Questionnaire	X
Total time	90 minutes

Height: Your height will be collected using a stadiometer. To complete this test, you must remove socks, shoes, and heavy outerwear. To perform this test you will stand up straight against the stadiometer on the wall and wait for measurements to be completed. This procedure takes up to 3 minutes.
Weight: Your weight will be collected using a scale .To complete this test, you must remove socks, shoes, and heavy outerwear. To perform this test you will stand up on the scale and wait for measurements to be completed. This procedure takes up to 3 minutes
Bioimpedance Analysis (BIA): We will measure how much body fat, fat free mass, and water you have by measuring resistance. To complete this test you must remove the shoe and sock from the right foot as well as all jewelry on the right side of the hand, wrist, ankle, or foot. Two electrodes will be attached to the right wrist and right foot. This test is painless and involves a small current passing between two electrodes on your wrist and ankle. To perform this test, you must lie still on an exam table while the BIA is running. This procedure takes up to 5 minutes. We will explain your results and provide a handout as a reference.
Dietary Intake and Food Security: We will ask you what you ate yesterday and measure how many calories, grams of: protein, fat, carbohydrates, and phenylalanine were consumed. To perform this test, we will ask you what foods you have eaten in the prior day, what time of day, we will ask the details of the food consumed (brand, how the food was prepared, frozen/raw/canned, how much was eaten), and we will ask you to confirm the 24-hour dietary intake. We will also ask you to fill out a survey about your household's food situation. These procedures take up to 25 minutes.
Physical Activity: We will ask you what activities you have participated in during the last 7 days, as well as the length of time in minutes for each activity in which you

participated. A score will then be calculated ranging from low to high physical activity. In addition to these questions, we will ask you to participate in a six minute walking test. You will be instructed to walk as far as you can along a hallway for a period of six minutes. These procedures take up to 15 minutes.
Bleeding Episodes: If you have hemophilia, we will obtain information the number of bleeds you have experienced from your clinic visits. To perform this test, we will retrieve historical data from EPIC electronic medical record. This information will be compared against individual body composition measurements.
In the future, your *information* may be given to *researchers* for other research studies. The *information* will be labeled as described in the CONFIDENTIALITY section.
If you have any questions, concerns, or complaints regarding this study now or in the future, contact Elizabeth Adams, PhD, RD at (503) 494-0981.

RISKS AND DISCOMFORTS:

Participation in this study involves some risk, discomforts, and inconveniences. These include:
Bioimpedance Analysis (BIA): During this test a small current will pass between two electrodes on your wrist and ankle. The battery source and low-voltage energy diminishes risk for shock. However, you should not have this test is you have a cardiac device (implanted defibrillator), because the BIA has not been tested in people with these devices.
Loss of Confidentiality: Although we take measures to protect your identity, there is a risk of loss of confidentiality.

BENEFITS:

You will not personally benefit from being in this study. However, by serving as a subject, you may help us learn how to benefit patients in the future.

ALTERNATIVES:

You may choose not to be in this study.

CONFIDENTIALITY:

We will take steps to keep your personal information confidential, but we cannot guarantee total privacy.
We will create and collect health information about you as described in the Purpose and Procedures sections of this form. Health information is private and is protected under federal law and Oregon law. By agreeing to be in this study, you are giving permission (also called authorization) for us to use and disclose your health information as described in this form.
The investigators, study staff, and others at OHSU may use the information we collect and create about you in order to conduct and oversee this research study and will store this information in a repository.
We may release this information to others outside of OHSU who are involved in conducting or overseeing research, including

- The Office for Human Research Protections, a federal agency that oversees research involving humans. This agency may review and copy your records.

We may also share your information with other researchers, who may use it for future research studies.

We will not release information about you to others not listed above, unless required or permitted by law. We will not use your name or your identity for publication or publicity purposes, unless we have your special permission.
Under Oregon law, suspected child or elder abuse must be reported to appropriate authorities.
Data from this study may be shared with other investigators for future research studies. Your data will include your name and other information that may identify you, including your diagnosis of hemophilia (if applicable). Other investigators who may receive your medical information for research will also be given information that may identify you.

We may continue to use and disclose your information as described above indefinitely. Some of the information collected and created in this study may be placed in your OHSU medical record. While the research is in progress, you may or may not have access to this information. After the study is complete, you will be able to access any study information that was added to your OHSU medical record. If you have questions about what study information you will be able to access, and when, ask the investigator.

COSTS:

There will be no cost to you or your insurance company to participate in this study.

LIABILITY:

If you believe you have been injured or harmed as a result of participating in this research and require treatment, contact Elizabeth Adams, PhD, RD (503) 494-6868.
If you are injured or harmed by the study procedures, you will be treated. OHSU does not offer any financial compensation or payment for the cost of treatment if you are injured or harmed as a result of participating in this research. Therefore, any medical treatment you need may be billed to you or your insurance. However, you are not prevented from seeking to collect compensation for injury related to negligence on the part of those involved in the research. Oregon law (Oregon Tort Claims Act (ORS 30.260 through 30.300)) may limit the dollar amount that you may recover from OHSU or its caregivers and researchers for a claim relating to care or research at OHSU, and the time you have to bring a claim.
If you have questions on this subject, please call the OHSU Research Integrity Office at (503) 494-7887.

PARTICIPATION:

This research is being overseen by an Institutional Review Board ("IRB"). You may talk to the IRB at (503) 494-7887 or irb@ohsu.edu if:

- Your questions, concerns, or complaints are not being answered by the research team.
- You want to talk to someone besides the research team.
- You have questions about your rights as a research subject.
- You want to get more information or provide input about this research.

You may also submit a report to the OHSU Integrity Hotline online at https://secure.ethicspoint.com/domain/media/en/gui/18915/index.html or by calling toll-free (877) 733-8313 (anonymous and available 24 hours a day, 7 days a week).
You do not have to join this or any research study. You do not have to allow the use and disclosure of your health information in the study, but if you do not, you cannot be in the study.

If you do join the study and later change your mind, you have the right to quit at any time. This includes the right to withdraw your authorization to use and disclose your health information. If you choose not to join any or all parts of this study, or if you withdraw early from any or all parts of the study, there will be no penalty or loss of benefits to which you are otherwise entitled, including being able to receive health care services or insurance coverage for services. Talk to the investigator if you want to withdraw from the study.

If you no longer want your health information to be used and disclosed as described in this form, you must send a written request or email stating that you are revoking your authorization to:
Dr. Elizabeth Adams, PhD, RD
Oregon Health & Science University
707 SW Gaines Street
Mail code: CDRC
Portland, Oregon 97239
E-mail: adamse@ohsu.edu

Your request will be effective as of the date we receive it. However, health information collected before your request is received may continue to be used and disclosed to the extent that we have already acted based on your authorization.

Your study participation will end after the study measurements are completed in one visit. If in the future you decide you no longer want to participate in this research, we will remove your name and any other identifiers from your information, but the measurement data will not be destroyed and we will continue to use it for research.

SIGNATURES:

Your signature below indicates that you have read this entire form and that you agree to be in this study.

Subject Printed Name	Subject Signature (18 years or older)	Date
Parent or Legal Guardian Printed Name (if subject is under 18)	Parent or Legal Guardian Signature (if subject is under 18)	Date

Person Obtaining Consent Printed Name | Person Obtaining Consent Signature | Date

We will give you a copy of this signed form.

_____ _____ _____

_____ _____ _____

Subjects ages 15-17:

Your signature below indicates that you agree to be in this study.

_____ _____ _____

_____ _____

Signature of Subject | Date

_____

Printed Name of Subject

Complete if the participant is not fluent in English and an interpreter was used to obtain consent. Participants who do not read or understand English must not sign this full consent form, but instead sign the short form translated into their native language. This form should be signed by the investigator and interpreter only.

Print name of interpreter: _____

Signature of interpreter: _____ Date: _____

An oral translation of this document was administered to the subject in _____ (state language) by an individual proficient in English and _____ (state language).

See the attached short form for documentation.

Appendix E

Body Composition and Health of Children with Hemophilia

Name: _____
Subject ID #_____ DOB:_____
Initials:_____ Consent signed:_____
Gender:_____
Age:_____

Clinic Appointment Date:_____ Time:_____

Anthropometric Measurements		
Height:	Percentile:	z-score:
Weight:	Percentile:	z-score:
BMI:	Percentile:	z-score:

Bioimpedance Analyzer Results		
Resistance		ohms
Reactance		ohms
Body Cell Mass	lbs.	%
Extracellular Mass	lbs.	%
Lean Body Mass	lbs.	%
Fat Mass	lbs.	%
Total Weight	lbs.	%
BMI		
BMR		Calories
Intracellular Water	Liters	%
Extracellular Water	Liters	%

Total Body Water	Liters	%
TBW/Lean Body Mass		
TBW/Total Weight		

Completed 24-Hour Multi-pass Food Record? *Circle One*

Yes
No

Dietary Intake Analysis		
Total Calories		
Grams of CHO:	Grams of Protein:	Grams of Fat:
% Kcal CHO:	% Kcal Pro:	% Kcal Fat:

Bleed Frequency
Number of bleeds over last 12 months:
Number of hospitalizations over last 12 months:

6 Minute Walk Test
BORG Scale Pre-Test:
BORG Scale Post-Test:
Laps Completed:
Distance:

Completed PAC-Q? *Circle One*

Yes
No

Completed USDA U.S. Household Food Security Questionnaire? *Circle One*

Yes

No

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