GAIT AND BALANCE IN CHILDREN WITH INHERITED METABOLIC DISEASE.

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ABSTRACT

Inherited metabolic diseases (IMDs) are major class of heterogeneous genetic rare disorders that are caused by a malfunction of one or more pathways of metabolism. Most IMD patients have neurological and musculoskeletal impairments which affect their gait and balance abilities. Therefore, it is vital to find sensitive and objective gait and balance measures that permit patients to be systematically followed and to quantify the effectiveness of existing treatments. In this thesis, the gait and balance parameters of six IMD groups (Niemann Pick type C, Hurler, Morquio, Maroteaux Lamy, Pompe, and Fabry) were assessed and compared to healthy individuals. Parameters were measured using sensitive measurement tools (Zeno Mat and accelerometers).

Results showed that decreased cadence and single support phase as a percentage of the gait cycle were the most frequently affected gait parameters in NP-C, Fabry, and Morquio. Fabry also have an increase in the stance %. Hurler and Maroteaux-Lamy both have decreases in single support %. In addition, Hurler have increased stride % while Maroteaux-Lamy have increased stance %. Pompe showed no abnormalities in gait parameters. There was no evidence of progressive change with height/age in differences between control and patient groups.

Balance sensing and adjustment (as measured by RMS, a proxy for sway area, and by jerk, a measure of smoothness of adjustment) were affected in Hurler, Morquio, and Pompe groups. While in NP-C only the jerk EC/EO difference was affected. Fabry and Maroteaux-Lamy showed no significant differences in balance parameters. There was no evidence of progressive change with height/age in differences between control and patient groups.

Correlations between gait and balance parameters for NP-C and Fabry patients showed that NP-C were similar to controls while Fabry patients showed some abnormalities in some correlations. These findings provide valuable information about gait and balance developmental changes in these diseases, which will help in evaluating the effectiveness of therapeutic interventions.

DEDICATION

To my lovely husband *JASSIM*

&

My angels *AMAL, EISSA & SHAMLAN*

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LIST OF ABBREVIATIONS

AGA	α-galactosidase A enzyme
AIC	Akaike information criterion
ARD	Average radial displacement
ASB	Arylsulfatase B enzyme
ASIS	Anterior Superior Iliac Spine
BCH	Birmingham Children Hospital
BOS	Base of support
CBCL	Child behaviour checklist
CI	Confidence intervals
COG	Centre of gravity
COM	Centre of body mass
COP	Centre of the pressure
CNS	Central nervous system
CP	Cerebral palsy
DCD	Developmental coordination disorder
EC	Eyes closed
EO	Eyes open
ERT	Enzyme replacement therapy
GAA	Acid alpha-glucosidase enzyme
GAGs	Glycosaminoglycans
GAI	General ability index
GALNS	N-acetylgalactosamine-6-sulfatase
GC	Gait cycle
GCP	Good clinical practice
HR-QOL	Health-related quality of life

HSCT	Hematopoietic stem cell transplantation
IDUA	Lysosomal enzyme alpha-L-iduronidase
IMDs	Inherited metabolic diseases
IQ	Intelligence quotient
ISway	Instrumented test of postural sway
KS	Keratan sulfate
LDL	Low density lipid
LOS	limits of stability
MPS	Mucopolysaccharidoses
MPS I	Hurler
MPS II	Hunter
MPS III	Sanfillipo
MPS IV	Morquio
MPS VI	Maroteaux-Lamy
MPS VII	Sly
MPS IX	Natowicz
MMT	Manual Muscle Testing
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
MS	Multiple sclerosis
N/A	Not applicable
NP	Niemann Pick
NP-A	Niemann Pick type A
NP-B	Niemann Pick type B
NP-C	Niemann Pick type C
NP-D	Niemann Pick type D
PD	Parkinson's disease

RMS	Root mean square of COP
ROM	Range of motions
SRT	Substrate reduction therapy
SI	Suspicion Index
TUG	Timed Up and Go
UCBT	Umbilical cord blood transplantation
VSGP	Vertical supranuclear gaze palsy

CHAPTER 1: LITERATURE REVIEW

1.1 Introduction:

Inherited metabolic diseases (IMDs) are major class of heterogeneous genetic disorders that are caused by a malfunction within one or more pathways of metabolism (Wraith, 2006). For most of these diseases it is the dysfunction of metabolic enzymes that leads to the accumulation of toxic metabolites, which interrupts the normal development of the central nervous system (CNS). Depending on the specific role of the dysfunctional enzymes, the severity of symptoms associated with IMDs can fluctuate widely. Mild symptoms can embrace physiological abnormalities such as skeletal dysplasia and impaired endurance (Davison et al., 2013; Wraith, 2006), while the severe symptoms includes mental retardation, CNS complications, and reduced life expectancy (Bendadi et al., 2014; De Laet et al., 2011; Masurel-Paulet et al., 2008; Thimm et al., 2011).

It is well established that IMDs, considered as individual rare diseases, are challenging to diagnose (Bendadi et al., 2014). Recently, the numbers of individuals diagnosed with IMDs have been gradually rising based on early and enhanced diagnosis tools and greater awareness. Taken together, IMDs have an incidence of <1 in 1000 (Cheema, Malik, Parkash, & Fayyaz, 2016). There is a revival of interest among the researchers to explore this area more in depth and it is vital to develop investigative methods to diagnose IMDs earlier. Operative treatment depends on early investigation, which could significantly improve the chance of a better outcome. Due to the rarity of the IMDs and the lack of research conducted in this area, most paediatricians have little experience of these conditions. As a consequence, confidence and experience in dealing with these patients is not well established.

Some IMDs can be identified by routine screening assessments at birth, while others are recognised only after a child or adult shows signs of a disorder (Karimzadeh, 2015). Early

recognition of the abnormalities and changes with IMDs leads to improved treatment chances and increases patients‟ life span and long-term quality of life (Santra & Ramaswami, 2015).

Treatment for IMDs depends on the severity and type of the disorder. Since there are several types of IMDs, which will be discussed more in the coming sections of this chapter, treatment recommendations may differ substantially, ranging from dietary constraints to liver transplants. On the other hand, functionally, most IMDs patients have neurological and musculoskeletal impairments which affect their gait and balance (Martin et al., 2008). Therefore, an investigation focusing on sensitive and objective measurement for gait and balance that permits IMDs patients to be systematically followed is vital and the aim of this thesis. Accurate and sensitive tracking of changes will help in evaluating the effectiveness of existing treatments and may prevent negative complications in future.

This literature review will, first, introduce specific IMD groups and, second, describe gait and balance measurement methods that are commonly used with developmental and neurological disorders and have attracted significant research attention.

1.2. Types of inherited metabolic diseases:

This thesis will study and focus on six IMD disease groups. The first disease group is Niemman pick (NP) and will concentrate on type C (NP-C). The second IMD patient group is Mucopolysaccharidoses. However, in this thesis only three disease groups (Hurler, Morquio, and Maroteaux Lamy) from the Mucopolysaccharidoses diseases will be studied. The fifth IMD patient group is Pompe, and sixth patients group included in this thesis is Fabry.

1.2.1. Niemman pick type C:

NP is an autosomal recessive storage disease characterised by expropriation of unesterified low density lipid (LDL) cholesterol and sphingolipids in fibroblast lysosomes (Floyd et al., 2007). The incidence is about 1:120,000 live births (Ginocchio et al., 2013). This value might be underestimated due to failure to consistently identify the disease, particularly because of the heterogeneous clinical presentation of NP and the diverse presentation times that different forms take. This leads to delayed diagnosis and obstacles to suitable care (Menget, Mougey, Thiriez, & Riethmuller, 2013). There are four different types of NP (type A, B, C, and D), each classified by the mutations of different genes (Vanier, 2010) and metabolic defects (Alobaidy, 2015). The life span of the NP patients varies from a few days to above 60 years. However, the majority of patients die between 10 and 25 years of age (Vanier, 2010). NP type A is considered the worst prognosis. That is because type A presents early, therefore most patients die quickly in early months (Héron et al., 2012). On the other hand, type B is mainly a visceral contribution, so the treatment of these patients will focus on this part mostly, which means they live longer than type A. Type C is typically a neurovisceral form with many neurological impairments. Thus, the majority of the NP patients diagnosed are considered to be under type C (Vanier, 2010).

Considering the difficulty of recruiting for all four types of NP, and the relative availability of NP-C patients who are followed by the Birmingham Children‟s Hospital IMD clinic, this thesis will focus only on NP type C (NP-C) of the 4 types. NP-C is caused by mutations in the NPC1 gene (95% of all cases) or NPC2 gene (4%) and probably another, until now, unidentified gene (1%) (Menget et al., 2013).

NPC1 and NPC2 genes cause severe destruction of intracellular lipid transport (Patterson et al., 2010). These gene mutations cause a cellular cholesterol trafficking defect which affects the liver, spleen and sometimes the lung (Vanier, 2010). Moreover, NP-C affects the CNS, which results in ataxia (70% of patients), supranuclear gaze palsy (70%), dysarthria (66%), cognitive disorders (62%), dysphagia (52%), dystonia (46%), seizures (33%) and cataplexy (26%) (Patterson et al., 2013).

NP-C patients can be diagnosed by using biochemical testing indicating impaired cholesterol esterification in cultured skin fibroblasts (the Filipin test) which is considered a definitive diagnosis (Floyd et al., 2007). Moreover, bone marrow aspiration can be a sensible test in extremely suspicious cases and then another constructive test can be done which is gene testing (Vanier, 2010). Recently, international clinical experts have developed the NP-C Suspicion Index (SI) to be used as a part of NP-C diagnoses and assessment for patients >4 years of age. This tool includes symptoms in three domains (visceral, neurological, and psychiatric), along with a family history, to present a risk prediction score for potential NP-C patients (Alobaidy, 2015). However, the effect of NP-C on motor processes (gaze palsy and ataxia) is particularly characteristic and, along with other measures, measures of motor control could contribute to a more reliable suite of indicators, especially in younger patients (under 6 years old).

In addition to these tests, brain imaging, along with eye movement changes could be a productive combination and can help in NP-C diagnoses and symptoms. In general, brain imaging in NP-C patients has shown decreases in volume of the cerebellum, hippocampus, subcortical grey matter, and variations in most white matter regions. Changes in cerebellar volume will be associated with measures of ataxia and ocular-motor function. While decreases in the volume of the hippocampus and thalamus are paired with progressive illness (Walterfang, Patenaude, et al., 2013). White matter disease is frequently extensive, and it is measured as fluctuations in diffusion imaging (Walterfang et al., 2010).

With regards of the life development of NP-C patient, it is well documented that NP-C can become apparent at different ages and, based on the age of onset the neurological symptoms and rate of neurological decline can be quite different. As a result, with earlier onset, a greater mortality rate may arise (Ginocchio et al., 2013). Even within a single type of NP disease (e.g. NP-C), there are different categories of age of onset and time course of the disease. There are five different categories of age at onset, and differences between symptoms according to age of onset are important for the assessment of the disease path and implications for therapy (Patterson et al., 2012). The first group is pre/perinatal group (< 2 months), where a family history with Lysosomal storage disease or perinatal hydrops fetalis may present. In this period, patients present progressive hepatosplenomegaly, unexplained jaundice and severe cholestatic hepatopathy. Furthermore, if the patient has a mutation in the NPC2 gene, fatal lung penetration and severe respiratory deficiency may develop, which usually leads to death at an early age (Alobaidy, 2015).

The second period will be defined as an early infantile period (2 months to two years). At this age, isolated hepatosplenomegaly is observed. At eight to nine months central hypotonia will develop, which will be part of early decline and delay in reaching developmental milestones (Vanier, 2010).

The third period is the late infantile period (2 to 6 years). Patients will develop isolated hepatosplenomegaly or splenomegaly. Between the age of 3 and 5 years, these patients will develop gait problems, ataxia, clumsiness and cataplexy (unexpected loss of muscle tone) which will lead to frequent falls (Ginocchio et al., 2013). Moreover, at this age patients will experience some language delay, hearing deficit and mental development impairments.

The fourth period is the juvenile period (6 to 15 years). Patients will start developing school problems: difficulties in writing, attention and learning disabilities. At this age also, vertical supranuclear gaze palsy (VSGP) can become apparent. In addition, due to ataxia, patients will have difficulties in walking and running and this will increase the risk of falls. At a later stage patients will experience swallowing problems which can lead to gastrostomy (Vanier, 2010).

The last period (Fifth period) is adolescent and adult (>15 years) where most of the patients have psychiatric problems such as psychosis, auditory and visual hallucination, depression, aggressiveness and social isolation. Furthermore, 25% of NP-C patients have been categorized as schizophrenic in this onset group (Patterson et al., 2013).

Management of NP disease varies according to type. Commonly, management focuses mainly on treating the symptoms. This includes neurosteriod substitution and substrate reduction therapy (SRT) (Floyd et al., 2007). These symptomatic treatments are primarily to improve health-related quality of life (HR-QOL) for the NP-C patients (Alobaidy, 2015). In general, NP-C is a progressive disease and patients need regular follow ups. Therefore, treatment should be recognized at diagnosis and revised frequently, aimed at enhancing or sustaining the physical and psychosocial wellbeing of NP-C patients and their families.

One of the first official specific drugs used for NP-C patients was Miglustat, which was approved in Europe in 2009 (Alobaidy, 2015). Miglustat is a small water-soluble, aminosugar molecule that reversibly blocks glucosylceramide synthesis (Patterson et al., 2010). This

medication works by interrupting or stabilizing the development of the disease by decreasing cell damage deriving from increasing oxidative stress (Ginocchio et al., 2013). This medication should be started immediately at the earliest period of neurological disease onset, and the dose must be adjusted based on the patient‟s body surface area (Alobaidy, 2015). A common side effect of the Miglustat is diarrhea (85%), flatulence (70%), weight loss (65%), and vomiting, which tend to reduce over time (Alobaidy, 2015). In general, pre-symptomatic patients are not given Miglustat due to its side effects. Miglustat therapy is also not suitable for patients who have shown severe neurological disease, because it is hard to detect any changes and improvements in the patient‟s condition (Patterson et al., 2015). The properties of Milgustat make treatment timing a challenge (not too early because of side effects, not too late because it won‟t help). It is crucial to know the earliest point when the disease starts to effect cognitive processes so that treatment maintains good cognitive function for as long as possible. Identifying this point in the disease process is an important goal. Sensitive assessments for pre-symptomatic patients need to be available and systematically administered, so that treatment can initiated at a primary onset of the neurological appearance.

One of the brain areas that is strongly affected by NP-C is the cerebellum, so most patients develop difficulties with gait, balance and coordination. Regular assessment of these patients by a professional physical therapist is needed to determined changes in gait and balance.

There is limited research in the literature that systematically measures gait and balance in NP-C patients. One such study, Sansare et al. (2018), aimed to assess gait, balance and upper limb coordination. They examined 10 NP-C patients aged from 4 to 23 years and compared with an age and gender-matched control group. The authors used a GAITRite mat, a Vicon Motion System, and the NeuroCom Balance SMART Equitest for assessing gait and balance. They found that some gait variables (velocity, step time, coefficients of variation of step time,

and double support) were significantly different from the control group, while others were not significantly different (cadence, step length, and step width). For balance, the authors found that limits of stability (LOS) which assessed dynamic postural control by measuring the centre of gravity (COG) during eyes open (EO) and eyes closed (EC) conditions was significantly faster than the control group. They concluded that their findings showed promising results for the research and clinical field. The Sansare study was the first study in this area to do instrumented measurement of gait and balance differences between the NP-C patients and a matched control grouped. Their finding, detecting asymptomatic early changes in gait and balance parameters in NP-C patients, could help in providing valuable information that allows treating patients at the appropriate time.

Although they have small and variable sample of NP-C in their study, effect sizes were large (0.8) for all gait, balance, and upper limb coordination, except for step length (0.6). This is an advantage. Therefore, this study showed that gait and balance measures could give an early indication of brain changes and postural instability.

In conclusion, it is known that NP-C affects gait and balance, but the specific changes in motor parameters that characterize NP-C have been less well studied. Which instrumented test measures will give the most sensitive and characteristic picture of NP-C and its progress, will be one of the important goals of this thesis.

1.2.2. Mucopolysaccharidoses (MPS):

MPS is a group of metabolic disorders caused by corrupted or absent lysosomal enzymes which are required to break down molecules called glycosaminoglycans (GAGs) (Chinawa et al., 2012). Children with MPS do not produce adequate amounts of one of the two enzymes

needed to break down these sugar chains into proteins and simpler molecules. As a result of this, GAGs accumulate in the cells, connective tissue, and blood over time. This accumulation may cause permanent progressive cellular impairment, resulting in facial dysmorphism, joint stiffness, organomegaly, contractions, myocardial enlargement, pulmonary dysfunction, neurological damage, and short stature, which, in turn, can impact patient gait and balance function (Dusing, Thorpe, Rosenberg, Mercer, & Escolar, 2006). MPS are classified into different types based on enzyme defect and accumulation of GAGs. There are seven types with associated non-MPS names: MPS I (Hurler, Hurler Scheie and Scheie), MPS II (Hunter), MPS III (Sanfillipo), MPS IV (Morquio), MPS VI (Maroteaux Lamy), MPS VII (Sly), and MPS IX (Natowicz) (Dualibi et al., 2016). Each type of MPS has a range of clinical indicators from mild to severe symptoms (see sections1.2.2.1, 1. 2.2.2, and 1.2.2.3). All MPS groups can be diagnosed based on either biochemical findings, e.g. increased urinary GAGs, decreased enzymatic levels, or by identifying the gene mutation that causes the deficient enzyme. Due to recruitment limitations, this thesis will focus on assessing the gait and balance abnormalities for three types of MPS [Hurler (MPS I), Morquio (MPS IV) and Marotequx-Lamy (MPS VI)].

1.2.2.1Hurler (MPS I):

MPS I is a rare IMD resulting from a deficiency of the lysosomal enzyme alpha-L-iduronidase (IDUA). MPS I has been divided into 3 groups: Hurler (severe), Scheie (mild), and Hurler-Scheie (intermediate). Patients are assigned to groups based on their clinical characteristics, such as the age of onset; the ratio of functional deterioration; and the affected organs (cardiac, pulmonary or CNS involvement).

Hurler is the most severe type in the MPS I group, with occurrence estimates between 1:76,000 and 1:164,000 (Aldenhoven, Boelens, & de Koning, 2008). The symptoms of Hurler appear either during the first 6 months after birth or after six months of age. The symptoms of the first six months are often present from birth, including mild facial dysmorphisms, hepato-splenomegaly, persistent rhinitis, frequent hernias and upper respiratory tract infections, and minor thoracolumbar kyphoscoliosis. On the other hand, the symptoms that appear after six months of age are known to be severe and develop into an advanced multi-system impairment. These symptoms include psychomotor retardation, organomegaly, impaired vision and hearing, severe musculoskeletal manifestations, and pulmonary and cardiovascular failure which leads to death in early infancy (Pastores et al., 2007).

The symptoms affecting the musculoskeletal system lead to numerous orthopaedic complications, which, in turn, will result severe discomfort and disability. Some of these orthopaedic complications include odontoid dysplasia, thoraco-lumbar kyphosis, acetabular dysplasia with following hip sub-luxation, and genu valgum, causing significant lower limb deformities (limited hip extension, overall thin lower limbs, and severe muscle wasting). In addition, most Hurler patients experience stiffness and contractures of the joints, which is usually combined with a limited range of motion (ROM) in the spine, elbows, wrists, hips, knees, and ankles. Moreover, most Hurler patients develop generalized muscle weakness. All these deformities and complications lead to a serious reduction in balance and walking ability (Bjoraker, Delaney, Peters, Krivit, & Shapiro, 2006). These musculoskeletal changes are similar to cerebral palsy (CP) patients, who share similar features to Hurler. Therefore, CP patients could be used to estimate the effect of these changes on balance and gait development in Hurler patients.

Hurler is considered to be a multi-systemic disease; therefore, it needs early intervention and supervision to improve patients‟ quality of life. The primary treatments of Hurler includes Enzyme replacement therapy (ERT), hematopoietic stem cell transplantation (HSCT) (Yasuda et al., 2015), and umbilical cord blood transplantation (UCBT) (Dusing & Thorpe, 2007). HSCT therapy is considered to be the best choice for young patients with severe iduronidase deficiency to sustain good cognitive function and to reduce the neurological deterioration (Orchard et al., 2010). However, these therapeutic interventions have a minimal effect on the orthopaedic outcomes and most patients will eventually need orthopaedic surgical interventions (Aldenhoven et al., 2015b).

Like NP-C disease, few studies have examined gait and balance for Hurler patients. One of these studies was done by Dusing et al. (2007), who examined the spatial and temporal gait parameters for 18 Hurler children aged from 19 to 96 months. In their study, they used a GAITRite walkway after UCBT treatment. They tested the step length, gait speed, and cadence which were normalized by height. Patients were compared to 438 aged-matched normally developing children (ages 14 to 131months). These tests were performed 1 to 4 times between 2.9 and 72.2 months post-UCBT. Their results showed that Hurler patients had significant slower normalized gait speed and shorter normalized step lengths compared to the control group at 24 and 36 months post-UCBT. On the other hand, there was no significant difference in normalized cadence between groups, but the normalized cadence decreased at a similar rate for both groups. By 48 months post-UCBT, the gait parameters of Hurler patients developed quickly, and were similar to control group participants. As a result of these findings, the authors concluded that patients with Hurler syndrome undergoing post-UCBT treatment had altered spatial and temporal gait parameters that normalised with time.

Regarding the balance changes, there was no study that investigated the balance changes in Hurler. However, as is mentioned earlier Hurler and CP patients share similar features and symptoms.J. Rose et al. (2002) stated in their study that CP patients had increased COP values in both eye conditions compared to a control group. Also, they found that there was a slight increase in average radial displacement (ARD) in EC condition compared to EO condition with CP patients but this did not reach the significance level. ARD is considered an indicator for a postural control deficit.

Given the musculoskeletal effects of Hurlers and their impacts on development of gait and balance, there is a need for a more comprehensive data on exactly which gait and balance parameters are affected, the relationship between parameters and how they change over time. A better understanding of the disease impacts can suggest effective treatment approaches and allow treatment effects to be quantified. Sensitive gait and balance markers can quantify the clinical severity and evolution of the disease. Our data will contribute to that effort.

1.2.2.2. Morquio (MPS IV):

Morquio has an incidence of 1:200,000 (Algahim & Almassi, 2013). Morquio results from the absence of one of two enzymes. Absence of N-acetylgalactosamine-6-sulfatase (GALNS), leads to Morquio A (MPS IVA). Absence of β-galactosidase, causes Morquio B (MPS IVB). These enzymes hydrolyse sulfate ester bonds and are required during the consecutive degradation of the glycosaminoglycans keratan sulfate (KS) and chondroitin-6-sulfate in the lysosomes (Geer, Skinner, Goldin, & Holden, 2010). The absence of GALNS leads to lysosomal accumulation of glycosaminoglycans, mainly in the connective tissues, which are rich in KS (e.g. cartilage, heart valve, and cornea; (Davison et al., 2013).

As a result of this accumulation, Morquio leads to many symptoms, including global psychomotor retardation, hypotonia, mild corneal clouding, coarsening of facial features, severe gross motor delays, with decreased muscle tone and strength, and short stature. Similar to other MPS types, Morquio is clinically varied, ranging from mild to severe skeletal dysplasia with early mortality. The skeletal dysplasia is mainly apparent in epiphyseal growth plates and vertebrae, and it is mainly verified by spondyloepiphyseal dysplasia with genu valgum, spinal kyphosis, pectus carinatum and odontoid hypoplasia (Hendriksz et al., 2014). However, the main cause of death in Morquio is respiratory failure.

The main treatment for Morquio children is bone marrow transplantation and recurrent orthopaedic surgeries. Enzyme replacement therapy (ERT) has shown promising results in Morquio treatment (Hendriksz et al., 2016).

In distinction to other MPS disorders, there is generally thought to be no CNS involvement in Morquio (Dvorak-Ewell et al., 2010a; Wraith, 2006) and preliminary studies have reported an absence of neuroanatomical abnormalities or cognitive impairment (Koto, Horwitz, Suzuki, Tiffany, & Suzuki, 1978; Vikram Kumar, Narayanan, Rama Rao, & Vasundhara Devi, 1979).

In contrast, a recent study by Davison et al. (2013) found that Morquio patients could have mild cognitive impairments. They studied the performance of 14 Morquio patients, aged from 5 to 17 years on a set of standardised intelligence quotient (IQ) measures, general ability index (GAI), and child behaviour checklist (CBCL). These tests were supplemented by magnetic resonance spectroscopy (MRS). They found that 3 out 9 Morquio children scored below 78 on the full IQ scale, which represents 37% of the sample. Additionally, 5 of 9 patients had some behavioural problems which were highlighted by the parents such as anxiety, somatic and attentional complaints. Also, they observed, in more than half the

patients (9 out 14), mild neuroanatomical abnormalities. These abnormalities involved prominent perivascular spaces, high signal white matter areas in the right frontal lobe, and mild asymmetry of the lateral ventricles. In the end, they concluded mild neurocognitive problems in Morquio children are probable given the role of KS and chondroitin-6-sulfate in the coordination of neuroaxonal connection formation during brain development in the foetal and neonatal stages (Miller, Sheppard, & Pearlman, 1997). Moreover, these findings from Davison et al. (2013) were in agreement Blundell et al. (2018). In Blundell et al. (2018), they examined cognitive function for 13 Morquio patients, using tasks of attention, language, and oculomotor function. Their results showed that Morquio patients have problems with sustained attention and with task preparation or reaction decisions. They concluded that Morquio patients showed mild cognitive impairments.

With regards to the musculoskeletal complications, there are very limited studies that have examined the gait and balance in Morquio patients. One of these studies, was conducted by Dhawale et al. (2013), who examined 9 Morquio patients aged 10.6 ± 4 years. They used an eight-camera Motion Analysis System and AMTI force plates to measure kinetics and kinematics data. Morquio patients had significant decreased forward velocity, stride length, and cadence compared to control participants. Dhawale et al. concluded that these differences were due to abnormal ROM and muscle strength. Although this study had a small sample size, which is the case in most studies dealing with this rare type of disease, Dhawale et al documented the first baseline gait pattern for Morquio patients. Consequently, this could be a foundation for estimating treatment effectiveness if treatments are expected to impact gait and balance.

Additionally, (Geer et al., 2010) studied two unrelated Morquio cases. In their study they found that both patients had musculoskeletal problems (generalized hypotonia and global psychomotor delays) that affected their gait and balance, resulting a delay in walking ability,

limb instability, and a postural complication. They concluded, that motor and cognitive development hardly progress beyond the 15-month level. However, motor function can be stable with early intervention therapy and could even show some improvement. Identifying the most affected gait and balance parameters in Morquio could help to support clinical decision-making during follow-up and to assess the effectiveness of different treatments. This thesis will aim to determine the most affected gait and balance parameters in Morquio patients.

1.2.2.3. Maroteaux-Lamy (MPS VI):

MPS VI was named after the doctors (Maroteaux and Lamy) who first discovered this disorder in 1963 (Maroteaux & Lamy, 1965). Maroteaux-Lamy incidence is 1: 300 000. Maroteaux-Lamy is caused by a deficiency of *N*-acetylgalactosamine-4-sulfatase (arylsulfatase B [ASB]) enzyme (Giugliani, Harmatz, & Wraith, 2007). The deficiency of this enzyme causes deterioration of the growth rate, dysmorphic facial features, skeletal and joint deformities, repeated ear infections, hepatosplenomegaly and upper-airway obstruction. Unfortunately, most of the patients with Maroteaux-Lamy become wheelchair dependent or bedridden due to skeletal deformities, joint abnormalities, and cardiopulmonary disease. All these abnormalities and deformities lead to physical limitations, which, in turn, will influence learning and development of motor skills. As a result of this, especially due to heart and respiratory abnormalities, Maroteaux-Lamy have a shortened lifespan (Quirino de Almeida-Barros et al., 2012).

Maroteaux-Lamy is, like the other MPS groups, treated by enzyme replacement therapy and hematopoietic stem cell transplantation, with additional supportive care for other symptoms.

Maroteaux-Lamy has an impact on skeletal development from birth (mainly in the hip), leading to an abnormal pelvis, dysplasia of the femoral heads, and coxa valga. Moreover, there are other musculoskeletal deformities acquired with time, such as stiffness, pain, and flexion contractures of the shoulders, elbows, hips, and knees which reduce ROM. It is well established that Maroteaux-Lamy does not produce progressive intellectual impairment. However, the physical limitations with Maroteaux-Lamy patients are likely to indirectly produce delays in motor skill development and learning (Giugliani et al., 2007).

It is well known that Maroteaux-Lamy patients have musculoskeletal deformities which lead to gait and postural balance abnormalities (Harmatz & Shediac, 2017). However, there is currently very limited literature on Maroteaux-Lamy, and no studies have assessed gait and balance or tracked treatment in Maroteaux-Lamy patients. Therefore, one of the aims of this thesis is to assess Maroteaux-Lamy gait and balance in order to determine the utility of these measures for tracking treatments that may impact deformities and to see if gait and balance measures are promising for following the functional effects of treatment.

1. 2.3. Pompe:

Pompe disease is a rare progressive disease. The incidence of this disease is 1:40,000 live births (Chien, Hwu, & Lee, 2013). It is caused by an absence of the enzyme acid alpha-glucosidase (GAA) which in turn hydrolyzes lysosomal glycogen. Accumulation of lysosomal glycogen occurs in many tissues, including skeletal tissues, heart and smooth muscle (Kishnani et al., 2006). The symptoms of this disease vary depending on the age of onset, organ involvement, and the rate of progression. The age of onset is classified into infantile and late-onset forms. Patients with the infantile form show symptoms in the first

months of life, including generalized muscle weakness and hypotonia, hypertrophic cardiomyopathy, feeding difficulties and cardiorespiratory failure. Cardiorespiratory failure is the most dangerous symptom and is the main reason of death for these patients by the age of one year. The late-onset form can present at any age, and the main symptom of this form is progressive skeletal muscle dysfunction. The main affected muscles are proximal lower limb, paraspinal trunk muscles, diaphragm and accessory muscles of respiration. The age of death for the late onset form can occur any time from early childhood to late adulthood, depending on the progression of the disease and the respiratory muscles affected. Moreover, there is no evidence of nervous system involvement in this group of patients (Case et al., 2015).

Treatment for Pompe is mainly preventative and supportive care with a high-protein diet. However, like most of the diseases mentioned above, ERT has shown good results and significantly extends survival for Pompe patients with the infantile-onset form. Therefore, the sooner ERT starts, the better the outcomes (Fukuhara et al., 2018).

Fukuhara study (2018) investigated the relationship between the genetic and clinical features for 38 Japanese Pompe patients. One of their findings was that 82.7% of these patients have muscle weakness and 29.6% of them are wheelchair users. They concluded that these patients‟ clinical features could be influenced by the timing of diagnosis and treatment. Therefore, it is important for this group of patients to have an early diagnosis and treatment to have a better outcome and to avoid any further complications.

In general, Pompe disease has been classified as a muscular disease. This is because of progressive muscle weakness which leads to reduced motor function, altered postural alignment and balance. Some studies (Chien et al., 2013; Kishnani et al., 2006) have found that Pompe patients having difficulties in walking. However, there are no studies measuring gait and balance in detail, and how these are affected in Pompe patients. Case et al. (2015)

only reported that Pompe patients who underwent standard ERT showed a decrease in ankle dorsiflexion, hip extension, and walked with steppage gait. However, these motor functions improved with a higher dose of ERT. Although the Case et al. (2015) study findings showed that Pompe patients had abnormal motor functions, they didn‟t provide quantitative information about the gait and balance parameters that were affected. The Case et al. (2015) results suggest that motor parameters may be a good way to track treatment effectiveness and changes to gait and balance can be related to important functional outcomes like instability and falls. This thesis will provide an initial look at gait and balance parameters for a small number of Pompe patients.

1.2.4 Fabry:

Fabry‟s disease is an X-linked lysosomal storage disorder, which has an incidence estimated as 1:40,000 to 1:117,000 in male new-borns (it mainly affects males; (Olivera-González, Josa-Laorden, & Torralba-Cabeza, 2018). The disorder of X-linked lysosomal storage occurs due to a lack of the α-galactosidase A (AGA) enzyme. Glycosphingolipids, accumulate (particularly globotriaosylceramid and galactosylceramide) in several tissues and cell types. Accumulation of these specific molecules leads to cellular impairment (inflammation and/or fibrosis), which in turn, causes an organ dysfunction that may affect the heart, kidneys, skin, and nervous system. Although this disease mainly affects males, some studies have reported that at least 43% of obligate carrier females have clinical manifestations (Wang, Lelis, Mirocha, & Wilcox, 2007; Wilcox et al., 2008). The range of the disease severity in female patients varies from asymptomatic to a severe phenotype that is similar to male patients who have the classic phenotype (Arends et al., 2017; Ortiz et al., 2018).

The symptoms in this patient group take a nonspecific form, and it usually needs many years to recognize the underlying nature of the problems. However, the most common symptoms are vascular dysfunction, neuropathic pain, hypohidrosis/anhidrosis, cornea verticillate, and microalbuminuria (Ries et al., 2005).

ERT for Fabry disease has shown promising results in treating adults. It decreases glycolipid storage in several organs and tissues, reduces pain, reduces cardiac hypertrophy, enhances peripheral nerve function and increases sweating (Schiffmann et al., 2017). There are no systematic indications as to the ideal age to start ERT. However, development of symptoms or signs associated with Fabry disease is an indication for ERT initiation.

Most studies agree that Fabry disease does not cause motor impairment. However, few studies have shown different findings. One of these studies is Löhle et al. (2015), who examined the clinical feature of neurodegeneration in 110 Fabry patients and compared them with age-matched control groups. The Timed Up and Go Test (TUG) was used to evaluate motor function (measuring gait and transfer speed) for both groups. They found that Fabry patients have a motor deficit, which results in slower gait and transfer speed. Moreover, they found that Fabry patients have postural instability and weak fine manual skill. Importantly, they reported that there was a significant correlation between the degree of motor function impairment and the clinical disease severity. In their conclusion, they stated that motor function deficits are an essential feature of Fabry disease.

Although Löhle‟s study reported good findings using the TUG test, it is worth mentioning that although TUG is considered to be a basic measurement tool for gait and transfer speed (Podsiadlo & Richardson, 1991), it has limited ability to predict falls and has a high error rate in test retest use (Barry, Galvin, Keogh, Horgan, & Fahey, 2014). Therefore, more reliable and valid measurements are needed.

Consistent with the behavioural effects reported in Löhle‟s study, some neuropathological studies (de Veber, Schwarting, Kolodny, & Kowall, 1992; Kaye, Kolodny, Logigian, & Ullman, 1988) have reported abnormalities in the substantia nigra, dorsal motor nucleus of the vagus, and neocortex in Fabry‟s patients.

In general, there are no studies that have investigated quantitative data from gait and balance in Fabry patients. Knowing the most sensitive gait and balance measures for Fabry patients could help clinicians to measure disease progression and quantify treatment benefits. Therefore, this thesis could add more detailed information about these patients‟ gait and balance measures and which parameters are affected more than others in order to identify the most effective treatment strategy.

The following table (Table 1.1) summarizes differences in patients‟ muscle strength, ROM, gait, and balance as noted in the studies reviewed in the text above.

Table 1.1: Summary table for all the patient groups muscle strength, ROM, gait, and balance.

Patient groups	Muscle strength	ROM	Gait	Balance
NP-C	√	=	√	√
Fabry	=	=	√	=
Hurler	√	√	√	√
Maroteaux-Lamy	√	√	√	=
Morquio	√	√	√	√
Pompe	√	=	=	√

√ Significant different between patient group and controls; = No significant different between patients‟ groups and controls.

1.3. Gait and Balance:

The ability to stand and walk normally with good balance is dependent on information from various systems, including visual, vestibular, brain, and sensory systems. Good gait and balance control are essential for the normal performance of activities daily living and avoiding fall injuries (Duarte & Freitas, 2010). The following sections will describe how gait and balance are assessed and define the parameters that are used to describe gait and balance functions.

It is well-known that an appropriate diagnosis of neurodegenerative disease is essential for early management. Detecting changes to gait and balance measures, may contribute to a set of measures that allow diseases to be diagnosed earlier. Characterising changes to gait and balance could help to identify distinct patterns that reflect neuro and musculoskeletal dynamics. Sensitive qualitative analysis of changes can help in tracking disease progression using functionally important measures and detecting when a patient‟s instability is reaching unsafe levels. As well, the techniques introduced here can capture treatment changes using measures that are important for activities of daily living (Wood, Cleary, Alderson, & Vellodi, 2009).

1.3.1 Gait:

In everyday, speech the terms "gait" and "walk" are used interchangeably. However, gait is a more general term for describing the action of locomotion, which is defined by the environment and the goal of the task (e.g. running or hopping), while walking is a type of gait (D. H. Sutherland, Olshen, Cooper, & Woo, 1980). There are several standard types of gait that have different phases and require different motor programmes (e.g. walk, jog, skip, run

and sprint). A gait requires complex coordination of sensorimotor action and the interaction between several supraspinal centres located in the basal ganglia, brainstem, cerebral cortex, and cerebellum (Petersen, Willerslev-Olsen, Conway, & Nielsen, 2012). The basal ganglia have the capability to rapidly adapt muscle patterns to changing task and environmental situations, so it play a role in selecting a motor strategy during adaptation (Bastian, 2008). In Parkinson's disease (PD) for example, patients are unable to alter their muscles and postural responses due to dysfunction in the basal ganglia and, as a result, they have problems starting, stopping, or sustaining movement (Chu, 2020).

The brainstem (particularly the Pons) is involved in controlling anti-gravity muscle tone, which, in turn, works on stabilising joints by contrasting the effect of gravity. Moreover, the brainstem works on receiving and integrating sensory information about balance disturbance, and then signals locomotor regions in the brain that control balance (Ferraye et al., 2014; Musienko et al., 2012) .The motor and premotor cortices are responsible for controlling leg movement and walking speed. The cerebellum is responsible for controlling how sensory inputs are integrated into the postural control system by affecting lateral sway and step width (Hanakawa, 2013). Damage of the cerebellum is the main cause of ataxic gait (abnormal or lack of voluntary coordination of movement) and increased gait variability. In general, all these centres stimulate the spine's central pattern initiator, which organises leg and arm movements into a rhythmic gait.

1.3.1.1 Gait Cycle:

Gait analysis is the methodical study of human locomotion. By analysing this locomotion, the gait phases, kinematic, and kinetic parameters of the human gait can be identified. In normal walking, muscles contract and relax in a specific cycle. This normal gait cycle is divided into

two phases. The first phase is a stance phase, which covers about 60% of the gait cycle (GC), and the second phase is a swing phase, which covers about 40% of the GC. Many muscles are active primarily in the stance phase, where the foot is in contact with the floor, or in the swing phase, where the foot is in the air (Figure 1).

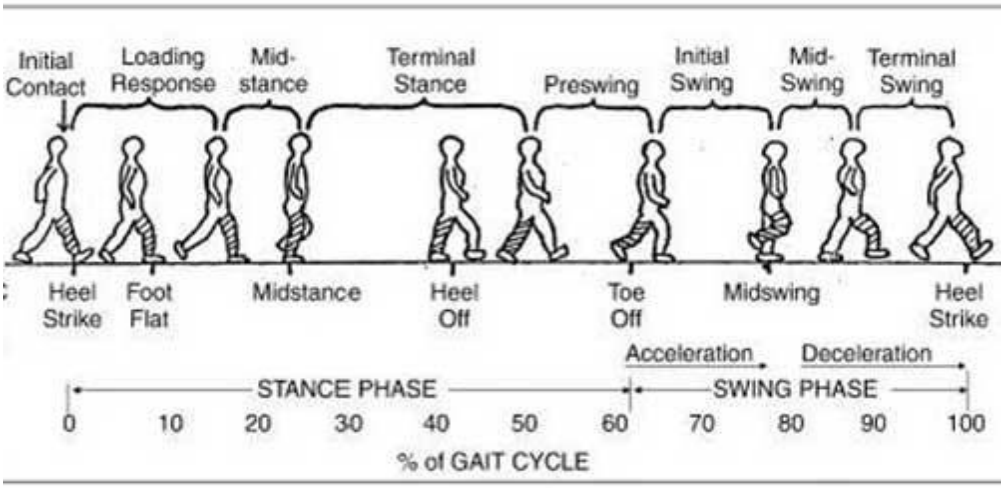


Figure 1.1: The normal gait cycle. The right leg is shaded.

The stance phase is subdivided into five phases. The phases take one leg as a reference point (the right leg in Figure 1.1). The stance phase begins with the initial heel strike of the reference leg on the ground. After that, there is the loading response, which ends at 10% of the GC. This is also called the double-stance stage, where both feet contact the ground. The mid stance phase follows until the 30% point of the GC. This is the first half of the single-limb support period where the reference foot (right foot in Figure 1.1) is in contact with the ground. Subsequently, the terminal stance ends at 50% of the GC and completes the first single-limb support phase with the right heel rising. The last part of the stance phase is the pre-swing phase, which is the second double-stance period and ends with the reference foot toe-off (right toe in Figure 1.1) at 60% of the GC. Any deviations (longer or shorter phase) during the stance phases could be an indicator of muscle imbalance and joint degeneration

that may lead to abnormalities in the lower limb joint ROM (Shultz, Sitler, Tierney, Hillstrom, & Song, 2009).

The other half of the gait cycle is the swing phase, which is subdivided into three phases. The first phase is the initial swing, which starts by lifting the reference foot from the ground and terminates by swinging the foot forward at 73% of the GC. The mid-swing phase follows, where the swinging limb is forward and the foot is clear from the ground, ending at 87% of the GC. The last phase is the terminal swing, which terminates when the reference foot contacts the ground and completes the GC at 100% (Tao, Liu, Zheng, & Feng, 2012). Any deviations in this phase could be an indicator of decreased balance and instability which may increase the risk of falling (Buderath et al., 2009).

Human gait can also be divided into steps and strides. A step is quantified by measuring the distance from left foot's heel strike to the right foot's heel strike. A stride, instead, is measured from the heel strike of the one foot to the following heel strike of the same foot. One stride is considered a single gait cycle (Kraan, Tan, & Cornish, 2017).

Gait characteristics and changes are described by temporal (time) and spatial (distance) parameters. Changes to temporal parameters often characterise abnormalities in children's gait, and some temporal parameters are best understood by normalising to the gait cycle (%GC; (Lythgo, Wilson, & Galea, 2011). Temporal parameters include step time, stride time, single-support time (one foot on the floor), double support time (both feet on the floor), and swing time (foot in the air). The step time is the time needed to take one step. The stride time is the time needed to complete a full gait cycle. Clearly, unless there are substantial asymmetries between steps, step time and stride time are highly correlated. An increase in stride time, step time, or double support time can reflect lower-limb muscle weakness,

especially in the gluteal muscles, which, in turn, could result in balance problems in children's gait (Lythgo et al., 2011).

The spatial parameters are mainly predictors of joint instability or orthopaedic pathology in the limbs (S. A. Rose, Õunpuu, & DeLuca, 1991). Any asymmetry in the step or stride length is considered a predictor of some musculoskeletal pathology e.g. muscles weakness, joint stiffness, or myopathy (Wood et al., 2009). Spatial parameters are determined by the stature of the child, especially the height and the leg length (Dixon, Bowtell, & Stebbins, 2014), so comparing across ages requires normalizing for height. Stride width is the average medio-lateral distance between both heels during terminal stance phase (Figure1.1), so irregular stride width is linked to lateral instability and can be related to postural control (Hoogkamer et al., 2015). Base of support is another spatial parameter, and it is the distance between the heel centre of one foot and the heel centre of the other foot during walking. In general, stride width and base of support are correlated. Irregularities in these parameters could be a sign of instability and gait or balance difficulties (Lythgo et al., 2011).

One of the spatial-temporal parameters is cadence, which is the number of steps taken over time. Normally, cadence decreases with increasing height, age, and with maturity. That is because an increase in age leads to increase in height which, in turn, increases step length. Any increase in cadence, especially if step lengths are shorter (need more steps) than normal, is a sign of an inefficient gait pattern (Wood et al., 2009).

Velocity is another spatial-temporal parameter that can be measured by calculating the distance covered in a unit of time, and variability in velocity is usually associated with an increased risk of falling (Katz-Leurer, Rotem, Lewitus, Keren, & Meyer, 2008). In general, increases in stride length and decreases in cadence lead to higher walking velocity with increased height and age.

Temporal-spatial gait parameters, together, reflect the overall state of children's gait and balance system. However, one must understand the development of children's gait first before attempting to explain or study the pathology of gait.

1.3.1.2. Normal development of children's gait:

Postural control maturity occurs consecutively in cephalo-caudal direction, which starts at two months of age with head control, followed by the trunk control, between 5 to 7 months, then postural stability in standing, between 9 to 12 months (McEvoy & Grimmer, 2005). Therefore, infants are first able to sit at six months of age, crawl at nine months, walking with support usually starts between 10 to 14 months and walking without support around 15 months. Children can usually run at 18 months (D. Sutherland, 1997).

Children start to walk with a wide base of support, hyper flexion of the hips and knees, their arms in abduction, and their elbows in extension. As they mature, cadence decreases, while step length and walking velocity increase. An increase in velocity is a natural consequence of an increase in step length. However, a longer step does take somewhat more time to complete, resulting in fewer steps per minute, or, in other words, a decrease in cadence.

A mature gait pattern begins between 7 to 10 years of age, but temporal-spatial variables continue to change with age and height (D. Sutherland, 1997). This happens when the child attains passable initial heel contact, rotation of the pelvic area, appropriate gait progression control, and synchronization of movement with the thoracic area (Moreno-Hernández, Rodríguez-Reyes, Quiñones-Urióstegui, Núñez-Carrera, & Pérez-SanPablo, 2010).

Selby-Silverstein et al. (2003) conducted a study to describe temporal-spatial gait parameters by using the GAITRite® walkway system for 90 healthy children, ages one to five years. They found that walking velocity, step, and stride length significantly increase with age and height. Moreover, temporal-spatial parameters can be affected and changed by motor and sensory maturation, co-ordination control and developmental factors (e.g., age, height, and weight; (McEvoy & Grimmer, 2005). Sensory and motor systems engaged in postural stability undergo a transition phase until they reach maturity by 7 to 10 years old in developmentally normal children. So, by reaching this age, an adult gait pattern will develop, involving, for examples, good upper body posture, efficient balance, smooth pelvic movement, and a completely developed heel to toe gait pattern.

In general, gait velocity, step, and stride length increase with age and height, while cadence decreases with height (Thevenon et al., 2015). Gait parameters also systematically change with weight. Obese children walk with decreased gait velocity and step length, and increased cadence. They also tend to walk in a more rigid pattern with less movement at the knee joint and a flatter foot during ground contact (Shultz et al., 2009). However, in this thesis individual‟s height, which is considered the main influence, was used as a scaling factor for normalizing gait variability.

1.3.1.3. Abnormal gait:

Normal gait is complicated, but pathological gait is even more complicated. There are several different pathologies that can influence gait. Many body systems influence gait, including the musculoskeletal, central nervous and cardio-respiratory systems. The GC is controlled by a combination of visual, vestibular, and proprioceptive together with motor programmes that

implemented coordinated movement. These functions involve a number of feedback and neuroanatomical centres which process the feedback for action, (such as primary sensory cortices), relate the feedback to ongoing action (cerebellum), and drive the required muscle groups with appropriate timing and intensity (motor cortex). Deficits or pathology in any of these systems and centres can produce gait and balance abnormalities in children (Lim, 2014).

The cerebellum has an important role in the neural control of gait. A defect in the cerebellum can cause characteristic unsteady walking with uncoordinated limb movement, which is referred to as a "cerebellar gait." Cerebellar gait involves a wide base of support and asymmetrical step length, which is shorter on the non-affected side when damage to the cerebellum is lateralised. Patients often shuffle while walking, leading to an increase in double support time (Fogel, 2012). These abnormalities in cerebellar ataxic patients are mainly a way of compensating for balance and co-ordination problems during walking and not the direct result of the cerebellar damage (Milne et al., 2014). However, if this compensation did not happen, the risk of falling in these patients would increase (Aprigliano et al., 2019). Numerous studies have investigated temporal-spatial gait parameters in children with pathology. Cherng et al. (2009) investigated the motor and cognitive effects on walking in fourteen children (aged 4-6 years) with developmental coordination disorder (DCD) and compared them with 28 age related control children. Due to the involvement of the cerebellum in DCD, DCD is considered to be a neuromotor disability disorder (Zwicker, Missiuna, Harris, & Boyd, 2012). Cherng et al. found that, DCD children had decreased walking velocity, cadence, and stride length, but increased double-limb support percentage. This pattern of results is not, by itself, a hallmark of cerebellar damage, because this pattern occurs whenever there is a source of instability (see below). This supports the view that these changes are a compensatory response. Cherng et al."s findings support the hypothesis that

DCD children have balance problems during walking, and they may have an increased risk of falling as a consequence.

The gait parameter findings in Cherng‟s study are similar to the findings of Wood et al. (2009), who investigated the gait pattern for 6 Mucopolysaccharide children (MPS type II, Hunter syndrome) aged between 3 and 8 years. They found that these patients have decreased cadence, asymmetrical step length, and an increased base of support. They concluded that Hunter children have an inefficient gait pattern with balance difficulties due to a severe decrease in the lower limb joints' ROM, musculoskeletal deformities, and neurological involvement.

Taken together, these finding suggests that it is important to combine gait and balance parameters findings with clinical examination such as ROM test and manual muscle testing to understand the full picture of a patient‟s status.

1.3.1.4. Method for gait assessment:

Gait analysis and assessments are essential for discovering gait abnormalities, making a diagnosis, verifying therapeutic outcomes, and evaluating patients' development (Bilney, Morris, & Webster, 2003). Measuring age-related gait changes in normally developing children to establish normative values for detecting gait changes is one of the aims of this thesis. An understanding of normal gait development, with standardised methods and reference values for the main gait parameters, is a necessary prerequisite to measuring abnormal gait in a methodical manner. In the following sections, gait measurement methods will be discussed.

1.3.1.4.1 Zeno mat or GAITRite® walkway systems:

The Zeno walkway system is a 5-metre electronic pressure sensor walkway linked by USB to a computer. It contains a total of 18,432 sensors which are implanted in a network with an active measurement area of 61 cm by 488 cm. The sensors in the mat are activated by mechanical pressure from foot contact and sensor data is used to produce distance and timed gait data. The walkway system is one of the most cost-effective, simplest, and clinically useful methods used to study gait in children. In addition, it has well-established reliability and validity compared to other gait methods and it is recommended for practice in paediatric populations (Kraan et al., 2017).

Zeno mat and GAITRite® are two specific examples walkway systems. The spatial parameters they record are step length, stride length, step count, step width, and base of support. The temporal parameters they record are velocity, cadence, swing time, stance time, and single and double support time.

Many researchers and physiotherapists in recent decades have incorporated the Zeno mat walkway system into research or clinical assessment because it is technically uncomplicated, and is portable, so it can be used anywhere (e.g. lab, clinic, or natural environment) (Menz, Latt, Tiedemann, San Kwan, & Lord, 2004). An important advantage of using the Zeno mat system with patients or paediatric populations, in particular, is that the subject walks over the sensor area without the encumbrance of markers or wires, unlike other methods such as motion capture. The data for each step within a trial can be rapidly and simply obtained (Bilney et al., 2003). The Zeno mat walkway is an extremely sensitive method for identifying any alterations in the gait parameters while walking (Lim, 2014).

Several studies support the concurrent validity and reliability of the GAITRite® or Zeno mat walkway systems when measured against the most common, golden-standard methods in

adults (Bilney et al., 2003; Lythgo et al., 2011; McDonough, Batavia, Chen, Kwon, & Ziai, 2001; Menz et al., 2004; Webster, Wittwer, & Feller, 2005). Gold standard methods include the chalk and ink-pad method, Clinical Stride Analyser, or the Vicon-512®. The Vicon-512® is a 3-D motion capture system considered to be the gold-standard method to measure gait variability. Webster et al. (2005) compared the validity of the GAITRite® system to the Vicon-512. They found that the GAITRite® system was a valid instrument for measuring spatial-temporal gait parameters. This was significant because the Vicon-512 system, which is costly, technically complicated to utilize, and labour intensive, is not appropriate for clinical settings. However, the walkway mat systems are much more applicable for clinical use.

In addition to studies in adults, there are some studies that have measured the validity, reliability, and repeatability of walkway systems in paediatric populations (Dusing & Thorpe, 2007; Holm, Tveter, Fredriksen, & Vøllestad, 2009; Lythgo, Wilson, & Galea, 2009; Moreno-Hernández et al., 2010). Moreno-Hernández et al. (2010) examined the gait of 133 healthy children to use their normal values as a reference to compare with children who have pathological gait patterns. In their study, children were between 6 and 13 years old and they walked for three trials on the GAITRite® walkway, first barefoot and then with footwear. The researchers concluded that the gait variability of the children was affected by age and footwear, but not by gender. Although they reported that some gait parameters increased with the footwear (e.g. velocity, step, and stride length), they did not consider the type of the footwear in their testing. If participants wore flats, boots, runners, or shoes with heels, gait variables could be affected in different ways. Testing children's gait while they are barefoot can present more accurate and consistent readings across individuals (Lythgo et al., 2009; Sathe & Hiwale, 2020).

Lythgo et al. (2009) recruited 980 healthy children (ages 5 to 13 years) and young adults (ages 18 to 27 years) to measure the basic gait variability while walking barefoot and with shoes. All the participants wore athletic shoes in the shoe condition and walked on a GAITRite® walkway for 6 to 8 trials. Their findings were similar to those of Moreno-Hernández et al. (2010) study. They found that footwear significantly increased gait speed, step, and stride length and decreased foot angle and cadence. However, they did not find significant differences in gait variability with age. They stated that gait is moderately steady after the age of 7 years and starts to be mature between 7 and 10 years old, especially for stance time %, single and double support %. This is comparable to what Dusing and Thorpe (2007) found when measuring gait in younger children (aged 1 to 10 years). They found that gait velocity increased with age until 7 years old, and then reached a plateau. If the sample in Lythgo et al. (2009) had been younger (e.g. 2 or 3 years old), it is likely that the differences with age would have been significant. There is a rapid linear improvement of gait variability from age 2 to 5, followed by a slower period of improvement from 5 to 7 years, after which improvement reaches a plateau (Holm et al., 2009).

Thevenon et al. (2015) found slightly different results in their study. They recruited 382 healthy children aged between 6 and 12 years old. They found that all of the temporal parameters differed significantly when comparing 6 to 7 to 9 year-old participants. They concluded that temporal parameters have a U-shaped development curve. These parameters (stride time, cadence, and stance time) were high in children, lower in juveniles and adults, then increase again in elderly. Although the current study population doesn‟t have elderly participants, Thevenon et al. (2015) explained that these differences are due to the fact that temporal parameters increase in proportion to height (from 110 cm to 130 cm) then reach a plateau. By normalising for children's height we can partial out the effect of height so that the parameters of children of different heights can be compared.

All of the previous studies used a walkway mat to gather data on normal children. It is necessary to look to other studies to assess gait abnormalities in children with pathological conditions.

Bladen et al. (2007) used a GAITRite® walkway with 26 boys with haemophilia from ages 7 to 17 years. They divided the sample population into three groups: the haemophilia asymptomatic group, haemophilia with arthropathy group and control group. They measured gait velocity, step length and time, stride time, swing and stance time, and single and double base support. The study results showed that the GAITRite® walkway was very sensitive in measuring early gait alterations and abnormalities in asymptomatic boys with haemophilia, where it was clinically undetectable. Usually haemophilia affects gait through bleeding into the synovial joint, which causes joint damage, muscle atrophy, and soft tissue contractures which, in turn, lead to an abnormal gait pattern. They concluded that using the GAITRite® walkway can identify early joint damage and musculoskeletal deformities in asymptomatic haemophilia patients.

Walkway mats have been used with other children with pathological conditions and have been shown to be suitable for following changes in gait parameters. It was used with Hunter syndrome (MPS II) patients by Wood et al. (2009). They measured gait parameters and did a follow-up measurement 10 to 16 months after a baseline measurement, while patients were undergoing ERT. They found various changes in the gait parameters between the baseline, first follow-up, and the second follow-up. They found, in both follow-ups, that the cadence increased, which is why patients have an inefficient gait pattern. They also identified asymmetry in the step length, which is a marker of joint and skeletal deformities. The researchers also found increases in the base of support and double support, which, in turn, lead to muscle imbalance and balance difficulties. These findings from Wood‟s study recall the primary results of Gabell and Nayak (1984), who found that double support and stride

width (which is similar to base of support) were balance related parameters. Gabell and Nayak (1984) study investigated the variability in gait of two temporal (double support and stride time) and two spatial (step length and stride width) parameters in relation to the control systems for 64 healthy individuals. They found after correlating these parameters with fall detecting questionnaire, that double support and stride width parameters were usually determined by balance control mechanisms.

Paciorkowski et al. (2008) found that stance time was increased when they measured patients with NP-C and this, in turn, affected their stability. They concluded that the gait changes could be related to a decrease in cerebellar white and grey matter volume which would affect motor control, for eye movements, saccadic gain.

All these studies indicate that a walkway mat is a reliable tool for measuring changes to gait parameters accurately and sensitively whether they are due to musculoskeletal, neurological pathology, or in healthy developing children.

In general, gait is about movement (during ambulation) and gait analysis is known to be a significant clinical tool for studying relationships between motor control and brain function in healthy individuals and in patients. Balance, in contrast, is the capability to sustain the centre of gravity of a body within a base of support with minimal postural sway by the integration of visual, vestibular, and somatosensory inputs within the CNS (Kraan et al., 2017). Gait and balance are, then, different domains, but they are strongly linked since they tend to influence one another. In the coming section balance and postural development will be addressed.

1.3.2. Balance:

Balance and postural control adjusts body position to keep it stable (De Araújo et al., 2014). Postural control is considered one of the important aspects of movement and is responsible for sustaining the body in a state of equilibrium, which depends on postural oscillations around a centre of mass. Postural control has two main functions: Firstly, postural orientation involves correction of posture in contradiction of gravity to maintain balance. Secondly, postural equilibrium works to stabilise the centre of body mass (COM) by the coordination of three general types of movement strategies with regard to the external world (Horak, 2006). Balance strategies can be divided into static balance, dynamic balance and reactive, anticipatory balance. Static and dynamic balance associate COM and the base of support (BOS), while reactive and anticipatory balance involves modifications made to correct unexpected shifts in COM and the BOS by neuromusculoskeletal activation (Westcott & Burtner, 2004).

Balance and postural development have been considered in multiple positions, including sitting and standing. However, it is vital to identify the development of balance and postural control in standing. This is because children‟s balance abilities while standing are particularly important for daily living activities (Majnemer et al., 2008).

The postural and balance system in humans includes a complicated set of somatosensory, visual, and vestibular signals, based on numerous brain regions, and musculoskeletal systems (Manor et al., 2010). These systems work together in order to sustain balance and postural control.

Body position is sensed using three primary signals from different systems. The first system is based on a visual signal that senses changes to optical flow from nearby surfaces (Assländer & Peterka, 2014). The second system depends on proprioceptive signals from

muscle tension. For example, sway forward will increase tension in muscles in the back of the thigh, and decrease tension in the muscles in the front. The third system is the vestibular signal from the inner ear that senses changes to body position using the semi-circular canals and otolith organs (Manor et al., 2010). These three systems are most important for controlling balance to sustain an upright posture and alignment by using active feedback mechanisms to produce corrective torque (Assländer & Peterka, 2014). This corrective torque works mainly to minimize the proprioceptive signals by minimizing the ankle joint motions.

However, Hansson et al.(2010) did a study to investigate the postural sway while isolating visual, vestibular, and proprioception systems. The visual system was isolated by asking participants to balance with eyes closed, while the vestibular system was isolated by rotating the head to the right and to the left with maximum neck extension. The proprioception system was isolated by asking participants to stand on firm and on foam surfaces. Hansson et al. (2010) found that when each of these three systems was isolated and balance was tested, all three systems have an effect on postural sway. However, vision had the most significant influence on balance and postural sway compared to vestibular and proprioceptive systems. This could be because vision provides richer information about external coordinates to place the body in relation to the surrounding environment, and, as a result, has a larger role in postural stabilization.

Additionally, Lee and Aronson (1974) reported that visual proprioceptive (visual + proprioceptive) information is more effective than mechanical proprioceptive information (proprioceptors in the joints--ankles and hips--and muscles corresponsive to mechanical force) in the maintenance of standing balance in children. In their study they tested body sway for 7 normal infants aged from 13 to 16 months. They moved an experimental room (three walls and ceiling) forward or backward while the participant stood on a stationary floor to check the participant‟s reactions. They found that visual proprioception sustains balance

when, for example, the visual feedback for backward body sway must persuade muscular action to cope a compensatory forward torque about the participant‟s feet. If this torque were sustained, the participant would sway forward until s/he lost balance. Nevertheless, when the participant was swaying forward, a conflict between mechanical proprioception and visual feedback would arise. If the front of the room was moved further away from the participant during forward sway, visual feedback would sense backward body sway and thus urge forward torque, whereas the mechanoreceptors would be recording the real forward sway of the body and, therefore, call for compensatory backward torque. Lee and Aronson (1974) conclude that infants first depend more on visual proprioceptive to maintain standing, then as a result of practice, the mechanical proprioceptive signal develops and reaches the same degree of efficiency as the visual proprioceptive signal.

The control of good standing balance needs collaboration between many systems in the body, including the eyes, vestibular system, muscles, and joints, which send feedback information about body position in the environment to a series of brain centres. These inputs are part of neural mechanisms that activate through the spinal cord, brainstem, cerebellum (coordination centre) and cerebral cortex (thinking and memory centre). In these areas, the sensory feedback is received and integrated. Then motor output signals are sent to locomotion regions in order to correct posture and restore the balance (Figure 1.2; (Zeng & Zhao, 2011).

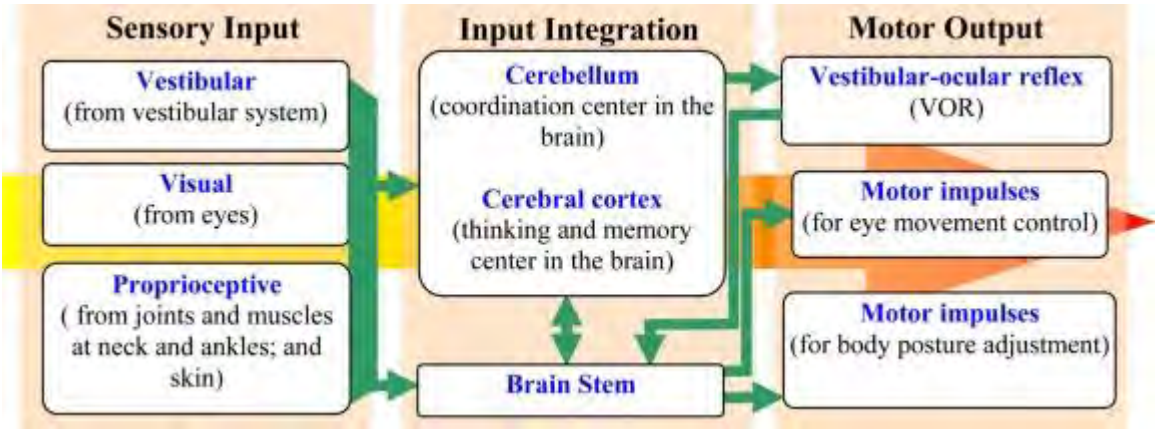


Figure 1.2: Balance control in Human (Zeng & Zhao, 2011).

The procedure for altering the sensory contributions to balance control is called sensory reweighting. Change in one sensory system is continuously compensated by varying the weights of other sensory systems (Assländer & Peterka, 2014). This reweighting is necessary in order to sustain a reliable level of sensory feedback to stabilize the body posture against gravity, without changing the general dynamic features of the balance control system. Early studies described little coordination between the sensory systems, with random weighting of information for children under 7 years of age (Forssberg & Nashner, 1982). More recent studies show that even though visual, vestibular and somatosensory systems are still maturing, children are capable of completing balance testing that disrupts the contribution of individual systems (Peterson, Christou, & Rosengren, 2006; Steindl, Kunz, Schrott-Fischer, & Scholtz, 2006), showing that systems that are not disrupted can compensate for disruption in the remaining systems.

On the other hand, these systems and signals could be interrupted by impairment to one or multiple systems through disease, injury or through aging progression. Impairments to balance and postural control can also linked to other symptoms such as vertigo, nausea,

vision problems, dizziness, fatigue, attention problems, reduced joint ROM, and muscle strength.

In general, children require fast muscular reactions in to response to balance disruption, which is accomplished by the somatosensory system (Roncesvalles, Woollacott, & Burtner, 2002). It is well documented that postural stability improves with age, with reductions in variance, velocity and frequency of sway during stance with both with (eyes open) and without (eyes closed) visual input (Cumberworth, Patel, Rogers, & Kenyon, 2007). However, coordination impairments and poor balance in children can be caused by damage to either central or peripheral parts of the nervous system. As we have seen in our discussion of gait, the cerebellum is one of the important elements of the CNS that is responsible for coordination and balance. Cerebellar impairment usually causes disturbance of the controlling system (coordination system) that controls motor commands in response to multimodal sensory input from the environment. This leads to clinical symptoms that may include, for example, slow, uncoordinated movement, sway and wobbling, wide base gait (ataxic gait), motor speech disorder (dysarthria), inability to judge distance (dysmetria), hypotonia, and numerous anomalies of eye movement (Jahn et al., 2008).
To date, only a few studies have investigated balance in children with the neurodegenerative diseases that this thesis focuses on (NP-C, Hurler, Morquio, Maroteaux-Lamy, Pompe and Fabry). However, potential effects on balance can also be informed by studies of adult patients with neurological disorders including stroke, and PD.

One of the studies conducted on children was done by Sansare et al. (2018), who examined 10 NP-C patients aged from 4 to 23 years compared to gender and age-matched controls. Sansare et al. used the NeuroCom Balance SMART Equitest for assessing balance in both EO and EC conditions. They found that when the patients were standing with EO or EC, they

swayed significantly faster than controls, especially in the EC condition. However, none of the NP-C patients in their study showed such a high sway velocity that it would be visually noticeable (i.e. detectable without sensors). Also, they found that postural sway velocity increased as disease severity increased. Finally, they concluded that abnormally increased sway when standing on a firm surface with EC showed that individuals with NP-C have reduced use of proprioceptive inputs and increased use of visual signals for postural stability.

1.3.2.1 Methods for balance assessment:

Some symptoms related to postural instability cannot be distinguished by a clinical exam. Therefore, an objective tool is vital for evaluating balance, especially in children. Most of the currently existing gold-standard tools and equipment, however, require a dedicated research laboratory and are not suitable for routine clinical use (e.g. force plates). On the other hand, functional assessments of balance such as the Berg Balance Test, the Functional Reach Test, and the TUG Test are quick to manage and do not need expensive equipment, but can only measure general and gross changes in balance. Thus, there is a need for a tool that can be used clinically, but is sensitive enough to pick up subtle changes to the balance system. New sensors may allow us to bridge this gap because they approach the sensitivity and accuracy of gold standard methods, but are portable enough for use in a range of clinical contexts. Our research uses one such system.

One of the important and gold standard tools used for assessing balance is the force plate. They can detect small changes in subjects‟ ability to maintain their balance. Silfies et al. (2003) investigated the effect of visual input on stability in EO and EC conditions for 13 healthy subjects. They used force plates to measure the centre of the pressure (COP) and

found that the area covered by the COP significantly increased in the EC condition. Rose et al. (2002) used force plates to investigate postural control for 23 CP children aged 5 to 18 years. They found that one third of the patients had increased COP, path length, average radial displacement, and the diffusion coefficient (the average rate at which the COP changes over time) was higher in CP patients, while mean sway frequency was lower compared to control. However, there were no significant EC/EO differences for these parameters. This is because CP patients used normal dependence on visual feedback to sustain balance. It can be concluded from this study that there was no impaired sensory reweighting in CP patients. Force plates produce gold-standard levels of accuracy and sensitivity, but their cost, size and non-portability makes them unsuitable for many clinical situations. These disadvantages also apply to motion capture cameras, which are another gold standard method for gait and balance assessment. This equipment records actions of human actors in 2D or 3D space using an array of video cameras and markers on critical body parts (Shiratori, Park, Sigal, Sheikh, & Hodgins, 2011). However, due to the cost of the software and the equipment, the need for a lab setup (non-portable), and the specific requirements for the space to operate in, motion capture is often not appropriate for clinical settings. The Zeno mat, described earlier in the context of measuring gait. Is capable of measuring fluctuations in the distribution of pressure over the sole of the foot during quiet standing. This could have been used as a measure of balance in the present study. However, a new approach to characterising balance in terms of rate of change of acceleration (jerk) of the trunk during standing has proven to be a very effective measure of balance. This measure was considered important in the present study and involves the use of accelerometers to characterise balance performance as described in the next section.

1.3.2.1.1 Accelerometers:

Accelerometers have emerged as a good alternative method for measuring balance and postural sway. Accelerometers are portable, low cost, non-invasive, easy to use, and can be applied outside the laboratory environment, which has made them popular for measuring postural control (Cleland et al., 2013; Covarrubias-Escudero, Rivera-Lillo, Torres-Castro, & Varas-Díaz, 2019; Mancini et al., 2012; Peters, Baker, Morris, & Sangeux, 2012; Saremi et al., 2006; Seimetz, Tan, Katayama, & Lockhart, 2012; Takeda, Tadano, Natorigawa, Todoh, & Yoshinari, 2009; Tao et al., 2012).

Accelerometers are attached to the upper and/or lower limbs of the body to measure acceleration in three orthogonal axes: anteroposterior (x-axis), mediolateral (y-axis), and vertical (z-axis) (Cleland et al., 2013; Mancini et al., 2012; Rowlands, 2007).

There are many accelerometer placement configurations for detecting physical activities, and each configuration allows different motion parameters to be measured. Some studies have reported that placing the sensor on the level of lumber spine (L5), or close to the iliac crest, is the optimal location to measure balance and postural sway (Kangas, Konttila, Lindgren, Winblad, & Jämsä, 2008; Mancini et al., 2012; Silfies et al., 2003). Therefore, this thesis will use L5 placement in order to measure postural sway in children.

Two control parameters that are sensitive to changes with disease are postural sway or root mean square of COP (RMS) and jerk (Mancini et al., 2012). Sway area or RMS is the movement in the horizontal plane around the centre of the gravity which reflects how the nervous system is managing sensorimotor effort to sustain stability. Jerk is the rate of change of acceleration and a measurement of the smoothness of sway and reflects the corrections made to maintain sway within an area that maintains stability. However, jerk is a relatively new measure and so it is reported in fewer studies. Mancini et al. (2012) reported that jerk

was the most sensitive measure for detecting changes in postural control. An elevated value of jerk means less smooth sway, and a lack of control in the postural sway corrections made by the nervous system.

A growing body of research has investigated the effectiveness, validity, and reliability of the accelerometers in measuring postural control (Covarrubias-Escudero, Rivera-Lillo, Torres-Castro & Varas-Díaz, 2019; Mancini et al., 2012; Palmerini et al., 2013). These studies agreed that accelerometer is an objective and a valid tool to measure postural control. Moreover, Palmerini et al., 2013 reported that accelerometer is a reliable tool to identify and quantify any postural differences between healthy and unhealthy groups. Therefore, it can be used to assess, follow-up, and to monitor disease progression.

In general, there is a lack of evidence in the literature about children‟s balance that is within the scope of this thesis‟s interest in neurodegenerative disease groups so the context for the studies presented here is drawn from other related literatures. Mancini et al. (2012) conducted two studies with adults to understand the posture control characteristics of patients with pre-symptomatic PD. The first study investigated the sensitivity and experimental concurrent validity of the instrumented test of postural sway (ISway) which used an accelerometer to measure sway and jerk. The second study examined the test-retest reliability and clinical concurrent validity of the ISway test. The accelerometer was placed on L5 as recommended by previous studies (Kangas et al., 2008; Silfies et al., 2003) and a comparison with concurrent force plate measurement was performed. They found that accelerometers were sensitive, valid, and reliable for measuring the effects of PD. Although generalizing this to results from other populations is difficult, some of the groups studied here share similar symptoms to PD. For example, NP-C patients have difficulty initiating movement and often experience tremors and ataxia due to deficits in the CNS. This usually increases lateral sway,

which can increase the risk of falling. Therefore, the ISway test was a good candidate for measuring balance changes NP-C patients and judging its wider clinical suitability.

Beside using accelerometer for testing balance and postural control, some studies have investigated accelerometers for fall-detection algorithms using different placements (Bourke et al., 2010; Kangas et al., 2008). Kangas et al. (2008) did a study to assess different low complexity fall detection algorithms by using triaxial accelerometers placed on the wrist, waist, and head. In their study, three participants (aged 38, 42, 48 years old) were recruited for an intentional fall task (forward, backward, and lateral). The intentional fall took place onto a mattress to calculate the vertical acceleration in different phases of the fall event. Kangas et al. (2008) found that placement of the sensors on the waist or head were efficient for detecting falls. Due to restrictions of the acceptance and usability of the head device in daily life, they concluded that a waist-worn accelerometer was optimal for detecting any postural instability and loss of balance.

In conclusion, this chapter has shown that patients with neurodegenerative diseases can have many abnormalities in gait and balance. Gait abnormalities can include increased cadence and base of support, as well as asymmetry in step length and decreased gait velocity (Kraan et al., 2017). Balance abnormalities include loss of standing balance as a result of increasing sway area and increasing jerk. These abnormalities can decrease the postural control and increase the risk of falling during daily activities (Mancini et al., 2012). Therefore, there is a need for clinically relevant and sensitive instrument to detect early changes in gait and balance in these patients before they lead to falls.

1.4 Aim of the thesis:

This thesis will investigate methods for accurate and sensitive measurement of gait and balance changes in specific neurodegenerative disease groups (NP-C, Hurler, Morquio, Maroteaux-Lamy, Pompe and Fabry).These measurements have not been extensively reported based on advanced measurement tools here: an the electronic walkway mat (Zeno mat) and accelerometers. Where similar reports have been made our measurements will add to a corpus of results that will be necessary to accumulate across research centres because of the small number of affected patients available and the difficulty of recruiting them. The types of measurement tools we use have significantly higher reliability and validity compared to other measurement methods (discussed above). By obtaining these valuable measurements of gait and balance parameters in different neurodegenerative diseases, we will contribute to an understanding of the development of changes in the gait and balance in these patients. This, in turn, will help to establish baseline gait and balance data, which can be referred to it in the future studies and used, for example, to evaluate treatment effects. Moreover, an understanding of how gait and balance changes can help the clinicians to improve their therapeutic interventions.

Therefore, this thesis aims, firstly, to characterise changes in gait parameters in different neurodegenerative disease patients and compare these changes with healthy control individuals. Secondly, it will characterise balance changes and determine whether patients show abnormal sensory reweighting of visual inputs. Finally, we will determine, where possible, whether relationships between gait and balance parameters (as measured by correlations) have been altered by the disease (recognizing the limitations that small samples impose).

CHAPTER 2: GENERAL METHODS

2.1. Research design:

This thesis used a cross-sectional experimental design, where the patients were compared with controls of corresponding age across a range of ages. This design allows comparison of many variables at the same time. This type of design can examine whether patient groups are different or not with respect to control participants. Also, the data from this design can be used for various research types, and findings can be analyzed from this design to generate new studies (Mann, 2003).

Unlike the cross-sectional experimental designs, a longitudinal experimental design would be difficult to apply with these patient groups. Difficulties recruiting, changes in some clinics‟ time, and the priority for patients to be seen by their physician before the researcher would make it hard for the researchers to see the patients at specific time points. Therefore, using a cross-sectional experimental design is an appropriate approach.

2.2. Study population:

2.2.1. Patients with neurodegenerative diseases:

Potential participants who were recruited in this thesis have inherited metabolic diseases (IMD). IMD patients were identified by the clinical care team in the IMD department of Birmingham Children‟s Hospital (BCH).

Beside the clinical care team, the research team sometimes helped in identifying IMD patients. This was achieved by accessing patient records, patients‟ medical notes and/or through observation during clinics, which, in turn, helped in assessing the suitability of potential participants. Initial contact with patients was always made by the direct care team.

Forty-two IMD patients were recruited for this thesis. The different types of IMD patient are shown in Table 2.1.

2.2.2. Control group:

A large group of control participants was recruited to cover the range of patient heights and ages (Table 2.1). Recruiting age- and height-matched healthy participants will enhance the external validity of the outcomes (Löhle et al., 2015). The control participants were recruited from nurseries, primary schools, and secondary schools. Children recruited via schools were given an information sheet about the study to be informed about it. If the children‟s parents or legal guardians agreed to participate in this study, a consent form was returned, or an opt-out form was not returned (according to school preference). Families were informed about their right to be freely withdrawn from the study at any time. Most of control testing was done in a school hall. One participant was called to participate, while the rest of the class was waiting in the other corner of the hall in order not to distract the participant who was doing the test. There were 294 healthy children recruited to the control group.

Table 2.1: Demographic information of participants in this thesis within each group.

Group	N	Mean/Age (years)	SD/Age (years)	Mean/Height (cm)	SD/Height (cm)
Control	294	13.08	5.53	145.62	21.70
Fabry	20	8.81	2.96	133.52	20.61
NP-C	9	8.28	2.80	127.75	18.73
MPS I	6	9.16	3.24	127.11	17.10
MPS IV	4	9.83	3.33	102.92	11.22
MPS VI	2	6.80	1.10	114.40	3.29
Pompe	1	6.00	0.00	117.00	0.00

N: Number of participants, SD: standard deviation, NP-C: Niemman pick type C, Hurler: MPS I, Morquio: MPS IV, Maroteaux-Lamy: MPS VI.

2. 3. Recruitment strategy:

The study was approved by the South Birmingham Research Ethics Committee, which follows the *Declaration of Helsinki*. The study REC reference is 11/H1207/7, the protocol number is RG_09_186, and the Amendment date was 20 March 2014.

Initial contact with patients to provide a study information sheet (Appendix 1 A) was made by the clinical care team. On the week following initial contact, the research team, who had received the appropriate good clinical practice (GCP) training, provided more detailed information and/or answered inquiries. If verbal agreement was obtained, parents were given a consent form (Appendix 1 B) to be signed. An English interpreter was provided, if participants did not have sufficient knowledge of English.

The testing session was held on the day that patients visited the hospital for their regular check-ups in the IMD clinic in order to minimise inconvenience for the families. Alternatively, depending on parents‟ preferences, testing sessions could be arranged in more convenient times or places, for example at the University of Birmingham or the patient‟s home. Copies of written consent and study information sheets were lodged in the patient‟s clinical records as well as in the research case file and kept safe.

The consent process for the patient was continued throughout the time that the patient remained part of the study and was under continual review. It was emphasized that the patient and/or family could decide to withdraw consent at any time and without needing to give any explanation and without any impact on the clinical services provided by the hospital. While, for the control participants most of them were tested in the school hall.

2.4. General inclusion and exclusion Criteria:

2.4.1. Inclusion criteria:

All genders groups and different ethnicity were included in this study. The most important inclusion criterion was that participants had to be able to walk at least 10 m without support, or with minimum support. The other important inclusion criterion was that participants had to be able to maintain a standing position for 5 minutes without support.

2.4.2. Exclusion criteria:

Exclusion criteria of this study included parents or legal guardians were unwilling to provide consent. Parents or legal guardians who were unwilling to continue their child‟s participation following acquisition of consent, or patients over 16 years of age lacked capacity to provide their own consent for participation their parents or legal guardians were consulted. Participants with recent (less than 9 months) lower limb surgery were excluded, as well as participants who could not walk without support for 10 metres, as well as, who could not stand unsupportive for 5 minutes.

2.5. Study record retention:

Research results recorded during this project will be stored for 25 years before deleting them. This is because these patients have developmental neurodegenerative diseases. It will be appropriate to maintain the possibility of linking individuals to data if a clinical or research need arises in the future (e.g. if there is a follow-up on patients in future longitudinal work). During this study, participant information (e.g. consent forms) were kept securely in a master file.

2.6. Assessment Tools and Outcome Measures:

Several measurements were taken for each participant in this study. Some of these required more skill and were collected by a specialist physiotherapist.

Demographic information, such as height, weight, and bilateral leg length were collected for each participant. In addition, leg length was measured to check any leg length discrepancy that could effect the gait pattern. The length measured was the distance between Anterior Superior Iliac Spine (ASIS) and the medial malleolus.

In the analyses that follow, gait and balance parameters were normalised for height and age. Body height was used for normalization because most subjects were above age 4. That is because using leg length for normalization is appropriate for children between 2 and 4 years since the proportion between leg and torso is progressively changing during these ages

((Guffey, Regier, Mancinelli, & Pergami, 2016). There has been no significant gender difference found in other studies using the same age range as this study (Lythgo et al., 2009; Moreno-Hernández et al., 2010; Thevenon et al., 2015), so gender was not included as a factor. These studies found no significant gender difference until participants reach adolescence, when the neurological and muscular-skeletal maturity is reached.

2.6.1. Range of Motion (ROM):

Joint flexibility is defined as the available ROM at a joint. A joint's ROM is generally measured by the number of degrees from the starting position of a segment to its position at the end of its full range of the movement. The most common tool to measure ROM is the double-armed goniometer (Figure 2.1) which was used in this study. This plastic goniometer was used to measure the total amount of available motion at a specific joint by measuring the joint angles. Goniometers has been found to be a good reliable and valid tool for measuring ROM in the research laboratory as well as clinical settings (Cranage, Banwell, & Williams, 2016).

In this study, only the lower limb ROM were measured, including; hip flexion, extension, adduction, and abduction, knee flexion and extension, and ankle dorsiflexion and plantarflexion. The testing position for each participant was modified according to their condition. For instance, if the participant could not lie down on his/her side or back to do some measurements, a modifying position, either sitting or standing, was used for the measurement.

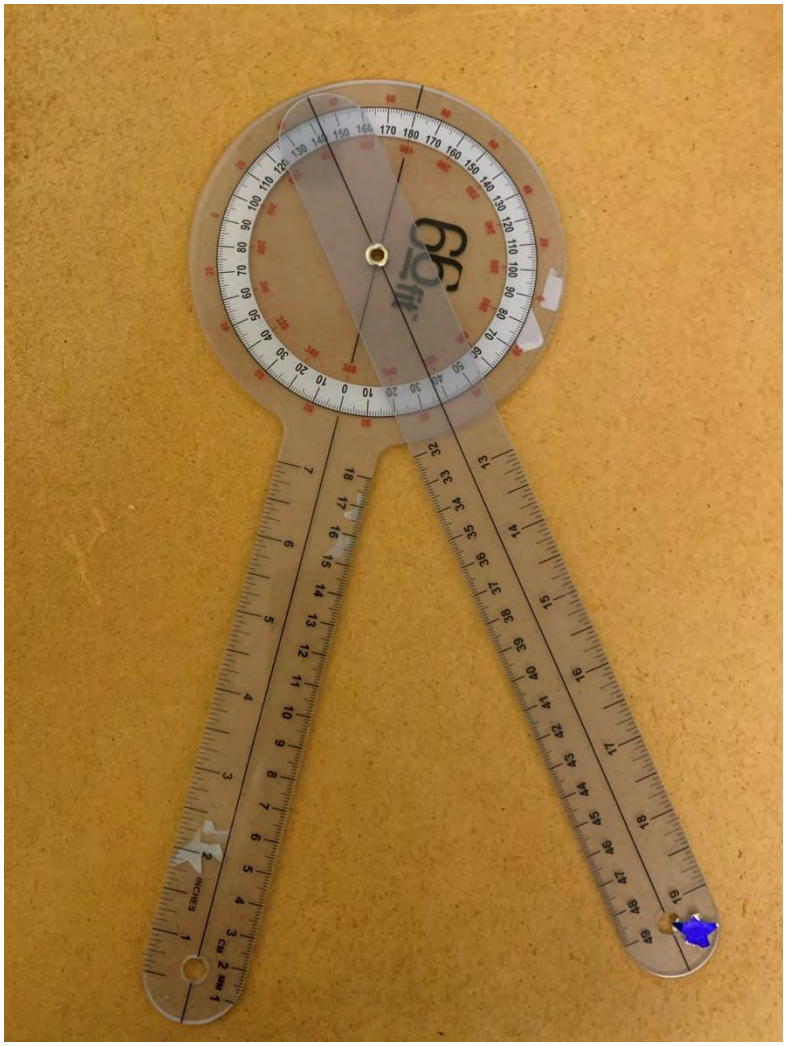


Figure 2.1: Double-armed goniometer.

2.6.2. Manual Muscle Testing (MMT):

Manual Muscle Testing is a technique that is used to assess the function and strength of individual muscles and muscle groups. This is achieved by performing a movement against the forces of gravity and/or manual resistance (e.g. resistance to a force created by pushing against the therapist‟s hand) through the available ROM. MMT is grading from grade 0 to 5. Grade 0 is described as no palpable or visible contraction in the muscle. Grade 0 involves no movement. Grade 1 involves a flicker of movement of the tested muscle. Usually grade 0 and 1 MMT refer to maximum muscle weakness. For grade 2, the muscle moves the joint through

the complete ROM with gravity eliminated. For grade 3, the participant is able to move the tested joint through its ROM against gravity. Grade 2 and 3 are considered to have moderate muscle weakness. Grade 4 involves joint movement through a full ROM against gravity, with moderate resistance from the therapist‟s hand. Individuals with grade 4 MMT have mild muscle weakness. Grade 5 is the same as grade 4 but with maximal resistance from the therapist‟s hand. An individual with grade 5 has no muscle weakness (Cuthbert & Goodheart, 2007). In this study, the muscle strength of the big muscle groups of the lower limb were measured, including hip flexors, knee extensors, and ankle dorsiflexors.

2.6.3 Gait testing:

A Zeno mat walkway system (Zeno mat walkway system, CIR Systems Inc., 376 Lafayette Rd, Sparta, NJ 07871, United States), considered an advanced technology for the kinematic analysis of gait, was used in this study (Figure 2.2).



Figure 2.2: Zeno mat walkway.

This electronic walkway can identify the timing of sensor activation (timing of footfall) and the relative distances between sensors (stride length), and then transfers this information into PKMASS software (Appendix 2 A) to analyze spatial and temporal gait parameters (Webster et al., 2005). The Zeno mat calculates more than 45 different parameters. There are many gait parameters that could be used to monitor a participant‟s walking status. However, because some of these gait parameters are essentially equivalent (e.g. step length and stride length) or complementary (like stance percent and swing percent). Only five parameters were examined in this study. These gait parameters included stride length, stance percent, single support percent, cadence, and stride width. These five gait parameters are the most common parameters that are checked and examined during physical therapy clinical assessment. Further details of the Zeno mat walkway will be provided in the results section of the gait results section (Chapter 3) and the gait R code in Appendix 2 C.

2.6.4. Balance testing:

Participants‟ static balance performance while standing was measured using accelerometers and then transfers this information into Mobility Lab software (APDM, Inc) (Appendix 2 B). Accelerometers are sensors that are attached to either upper or lower limbs of the body to assess daily physical activities by measuring acceleration in three orthogonal planes: vertical (Z axis), mediolateral (Y axis), and anteroposterior (X axis; (Cleland et al., 2013) (Figure 2.3).

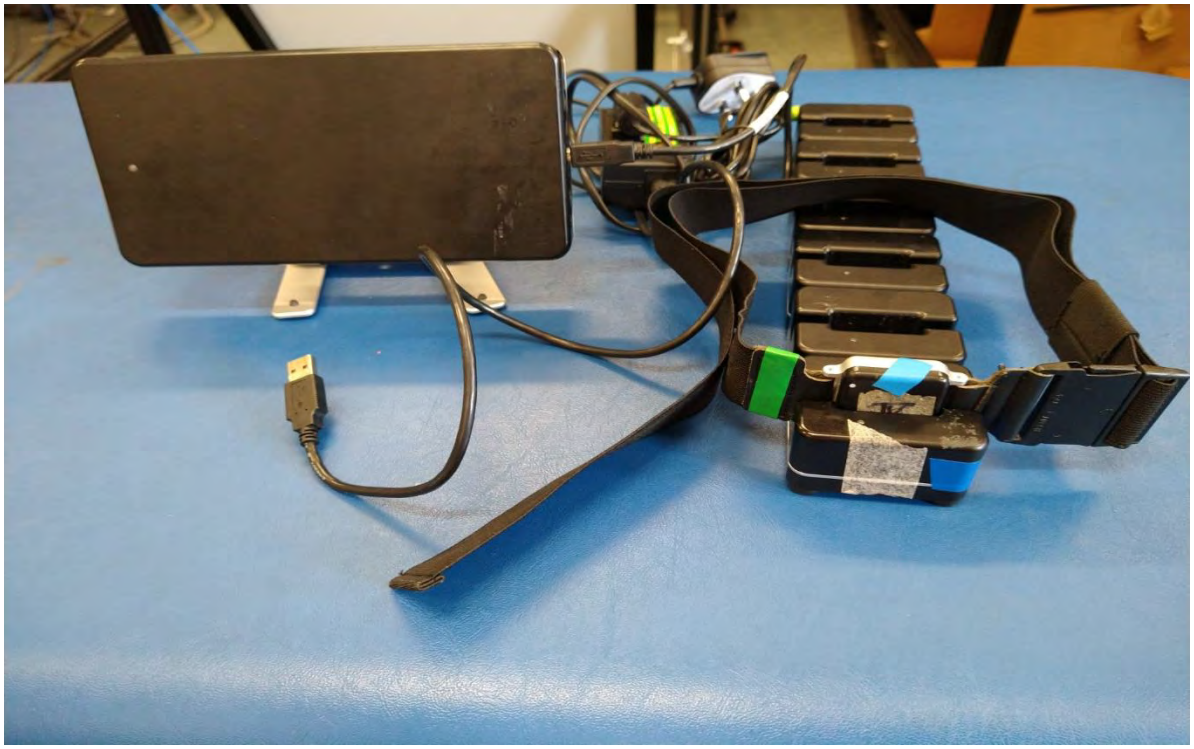


Figure 2.3. Accelerometer (light blue tape) slotted in charger (masking tape) attached to waist belt (green tape).

In this study, two parameters were analyzed: RMS and Jerk. Jerk is the „smoothness" of sway from the time derivative of acceleration. Jerk was calculated as the follows ((Mancini et al., 2012):

$$[m^2/s^5]\ JERK = \frac{1}{2}\int_0^t \left(\frac{dACCL_{AP}}{dt}\right)^2 + \left(\frac{dACCL_{ML}}{dt}\right)^2$$

Where t= length of time, ACC= acceleration, AP= anteroposterior, ML= mediolateral, and dt= change in acceleration.

On the other hand, RMS is computed as the area included in the acceleration equivalent of the sway trajectory, measured per unit of time (m/s^2) ((Prieto, Myklebust, Hoffmann, Lovett, & Myklebust, 1996), Equation 6).

$$\text{RMS} = \sqrt{\frac{1}{N}\Sigma\, RD[n]^2}$$

where RD = resultant of AP-ML distance and n= number of observations in the sample.

Calculations of these two parameters was done outside the Opal package, based on raw acceleration values (R code in Appendix 2 D). A detailed procedure of how the balance parameters were measured will be explained more in the result section of balance chapter (Chapter 4).

2.7. Data statistical Analysis:

Algorithms for analysis, cleaning, cutting of the data and statistical evaluation of the outcomes were written in R (version 3.6.1). Where mixed models were calculated the package lme4_1.1-19 was used. Differences between patient groups and control groups were statistically significant when $p < 0.05$.

Since the level of performance on the gait and balance task changes with age and height as children get taller and their motor control systems mature, outlier elimination and comparisons across ages need to take development into account (Dixon et al., 2014). This was done by fitting a developmental function to control data before other operations. Therefore, in order to determine the gait and balance changes in the patient groups, it was necessary to understand normal developmental changes in healthy participants first.

Each subject‟s mean from three trials of gait testing and three trials in each condition of balance testing were used for statistical analysis. Linear, quadratic or asymptotic models were

used to predict systematic change with height. Models predicting additional change due to age were fit to residuals from the best height model and new residuals calculated if there was an additional contribution of age after height. Residuals from the best models were analyzed using linear mixed models to compare patient groups to controls.

Outlier observations in the control group were identified by dividing participants into 7 height bins. The mean and the standard deviation (SD) for each height bin were determined and a cut-off of 3 SD above the mean for each height was set. Any points above 3 SD boundary were eliminated as outliers.

Selection of linear, asymptotic or quadratic functions to describe the developmental trajectory for means or boundaries was done using Akaike‟s Information Criterion (AIC; the model with the lowest value was the best model). Absolute AIC values are not interpretable, but the difference in AIC between the best model (lowest AIC value) and other models is interpretable. $\Delta AIC < 3$ means that two models make essentially equivalent predictions. Differences above 3 provide less support for an alternative model until ΔAIC reaches around 10, where there is essentially no support for an alternative model. This study will report the best model or theoretically more plausible models where $\Delta AIC<3$ (e.g. quadratic and asymptotic models may provide essentially the same fit, but an asymptotic model could be more appropriate theoretically given that no deterioration with age is expected in controls who, at their oldest, are in their twenties).

The preferred model predicting dependent variables using height or height and age was estimated for control values and residuals for both controls and patients were calculated to normalise across changes in age and height. Further analysis comparing groups was conducted on the residuals from the best-fitting models.

Either bootstrap analysis or mixed-effect models were used to test for differences between patients and controls. Mixed-effect models included a random term for participants.

Bootstrap models sampled participants rather than individual observations (i.e. all observations from a participant were picked together). For mixed-effect models, a likelihood ratio chi-square (G^2) test was used to compare models with and without a critical predictor, and statistical significance was set at $p < 0.05$. Mixed effect models were estimated using the R package *lmer*.

Bootstrap methods were used to assess differences between groups by re-sampling the observed data with replacement. Bootstrap methods are good for confidence intervals. Repeated samples with the same N as the patient sample were drawn from the control data (once a sample was drawn it was put back in the pool and could be drawn again – i.e. sampling was done *with replacement*). If the patient mean was within the CI produced by the bootstrap of control values, this indicated that the patient sample could have come from the control population and controls and patients were not reliably different. If the patient mean was outside the interval derived from control samples, this indicated that the patient sample was very unlikely to have resulted from sampling the control population, showing that patients were significantly different from controls.

In order to improve the accuracy of the bootstrap result, a double bootstrap routine was used to estimate and correct the single bootstrap CI, which can be important for small samples (McCullough & Vinod, 1998). To estimate the influence of a small number of extreme values, which were sometimes included in patient data, a new bootstrap CI was calculated after eliminating patient values that were > 3 SD from control mean. If the original bootstrap tells us patients were different, but the second bootstrap, without extreme values, says they are not different, we know that the first difference depends entirely on the extreme values. If both bootstrap results indicate a difference, we know the difference is not just due to a small number of extreme values.

If a patient group had fewer than 5 individuals, it was considered too small for group-level analysis and only individual analyses were carried out. These are reported in the section devoted to s-scores. An s-score is similar to a z-score with some differences. It captures how far a patient score is from the control mean in terms of control standard deviations. The mean and SD that we used to calculate the s-score in the formula below, however, are from a *sample*. They are not population values, as a z-score assumes, so the formula is slightly different: (patient score – $mean_{control}$)/$sd_{control}$*(sqrt(1 + 1/N)). S-scores show which individuals were clearly inside and outside the control range. Residuals that removed the influence of height and age were used to calculate the 95% prediction interval for different height bins (residuals remove the influence of height/age on mean values, but because the *variance* of the data can change with height/age, it is necessary to calculate prediction intervals boundaries at different heights). Upper and lower cut-offs for prediction intervals were estimated using constant, linear, quadratic or asymptotic functions that were fit to the boundary points from each height bin. The best function was chosen to smooth the interval boundary as described above for the mean and outliers. With the boundary defined, the smoothed SD value for controls can be calculated. This, then, is used in the formula for the s-score. Patients inside and outside the 95% prediction interval for controls could, as a result, be marked in a way that was consistent with the smoothed 95% prediction interval.

CHAPTER 3: GAIT

3. Gait:

3.1. Gait methodology:

Chapter 3 will report gait data from neurodegenerative patients and the healthy controls. Initially, this chapter will explain the methodology that used to collect the gait data in both groups. The gait results section is divided into 5 sections. The first section will report the gait results for the control group only. Three sections will present the gait results from NP-C, Fabry and Hurler (MPS I) patient groups. Finally, the other patients‟ groups with small N [Morquio (MPS IV), Maroteaux Lamy (MPS VI), and Pompe] are reported in a single section.

3.1.1. Gait test procedure:

participants were asked to take off their shoes. Each participants stood behind a designated starting line (usually one metre before the Zeno mat), and waited for a signal to start walking. The participant was asked to walk normally up and down on a Zeno mat that containing sensors to record their gait parameters (cadence, stride length, stance percentage (%), stride width, and single support percentage (%)). While walking, the participant was asked to hold a plastic ring in his/her hand (approximately the size of a bracelet) and placed it in a basket 1 metre away from the other end of the Zeno mat. Before returning back, the participant was asked to pick up another ring from the basket, turn and walk back the full length of the Zeno mat to the starting position. Using, the ring during walking helps to establish a goal and promote less self-conscious attention to walking itself (by using a target point). Also, this made it easy for younger participants to walk on the Zeno mat to the end and then walk back. Walking on the Zeno mat up and down was considered 1 trial. In this study, each participant

was asked to perform 3 trials. The data from each participant were transferred from the Zeno mat to a laptop and presented in PKMAS software. The gait cleaning process was done within the PKMAS by identifying each separate footsteps and footfall pattern. So, any irregular footsteps can be cut or cleaned before exported for analysis. For example, if less than half of the foot is visible or the if the participant walked in the middle of the mat and then stopped or turned back, we can clean or cut these irregular footsteps. In this thesis few cuts of irregular steps were necessary and for a small number of participants (20 % of all subjects). These were mostly young participants. No trials were discarded or excluded based on cleaning.

After that, analysis for spatial and temporal gait parameters for each participant was done.

In this thesis five gait parameters were analysed: cadence, stride length, stance percentage (%), stride width, and single support percentage (%) (see definition for these measurements in the introduction, section 1.3.1.1, p: 23)

3.1.2. Gait statistical analysis:

In this thesis residuals data based on the best control model, control and patients‟ results were compared. Mixed effect models were used with a random term for participants. A likelihood ratio chi-square (G^2) test was used to produce a *p*-value for assessing fixed effect, and statistically significant was set at $p < 0.05$.

The full details of statistical analysis were explained before in chapter 2 (general methods) (see section 2.7, p:58).

Before plotting the gait parameters, right and left leg data were checked for any asymmetry. None of the controls or patients were noted to have a significant asymmetry. Therefore, a mean number for right and left legs was calculated for ease of use.

3.2. Gait results and discussions:

3.2.1. Control group results:

Stride length:

There were 9 outliers out of 885 data points for the stride length data for control. The best model for the stride length mean was an asymptotic function of height (linear ΔAIC = 124.8, constant ΔAIC = 910.9, and quadratic ΔAIC = 5.82) (Figure 3.1). There were no grounds for an additional effect of age (F= 0.33; p = 0.56).

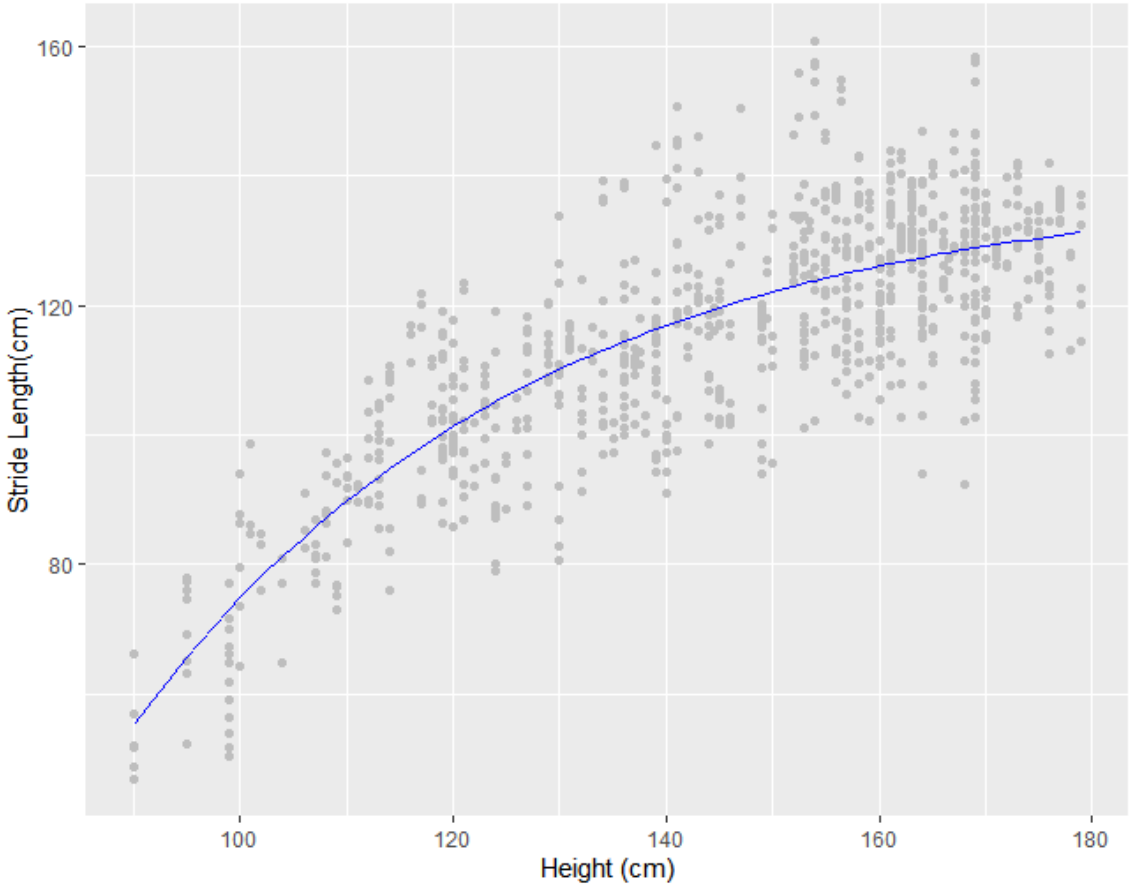


Figure 3.1: Control data (grey dots) without outliers for raw stride length as a function of height. Blue line is the fitted mean.

The upper cut-off for the 95% prediction interval on residuals was best modelled by a quadratic function, but there was little difference between quadratic and constant models (constant ΔAIC = 0.95). Moreover, when a small number of the tallest heights were removed, the constant model was the best model for upper cut-off. This showed that the quadratic advantage was driven by a small sample at the tall end of the participant range, so a constant function was used. A constant function was also the best function for the lower cut-off (linear ΔAIC = 1.9, quadratic ΔAIC = 3.3, and asymptotic ΔAIC = 4.1) (Figure 3.2).

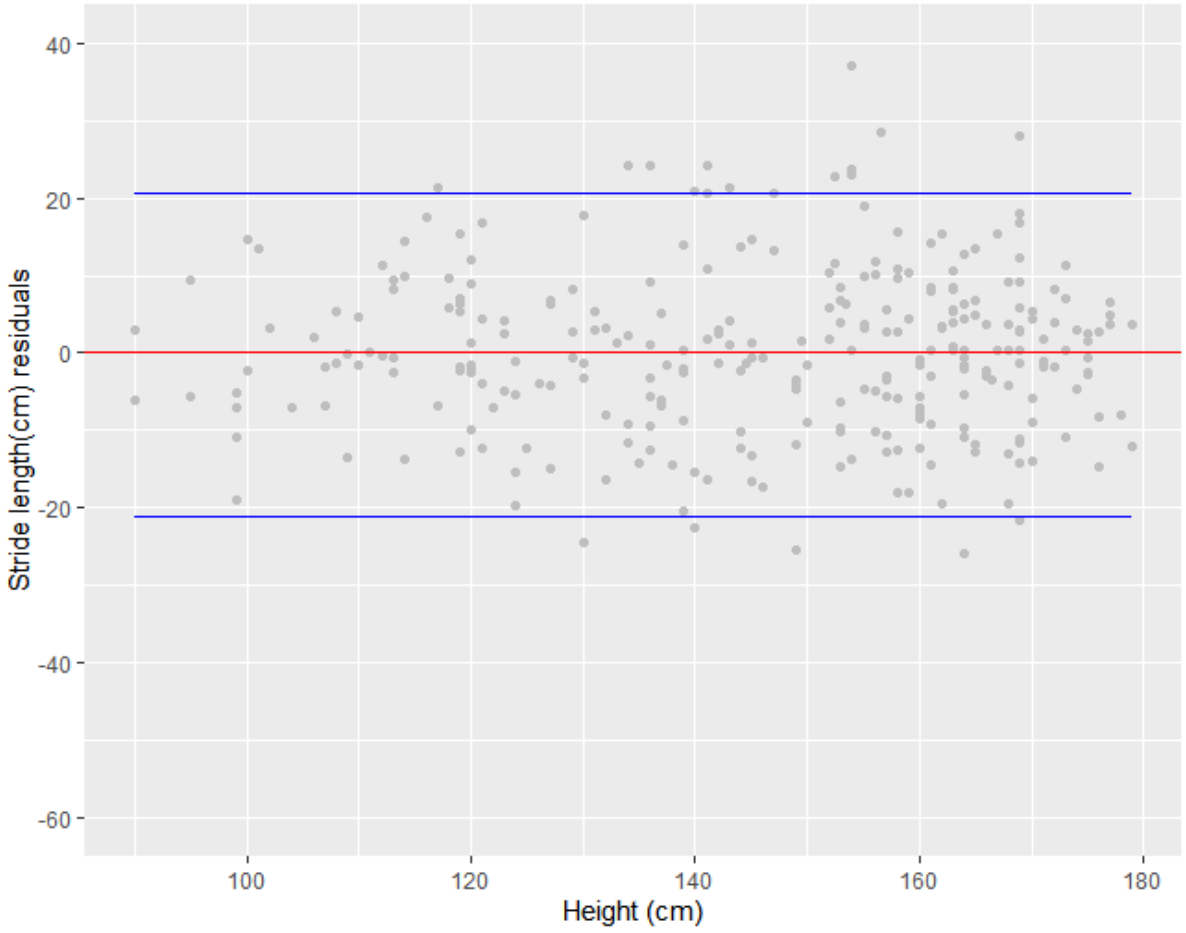


Figure 3.2: Stride length residuals as a function of height. The red line is the control mean. The blue lines are the upper and lower cut-offs for the 95% prediction intervals for controls.

Stance percentage (%):

There were 16 outliers out from 885 control observations for stance percentage.

The best model for stance percentage was a quadratic function of height (linear Δ AIC = 58.6, constant ΔAIC = 274.1, and asymptotic ΔAIC = 140.7). Figure 3.3 revealed that stance % initially doesn"t change and then increases once height is above a certain value (around 130-140 cm).

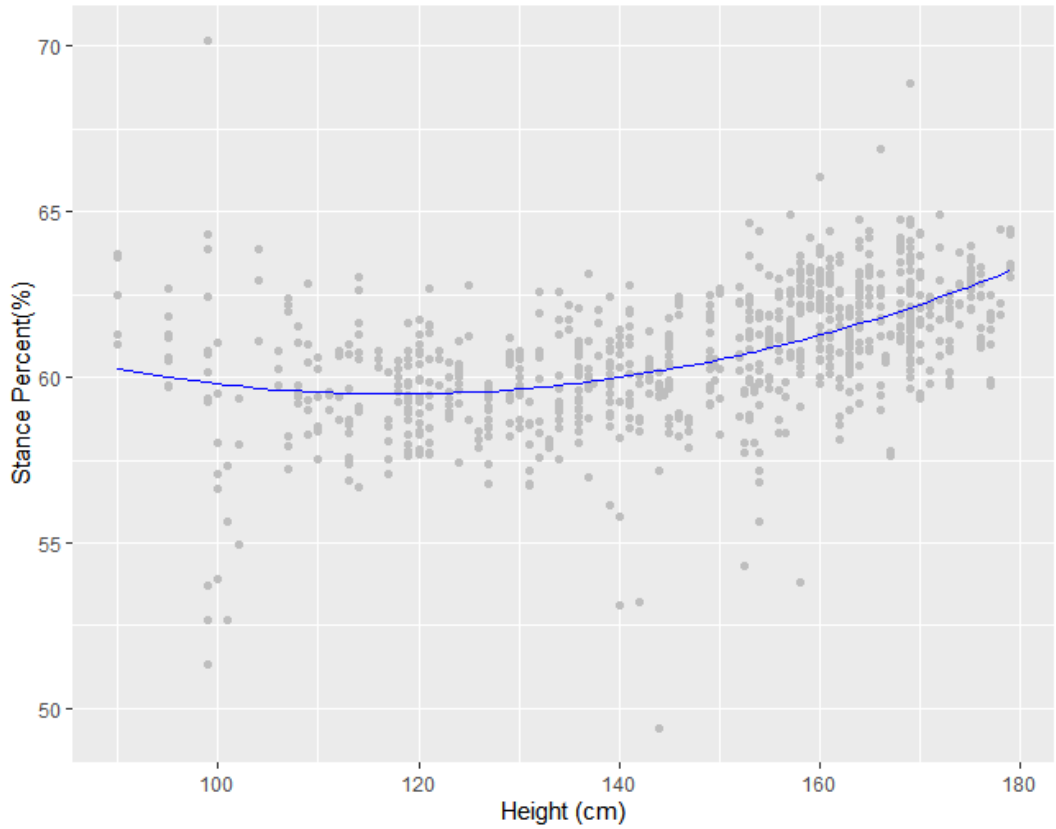


Figure 3.3: Control data (grey dots) without outliers for raw stance percentage as a function of height. Blue line is the fitted mean.

There was a significant effect of age after height had been accounted for (F= 11.14; $p <$ 0.001) and that was best modelled by a quadratic function of age (asymptotic ΔAIC = 20.3, constant ΔAIC = 18.07, and linear ΔAIC = 4.8).

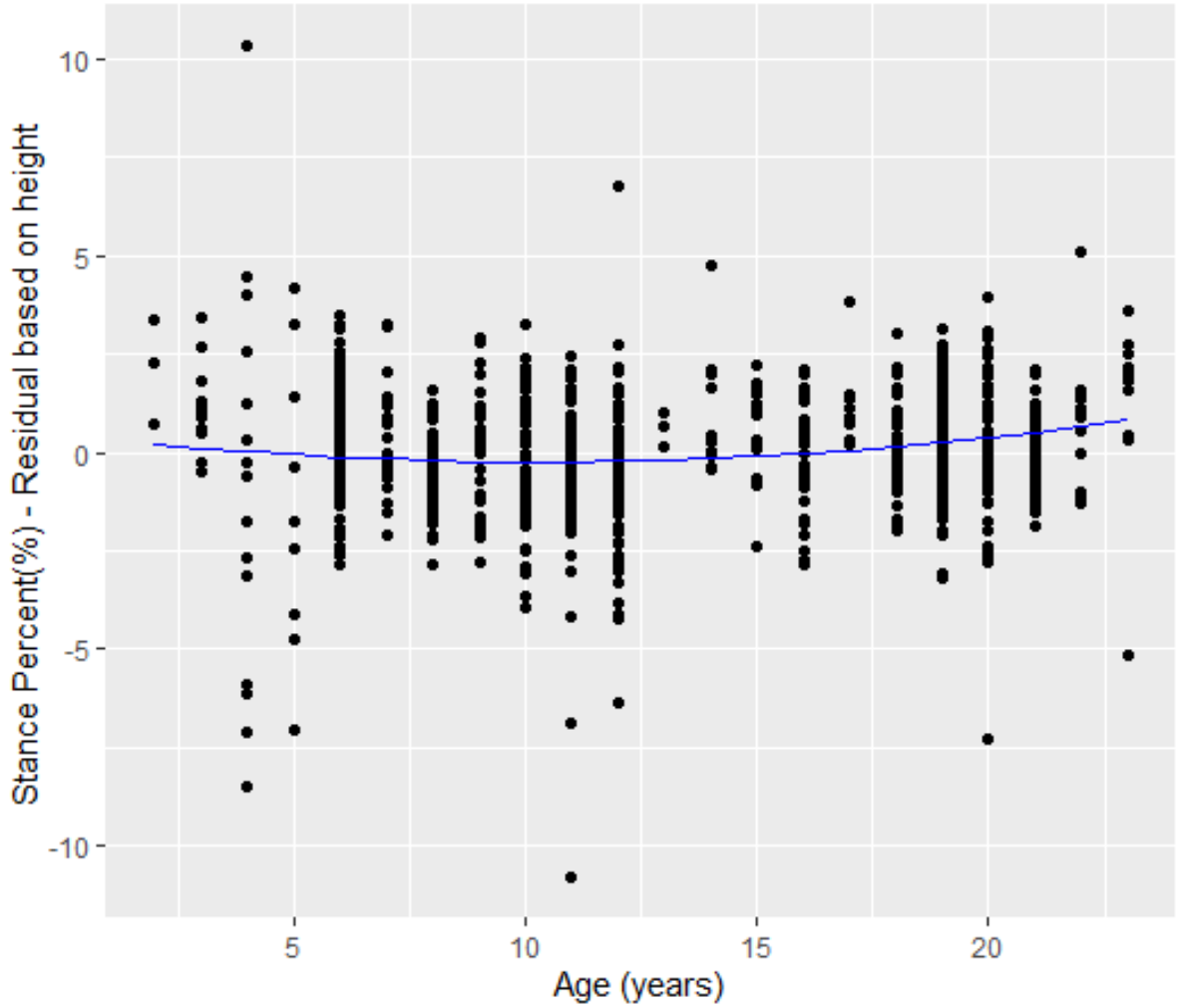


Figure 3.4: Control data (black dots) without outliers for raw stance percentage as a quadratic function of Age. Blue line is the effect of age.

Asymptotic functions were the best functions for the prediction interval upper (quadratic ΔAIC = 16.16, constant ΔAIC = 23.64, and linear ΔAIC = 20.49) and lower cut-offs as a result of higher variability in younger participants (quadratic ΔAIC = 5.34, constant ΔAIC = 16.6, and linear ΔAIC =14.31; Figure 3.5).

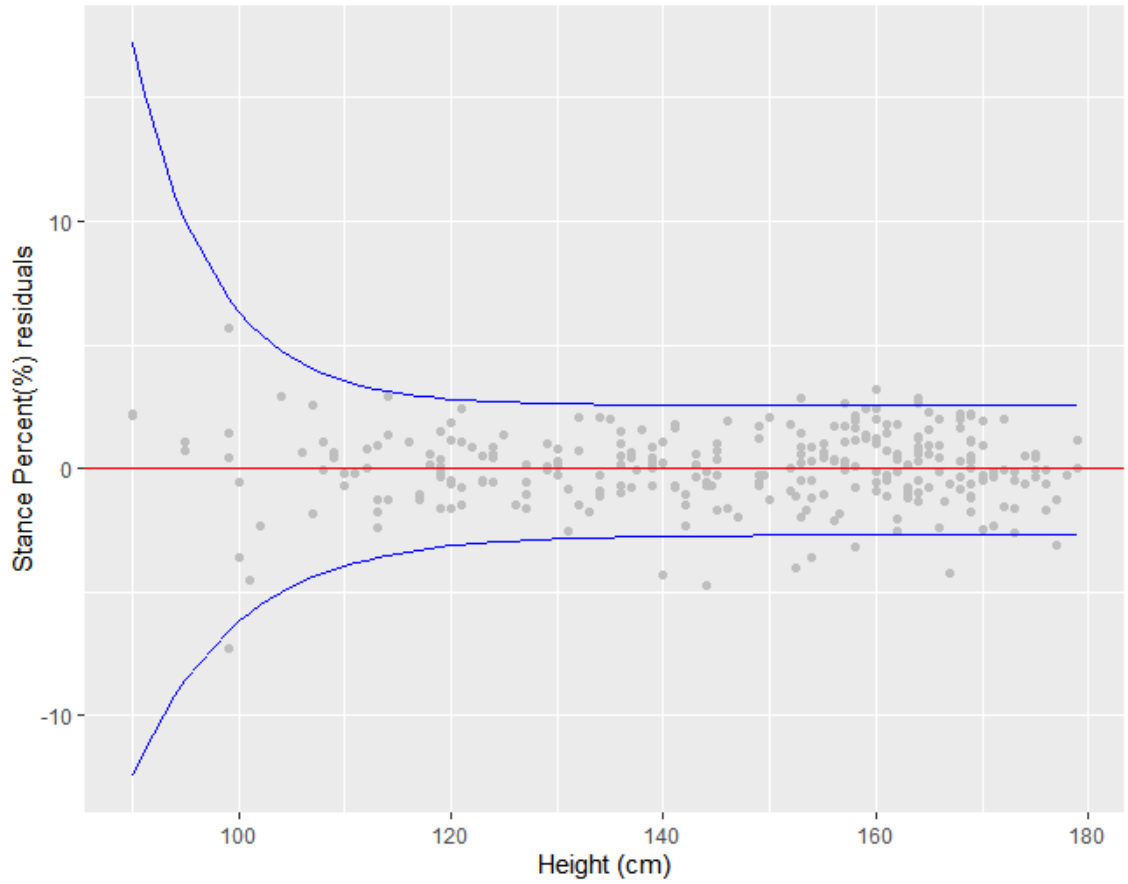


Figure 3.5: Stance percentage residuals as a function of height. The red line is the control mean. The blue lines are upper and lower cut-offs for the 95% prediction intervals for controls.

Single support percentage (%):

There were 4 outliers out of 885 single support percentage data points. The best model for single support % was a quadratic function of height (linear ΔAIC = 97.49, constant ΔAIC = 311.47, and asymptotic ΔAIC = 183.06; Figure 3.6). There was an initial increase in the single support % for heights between ~ 90 to 130 cm and then above 130 cm single support % decreased.

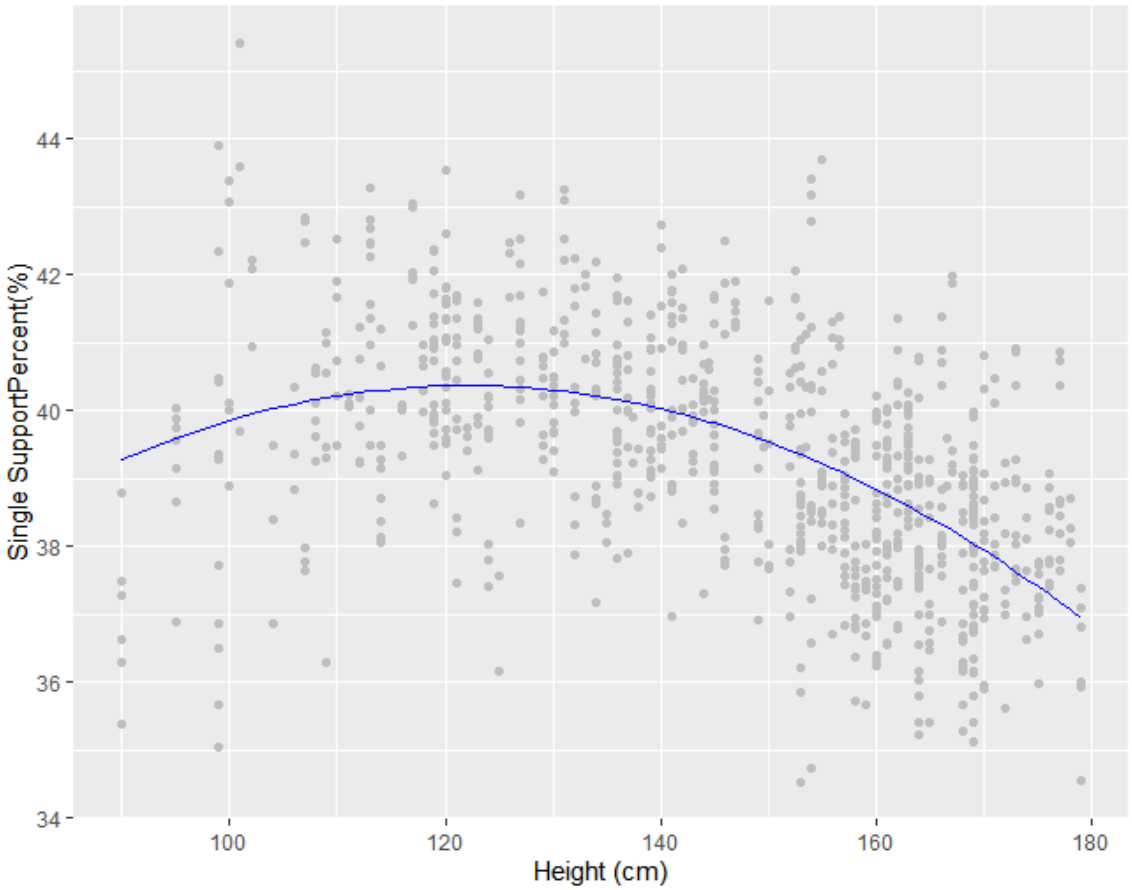


Figure 3.6: Control data (grey dots) without outliers for raw single support percentage as a function of height. Blue line is the fitted mean.

There was a significant effect of age after the effect of height had been removed (F= 18.9; $p <$ 0.001) with a quadratic function capturing best the effect of age (asymptotic ΔAIC = 27.1, constant ΔAIC = 33.3, and linear ΔAIC = 22.8). Final residuals that were entered into our analyses were based on removing effects of both height and age.

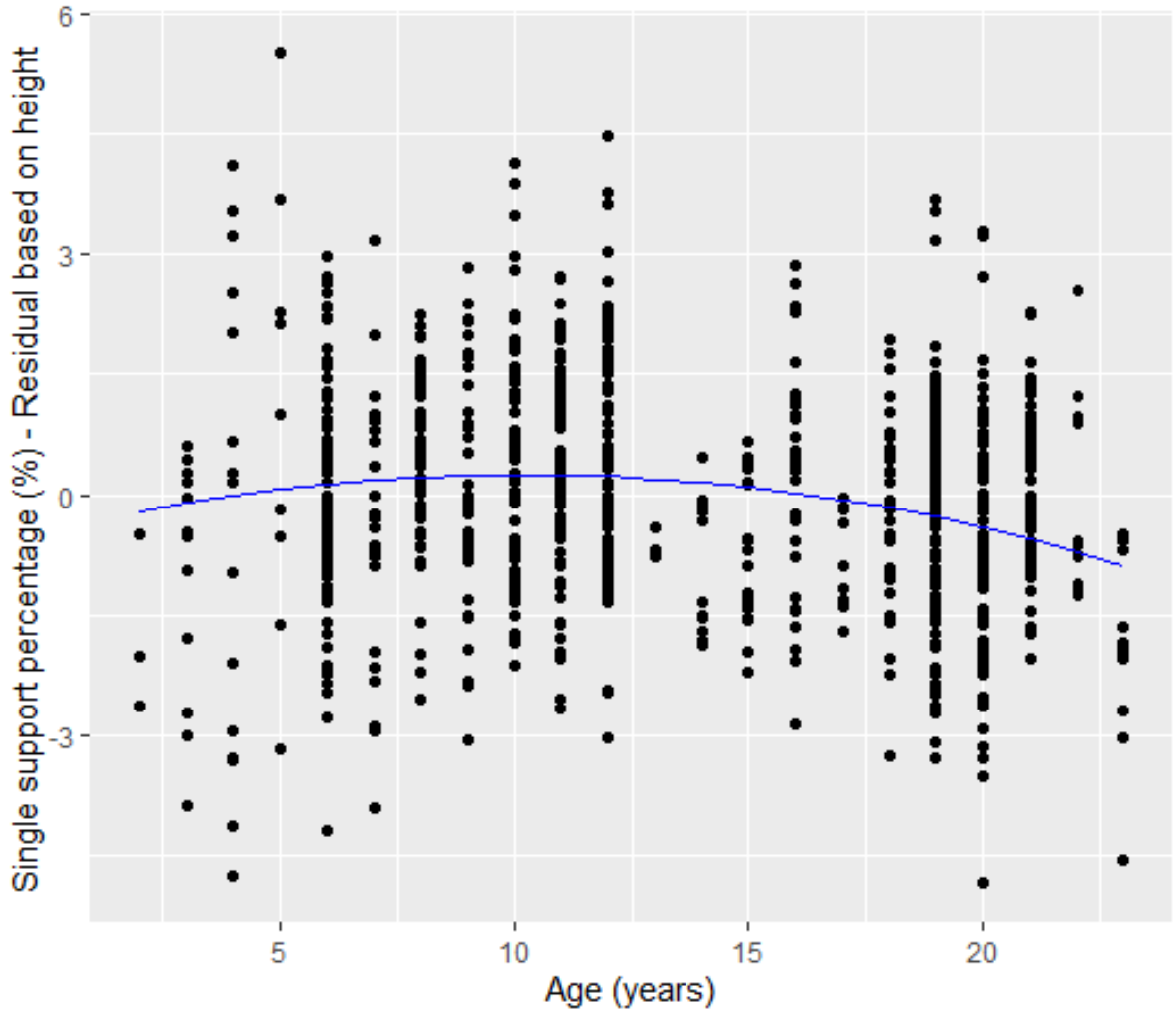


Figure 3.7: Control data (black dots) without outliers for raw single support percentage as a function of Age.

A quadratic function was best for the upper prediction interval (asymptotic ΔAIC = 36.47, constant ΔAIC = 11.38, and linear ΔAIC = 10.42) while an asymptotic function was best for the lower cut-off (linear ΔAIC = 13.87, constant ΔAIC = 17.17, and quadratic ΔAIC = 10.51). The increase in the prediction interval for the tallest participants may be an artefact of the relatively small number of control participants in this range. However, using a quadratic function for the cut-off was a conservative choice in this context, and there were no patients who fall in the range of the tallest heights.

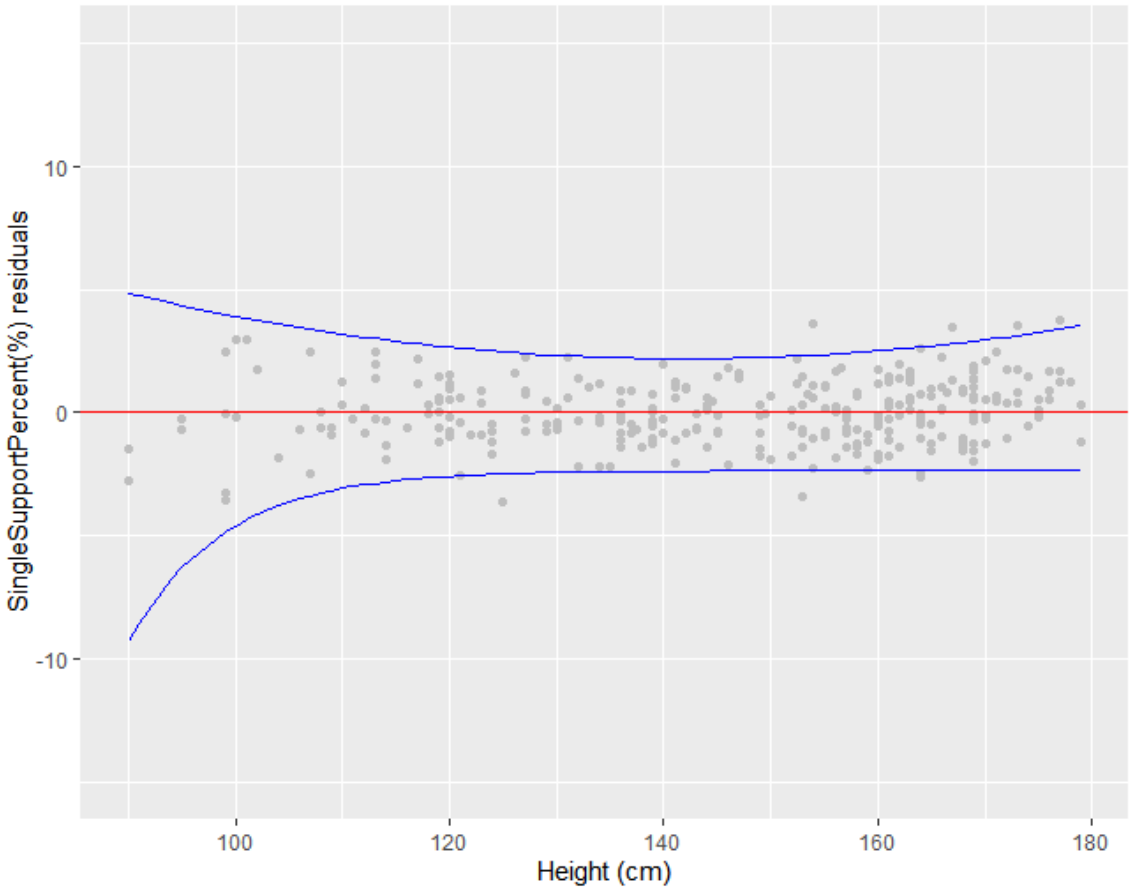


Figure 3.8: Single support percentage residuals as a function of height. The red line is the control mean. The blue lines are the upper and lower cut-offs for the 95% prediction intervals for controls.

Cadence:

There were 8 outliers out of 885 data points from the controls. The best model was linear function of height (asymptotic ΔAIC = 56.62, quadratic ΔAIC = 1.93, and constant ΔAIC = 653.3; Figure 3.9). Cadences had an inverse relationship with the participant‟s height. As heights increased, the cadence decreased.

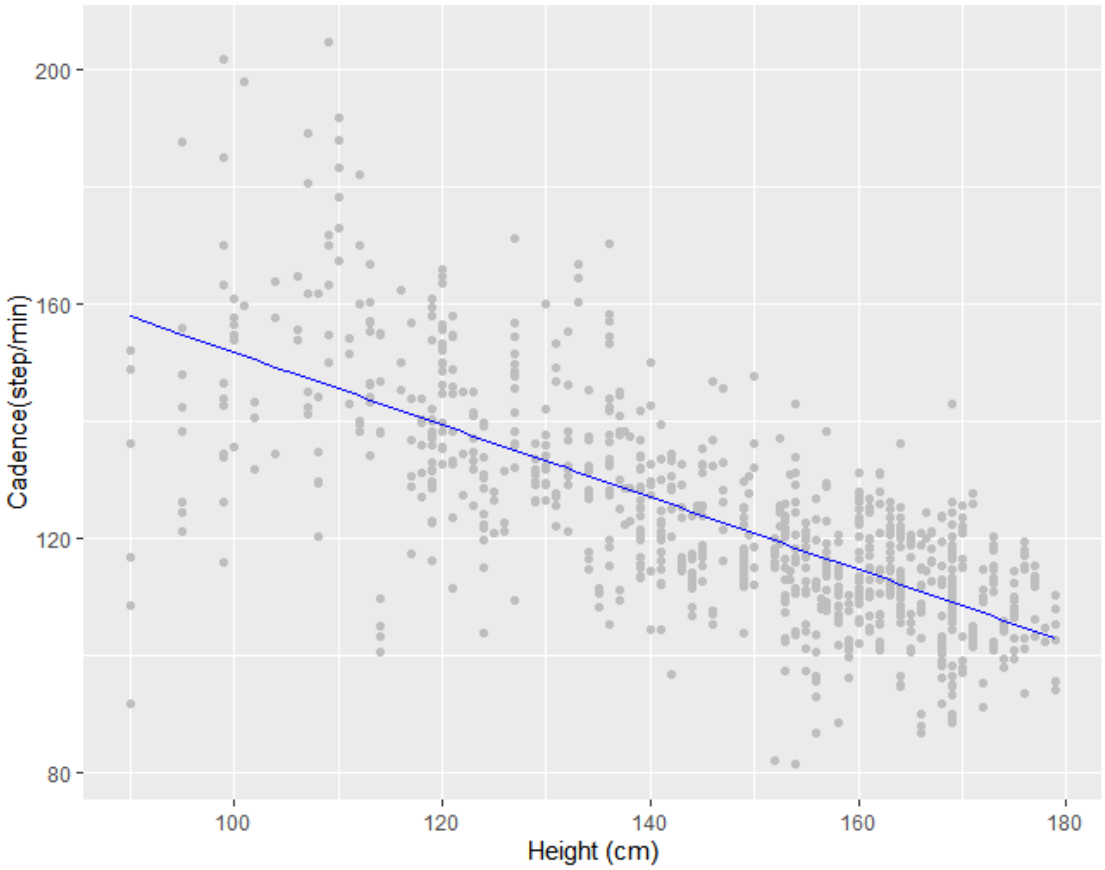


Figure 3.9: Control data (grey dots) without outliers for raw cadence as a function of height. Blue line is the fitted mean.

There was a significant effect of age after height (F= 9.4; $p < 0.001$) based on a linear function of age (Figure 3.10). With each year, cadence decreased by 0.24 steps per minute.

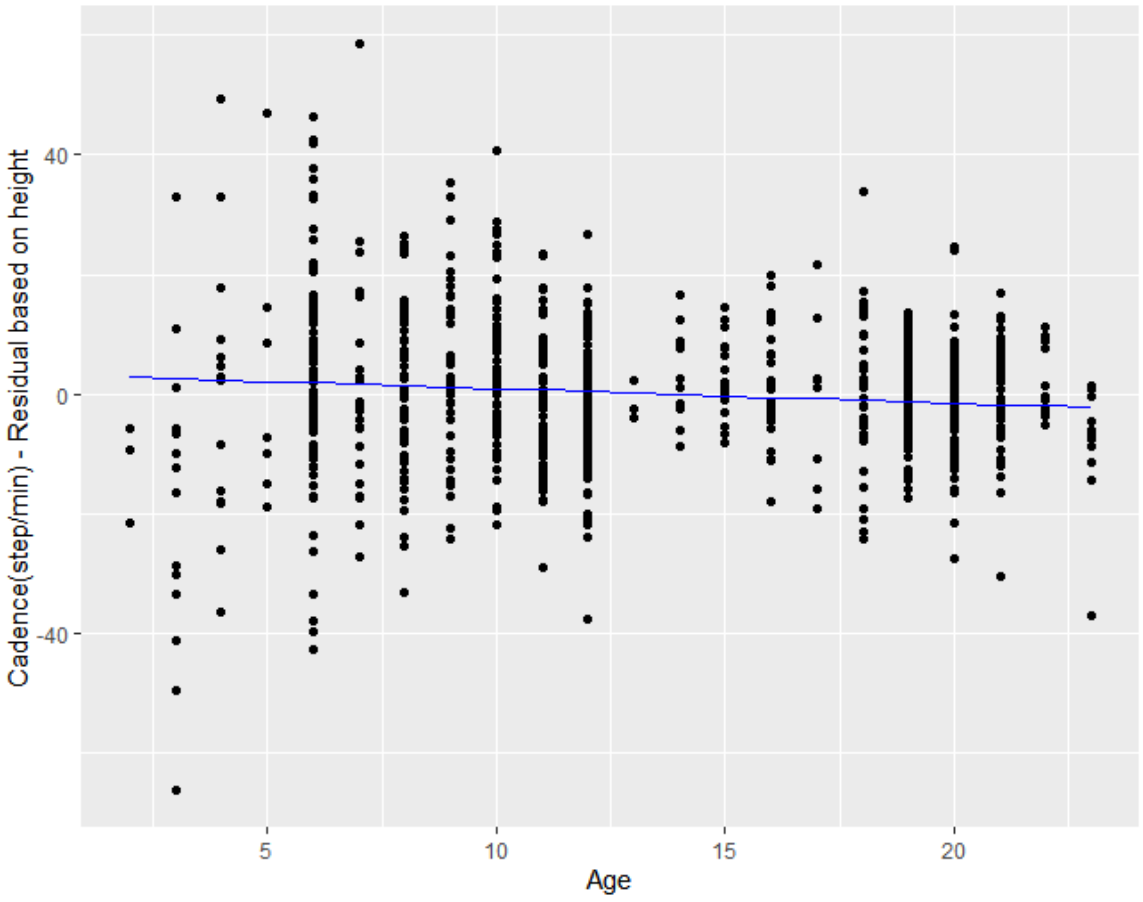


Figure 3.10: Control data (black dots) without outliers for raw cadence as a function of Age.

The upper boundary of the 95% prediction interval was best fit by a quadratic model, (linear ΔAIC = 5.5, asymptotic ΔAIC = 1.3, and constant ΔAIC = 13.3), while an asymptotic function was the best function for the lower cut-off (linear ΔAIC = 15.48, quadratic ΔAIC = 12.1, and constant ΔAIC = 20.92; Figure 3.11).

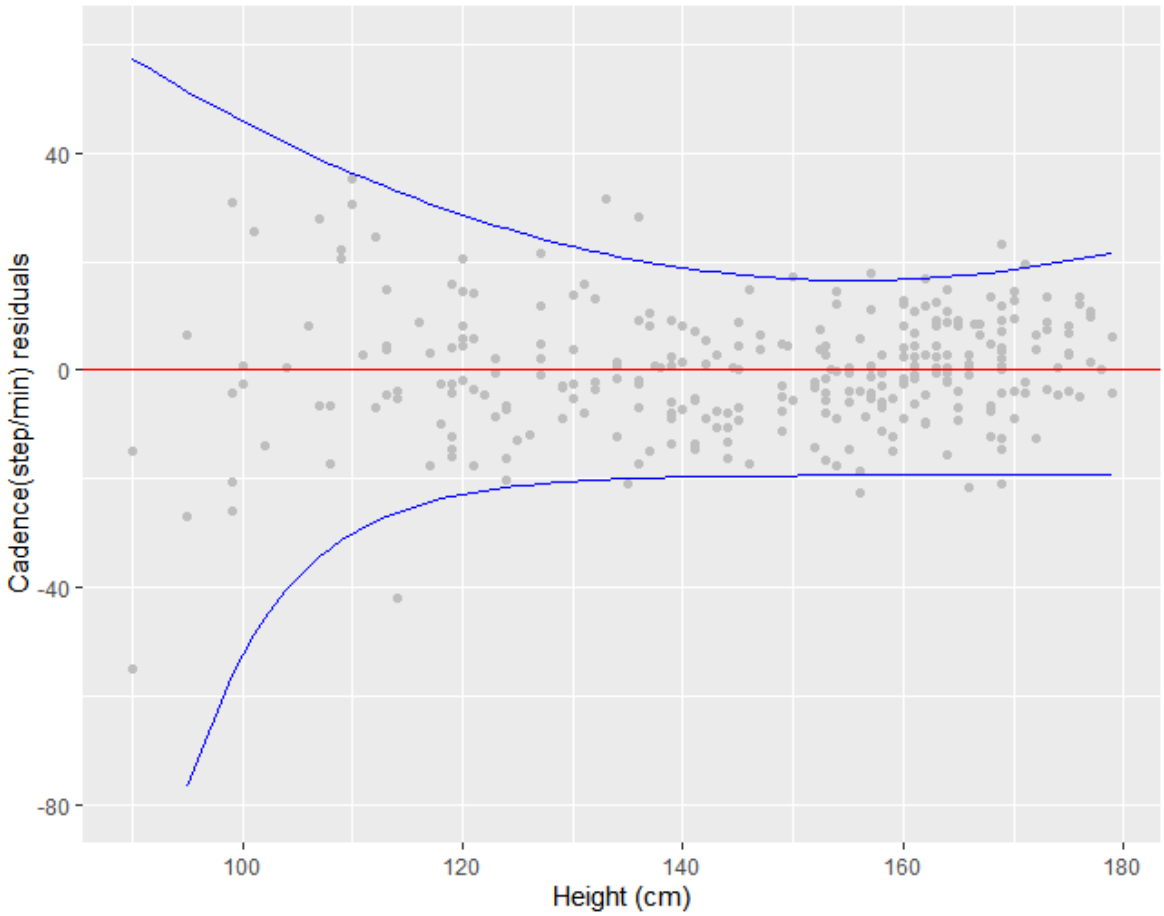


Figure 3.11: Cadence residuals as a function of height. The red line is the control mean. The blue lines are the upper and lower cut-offs for the 95% prediction intervals for controls.

Stride width:

There were 7 outliers out of 885 data points in the stride width data. The best model for stride width was a quadratic function of height (linear ΔAIC = 15.1, constant ΔAIC = 13.83, and asymptotic ΔAIC =1.5; Figure 3.12). However, it is difficult to see why, based on theory, stride width for older or taller participants should increase after an initial developmental decrease (Romano et al., 2018). In addition, a small number of participants are responsible for the increase at the tallest measures (Figure 3.12). Because there is little difference between a quadratic and asymptotic model, and an asymptotic model is more theoretically

plausible (asymptotic ΔAIC = 1.5), an asymptotic function of height was used. There was no effect of age after the effect of height was removed (F= 1.23; p = 0.26).

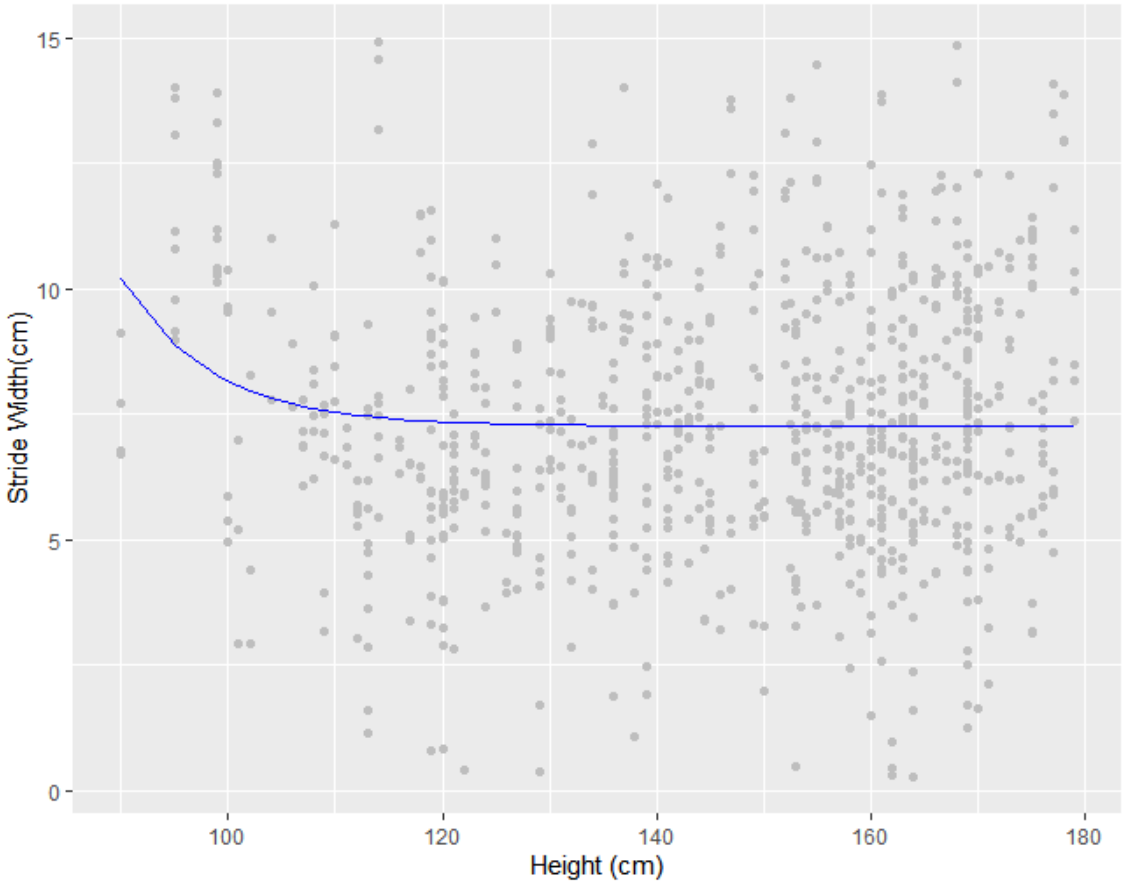


Figure 3.12: Control data (grey dots) without outliers for raw stride width as a function of height. Blue line is the fitted mean.

A quadratic function was the best function for the upper cut-off of the 95% prediction intervals, while constant function for the lower cut-off (upper: asymptotic ΔAIC = 23.44, linear ΔAIC = 1.95, and constant ΔAIC = 1.98; lower: linear ΔAIC = 1.16, asymptotic ΔAIC = 15.19, and quadratic ΔAIC = 3.16; Figure 3.13).

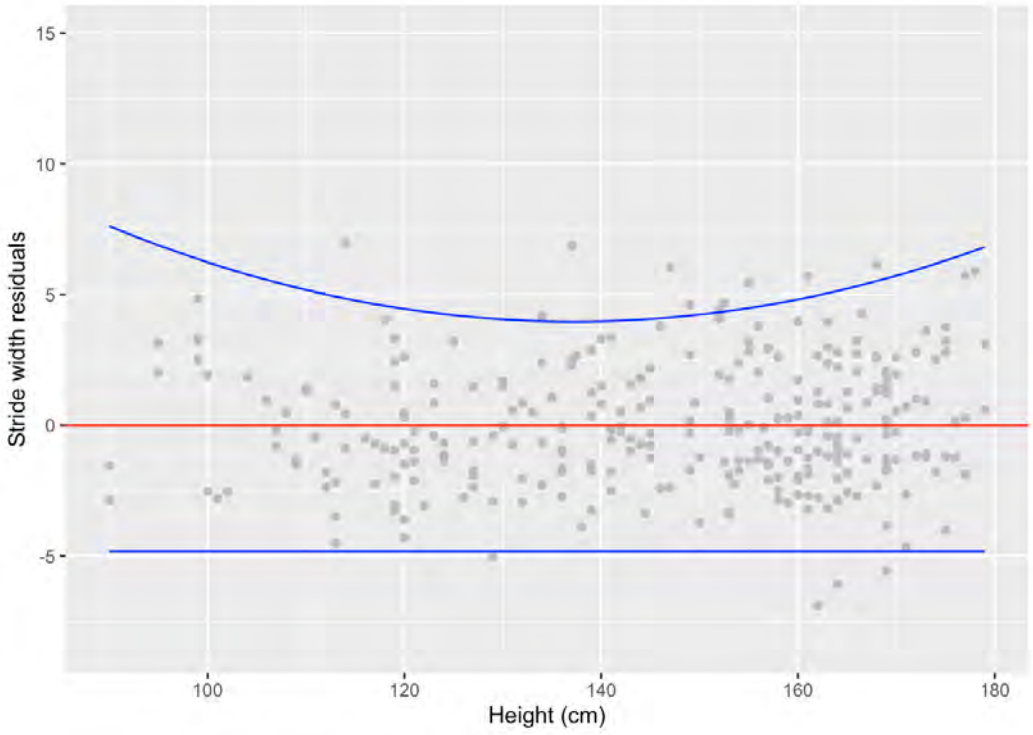


Figure 3.13: Stride width residuals as a function of height. The red line is the control mean. The blue lines are the upper and lower cut-offs for the 95% prediction intervals for controls.

Table 3.1: Summary of control group gait results.

Gait Measurements	Best function of height	Best function of Age	Direction of the trajectory	Measurements stabilization	Best function for the upper cut-off	Best function for the lower cut-off
Stride Length	Asymptotic	N/A	Increase with height	Continuous development	Constant	Constant
Stance %	Quadratic	Quadratic	Increase with height	Late childhood	Asymptotic	Asymptotic
Single Support%	Quadratic	Quadratic	Decrease with height	Late childhood	Quadratic	Asymptotic
Cadence	Linear	Linear	Decrease with height	Continuous development	Quadratic	Asymptotic
Stride Width	Asymptotic	N/A	Decrease with height	Middle childhood	Quadratic	Constant

In conclusion, most gait measures showed clear developmental changes and most included a period of more rapid change that stabilises with height and age. Table 3.1 showed approximate adult capacity was reached in the late childhood years for stance % and single support %. This is because after height 120 to 130, lower limb growth increased faster than younger children (Froehle et al., 2013). While, adult capacity was reached in the middle childhood years for stride width. However, stride length and cadence showed a linear trend across the whole range of height sampled.

3.2.2. Control group discussion:

Understanding the normal gait development with healthy individual helps to in identifying the abnormal developmental changes in diseased patients. In the present study, healthy aged and height matched group were recruited to investigate their gait developmental pattern and compare them with the specified neurodegenerative disease (NP-C, Hurler, Morquio, Maroteaux-Lamy, Fabry and Pompe). The findings of the present study showed a number of systematic changes during healthy development. Stride length increased with height, while single support % and cadence decreased with height. In regard to the stance %, finding in the healthy individual showed no significant difference and changes in younger children. Finally, the stride width, after an initial decrease in slide width, it remains constant above a height of around 130 cm.

These present findings are consistent with the developmental gait patterns described in the literature (Dusing & Thorpe, 2007; Selby-Silverstein et al., 2003; D. Sutherland, 1997; Thevenon et al., 2015). In general, these literatures came in conclusion that performance of normal development children have shown that spatiotemporal gait measurements seem to develop in a specific direction for a certain period of time. Children of older age and more height showed improve spatiotemporal gait measures especially in stride length, single support %, and cadence.

The finding of the present study revealed that **stride length** always increase constantly with height (Figure 3.1). This finding came emphasising to Thevenon et al. study (2015) finding about the stride length. In their study, they examined gait in 382 children aged 6 – 12 years old. Their results showed that the step length and stride length increased continually with height. However, they found that step time, cycle time, swing time, single support time and double support time increased with height only until the children were reached 110 cm to 130

cm tall. Then a plateau was reached or slight deceased. Moreover, the present study‟s findings regarding to stride length are supported with findings from the Moreno-Hernandez et al. (2010) study, who found that age has a large impact on the stride length. This was seen in older participants who had increase stride length compare to young participants. Taking into consideration the differences in testing producer between the Moreno-Hernandez‟s (foot wear and barefoot) and the present study (barefoot only), the findings were consistent in showing that both age and height have influence the stride length. This could be presumed due to the maturation process of stature and the neuromuscular system(Selby-Silverstein et al., 2003; D. H. Sutherland et al., 1980).

With regards to **stance %**, the present study results showed that there was no significant different in stance % in younger children. However, the changes started to be gradually increased after the height of 130 cm (late childhood). This result was in comparable to Thevenon et al (2015) results, who used the GAITRite walkway system in their study. Although Thevenon et al did measure the stance time (instead of stance %), the finding showed that stance time was gradually increased with children above 130 cm. Both findings from Thevenon‟s et al study and the present study suggest that stance phase (incudes time and percentage) was initially not changed then started to change with healthy children above certain height (130 cm) due to lower limb linear growth (lower limb length) (Froehle et al., 2013). For the first years of child life, the growth of the lower limb length is little compared to the growth and the length of the lower limb after the height of 130 cm, which become more and faster (Froehle et al., 2013).

In term of **single support %,** the present study had shown that height can contribute on the single support % with healthy individual. The present findings showed that single support % increased until the children were approximately 120 cm in height. Then, started to gradually decrease as children and adults become taller. This findings is in agreement with Lythgo et al.

(2009) who reported that there was a significant reduction in the single support % with young adult group (Above ~ 120 cm). Findings from the Lynthgo et al. study and the present study indicate that the gait pattern become more mature after the healthy individual reached 120 cm in height (approximately between 7 to 10 years of age) due to lower limb growth. This conclusion regarding the single support was coherent with Thevenon et al. (2015).

The **cadence** parameter is often reported because it considered as a reliable indicator of gait intensity (Jerome et al., 2015). The present study found that cadence has a reverse relationship with height. This was observed when the taller healthy individual made a fewer steps per minute compared to the shorter individual (Figure 3.9). That is because healthy individuals roughly match velocity while walking. Lythgo et al (2009), reported the same results. However, in their study the age factor (instead of height, in present study) was compared cadence with healthy individual (n =980). They found that cadence was reducing significantly with age ($p < 0.001$). This finding is supported by Thevenon et al., (2015) who demonstrated that cadence was decreased with height and age within healthy individuals. These findings indicate that younger children have a high and fast cadence. However, it starts to rapidly decrease the height and age increasing within the healthy individuals. In general, it can be understood that both of age and height have an influence on increasing stride length and decreasing cadence, which in turn lead to increase walking speeds.

According to **stride width** results, the present study observes that younger children (< 120 cm) tend to have a wider stride width. That is because younger children usually tend to have increase hip abduction, which affect directly on increasing stride width (Romano et al., 2019). Moreover, the data in the present study showed that stride width decreased with the height until reaching 120 cm. Then, stride width become constant throughout the increasing height within healthy individual. In general, stride width is one of the factors that related to

balance control. Increasing or decreasing in the width might indicate lack of compensation for instability and could influence to falls (Gabell & Nayak, 1984).

Few studies have investigated stride width with age, instead of height like the present study. One of these studies done by Rose-Jacobs (1983) who reported that healthy children aged 3 to 5 years had no significant differences in stride width. Moreover, there are other factor that can affect the stride width rather than age and height, which is gait velocity. Thomas et al. (2017) did a study aimed to investigate the impact of slow walking on stride width in 14 healthy young adults walking on treadmill. They found that stride width was significantly increased with slower walking (3.3 ± 0.3 km/h). They conclude that slower gait velocity decrease monitoring and body correction which increased the stride width compared with fast and preferred gait velocity. Based on this finding, the present study used the preferred gait speed in order to enhance body control and to get more accurate results about the stride width.

Overall, healthy child‟s gait will not be symmetrical and will remain changing in terms of spatial and temporal patterns up until the child is completely full-grown (Moreno-Hernandez et al., 2010). In the present study, a large number of controls was tested spanning the age ranges of interest and it is reasonable to assume that developmental changes are relatively smooth. These two factors mean that this thesis sample gives pretty stable estimates of control means and control confidence intervals to use when there is a need to assess results from patients.

In general, almost all gait parameters findings with healthy individual were similar to previous studies (Lythgo et al., 2009; Moreno-Hernández et al., 2010; Thevenon et al., 2015). This indicates the coherent of the present study data to be compared with neurodegenerative disease.

3.2.3. Patients groups results:

Residuals for patient data were calculated using the functions established in controls. Patients outside the 95% prediction intervals for controls represent individuals who are clearly different from the control group. If patients and controls do not differ, and patients are essentially a (smaller) random sample from the control population, about half of the patient values should be above and half below the control mean. When most values are below than the control mean, even if they are not outside the control range, there is evidence of reliable group impairment. Also, when there are differences and a small number of extreme values, two analyses were done; one with and one without the extreme values.

Moreover, we used a linear mixed model with a random term for participant to predict residuals from a model with an interaction between height and group. If patients/control differences get larger over time, the interaction between height and group will be significant. This interaction was only significant for stance percentage in NP-C patients, but was not significant when extreme values were removed.

It is important to remember, of course, that cross-sectional data progressive difference will only be significant when change over time exceeds the individual differences between patients. So, a non-significant result should be interpreted with quite a lot of caution, particular when the diseases make it clear that change over time does happen.

However, for all other parameters and in all other patient groups the interaction was not significant (all $p > 0.1$).

3.2.3.1 NP-C patients:

Stride length:

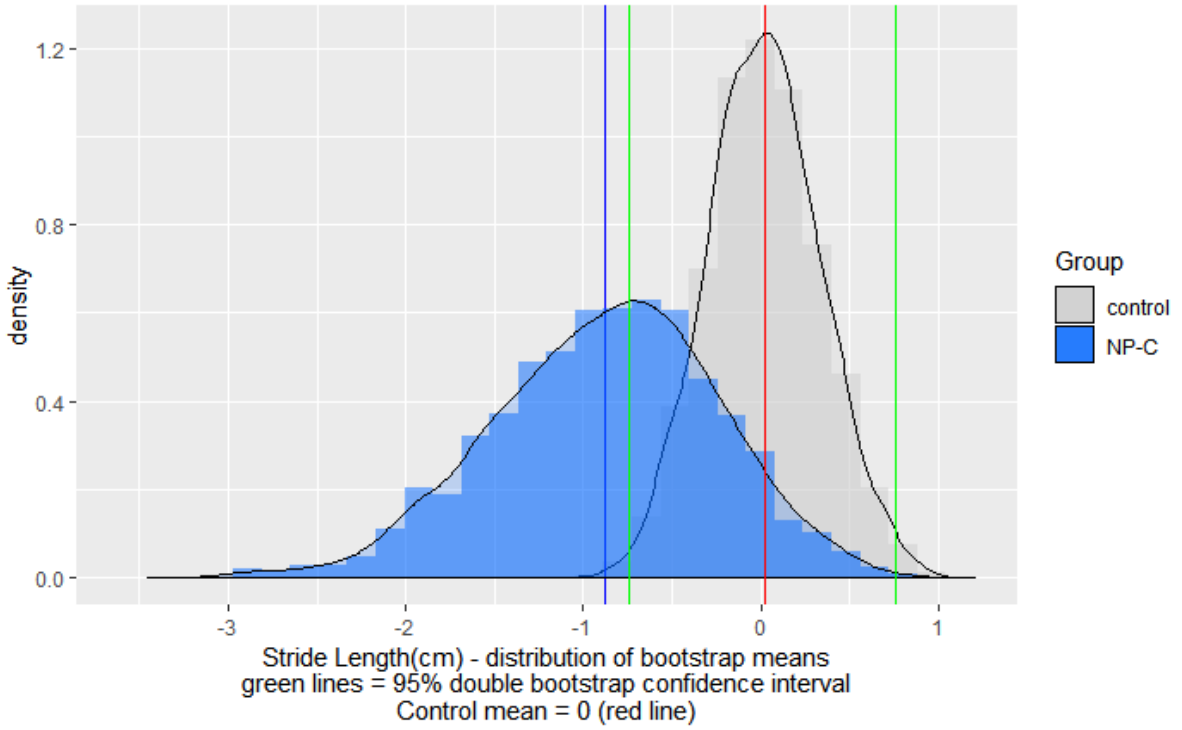


Figure 3.14: The distribution of bootstrap means for NP-C patients and controls in stride length. Green lines are the 95% confidence intervals. Red line is the control mean. Blue line is the patients mean.

Figure 3.14 showed that the control bootstrap mean was 0.013 and the CI for control group stride length were (-0.74, 0.75), and the patient bootstrap mean (-0.88) on the boundary, in this case, just outside the control intervals. The observed stride lengths from NP-C patients would be unusual from a sample of controls. However, most of the patients were below the control mean. On average, NP-C patients had a 14.2 cm shorter stride than controls. This difference is, however, influenced by a few patients with very short strides.

After removing the extreme values (n = 2) (Figure 3.15) to eliminate the small number of more extreme patient values (section: 3.2.1, p: 64), control and the patient means were very close, so there with little difference between both groups (Appendix 3 Figure 3.A1).

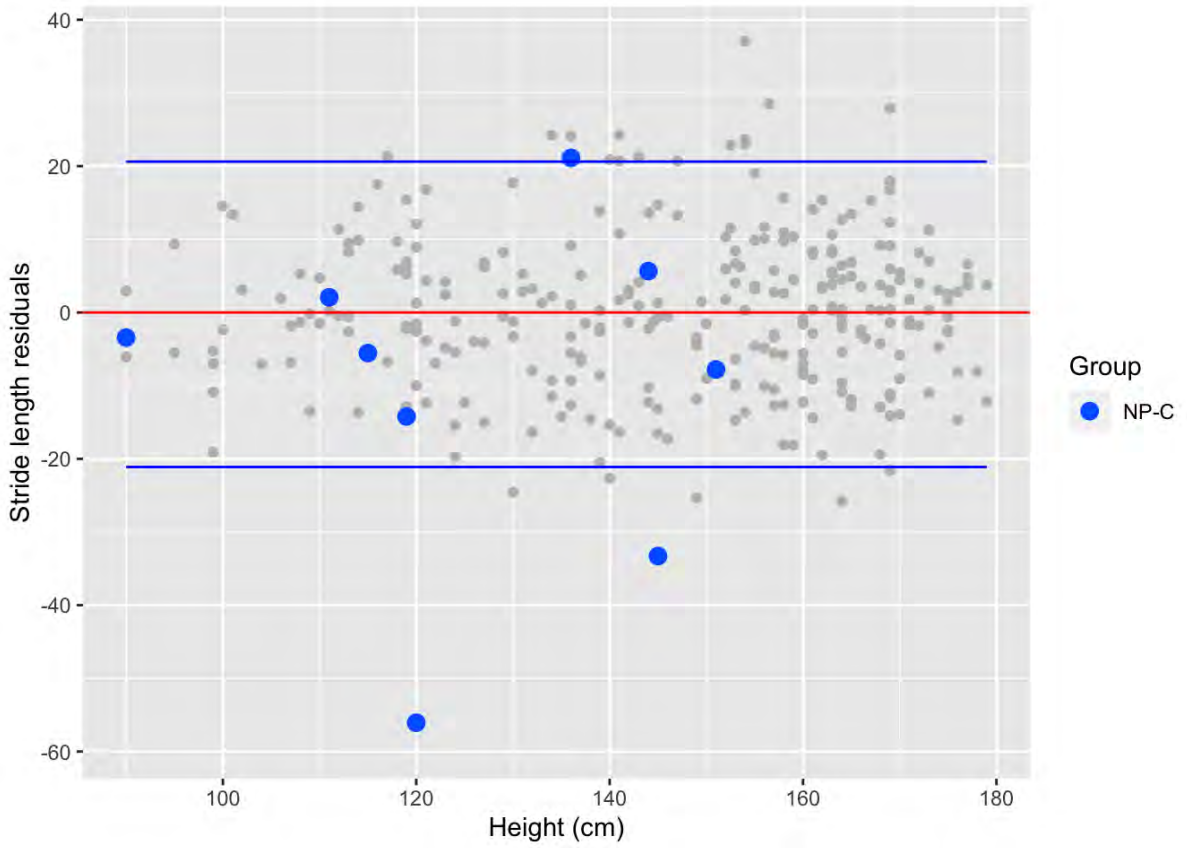


Figure 3.15: Stride length residuals as a function of height. The red line is the control mean. The blue lines are the upper and lower cut-offs for the 95% prediction intervals for controls. Grey dots are the control data and the blue dots are the NP-C patient‟s data.

Stance percentage (%):

Figure 3.A2 (Appendix 3) revealed that the patient bootstrap mean (2.84) was outside the control group CI (-0.71, 0.62) and control bootstrap mean (-0.002). Thus, there was a significant difference between NP-C patients and control group in stance percentage. NP-C patients spent 2.5 % more time in the stance phase of the gait cycle than controls. However, this difference was influenced by a few patients with very high stance %.

Figure 3.16 showed the extreme values (n = 2) in stance % for NP-C patients. After removing these extreme values, the control and the patient means became within these intervals (Appendix 3 Figure 3.A3). Therefore, there was no different between both groups in stance %.

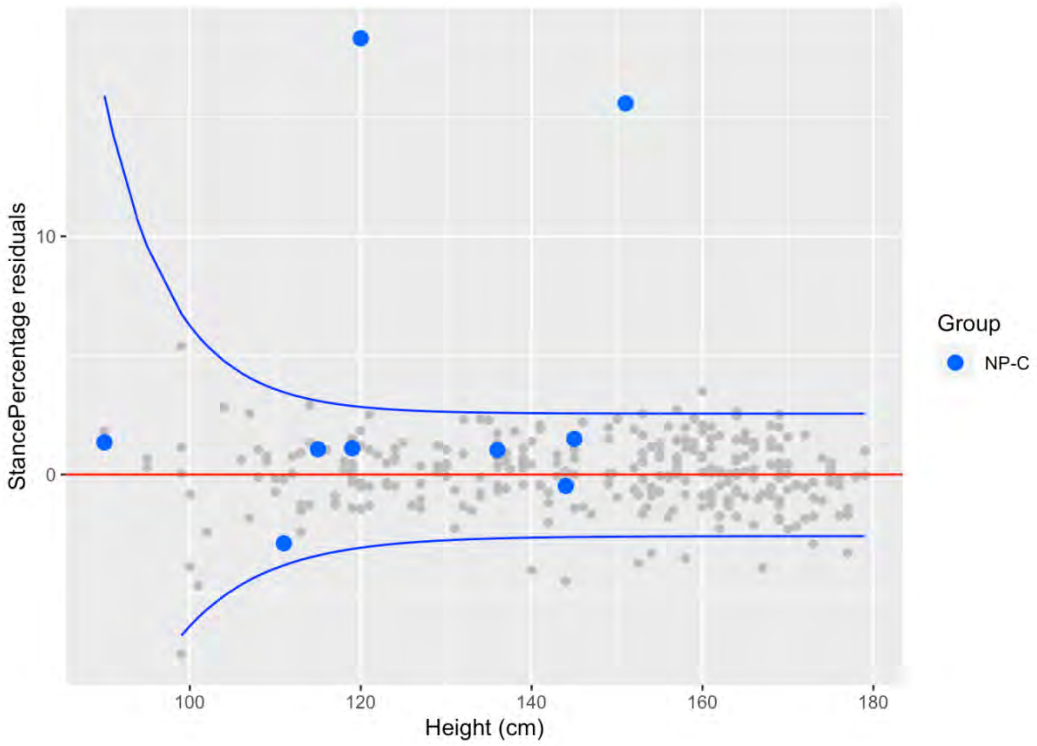


Figure 3.16: Stance percentage residuals as a function of height. The red line is the control mean. The blue lines are upper and lower cut-offs for the 95% prediction intervals for controls. Grey dots are control data, blue dots are the NP-C patient‟s data.

Single support percentage (%):

With regards to the single support %, the control group bootstrap mean was (-0.002) and the CI was between -0.71 and 0.69 (Appendix 3 Figure 3.A4). The patient bootstrap mean of the single support % was -2.05 and was outside these intervals, which indicates that there was a significant difference between NP-C patients and control group in single support %. NP-C patients spent 2.2% less of the gait cycle with only one foot in contact with the ground compared to control group.

After removing the extreme patient values (n = 1) which was shown in Figure 3.17, the patient mean was still outside the 95% CI (Appendix 3 Figure 3.A5). Therefore, still there was a significant difference between both groups in single support %.

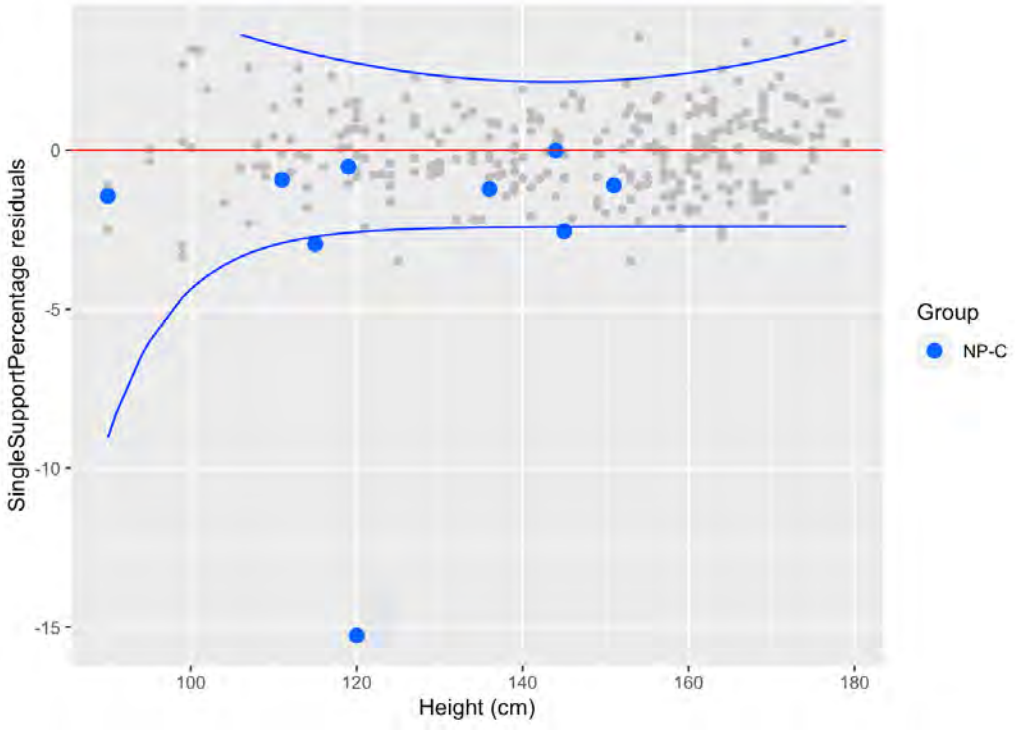


Figure 3.17: Single support percentage residuals as a function of height. The red line is the control mean. The blue lines are the upper and lower cut-offs for the 95% prediction intervals for controls. Grey dots are control group data, blue dots are NP-C patient‟s data.

Cadence:

Figure 3.A6 (Appendix 3) showed the cadence results for NP-C patients. The control group CI was between -0.65 and 0.76, while the control bootstrap mean was -0.002. The patients bootstrap mean (-1.87) was outside these intervals. The NP-C patients were 1.9 steps/min less in cadence than control group.

In figure 3.18, two extreme NP-C patients‟ data were shown. After removing these extreme values, the patients mean was still outside these intervals (Appendix 3 Figure 3.A7). Therefore, there was a significant between these groups in cadence after removing extreme patients‟ values.

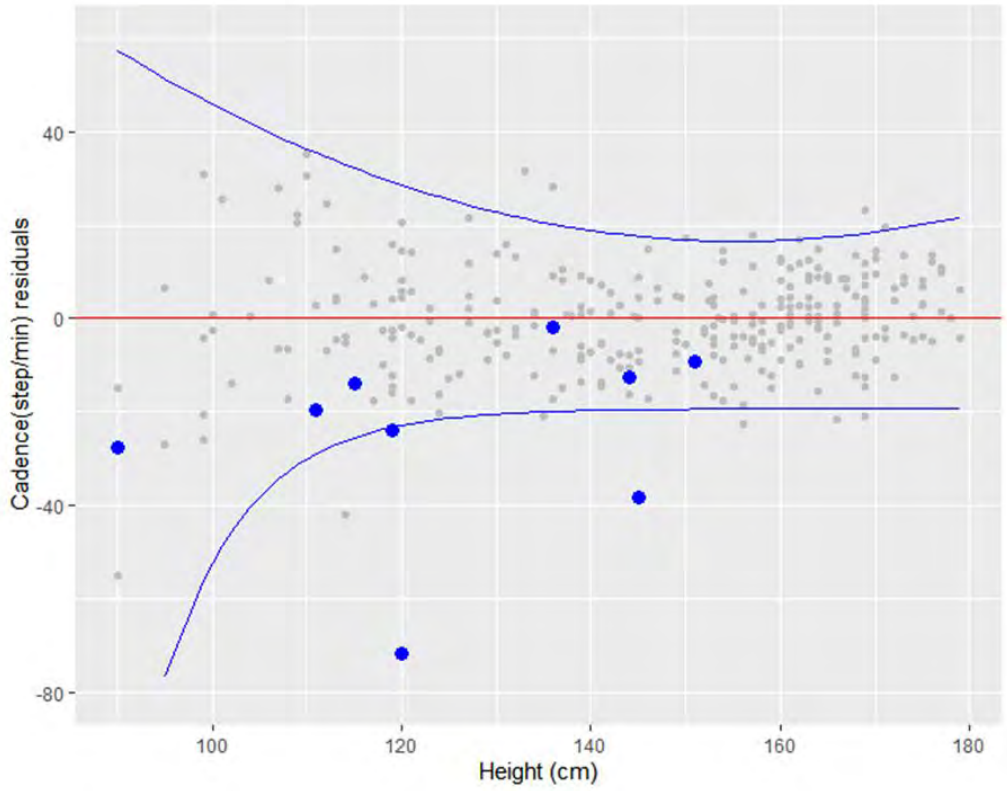


Figure 3.18: Cadence residuals as a function of height. The red line is the control mean. The blue lines are the upper and lower cut-offs for the 95% prediction intervals for controls. Grey dots are the control group data, blue dots are the NP-C patient‟s data.

Stride width:

The control bootstrap mean was 0.013 and the CI for stride width was between -0.61 and 0.97 (Appendix 3 Figure 3.A8). The patient bootstrap mean (1.65) was outside these intervals in this figure. Therefore, there was a different between NP-C patients and control group in stride width. NP-C patients have 1.6 cm wider stride width compared to the control group.

After removing the extreme patient values (n = 3) which was showed in Figure 3.19, the patient mean was within the CI of controls (Appendix 3 Figure 3.A9). Consequently, there was no different between NP-C patients and control group in stride width after removing these extreme values. However, because the patient mean was nearly at the edge of the control CI it means that still the stride width could be affected in this group.

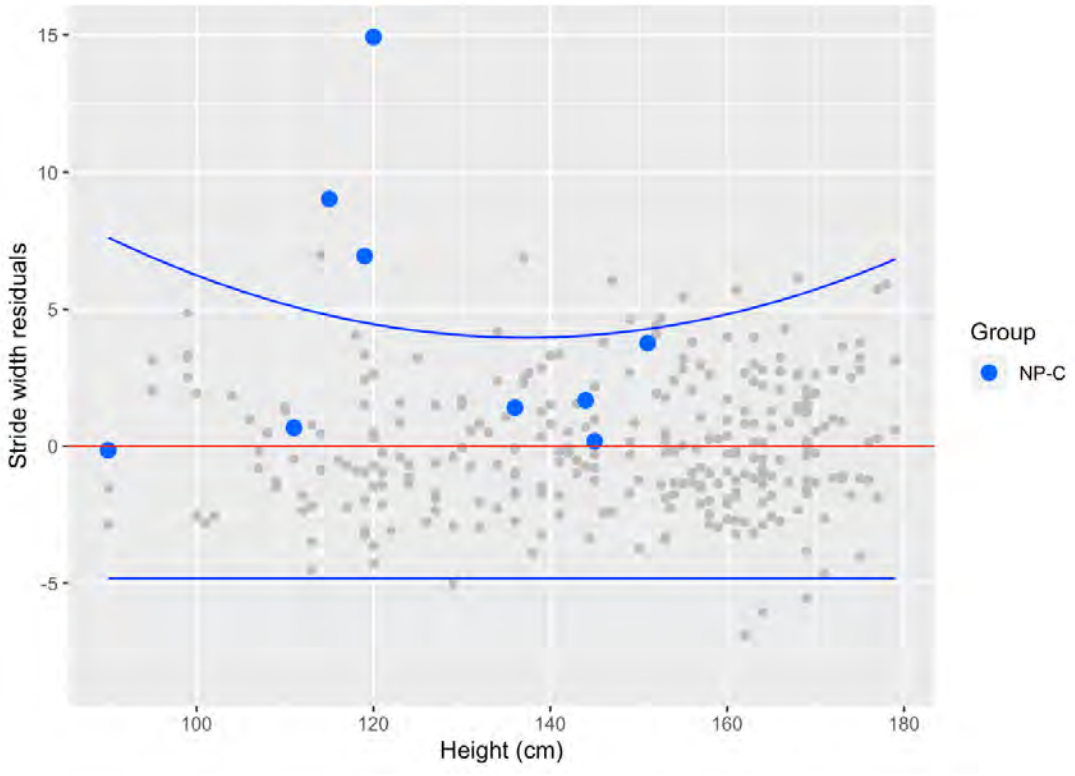


Figure 3.19: Stride width residuals as a function of height. The red line is the control mean. The blue lines are the upper and lower cut-offs for the 95% prediction intervals for controls. Grey dots are control data, blue dots are NP-C patient‟s data.

Table 3.2: Summary of NP-C patient group gait results.

Gait Parameters	Data with Extreme values	Data without Extreme values	The Direction
Stride Length	Different than control	Not different than control	Less stride length
Stance %	Different than control	Not different than control	More stance %
Single support %	Different than control	Different than control	Less single support %
Cadence	Different than control	Different than control	Less Cadence
Stride Width	Different than control	Not different than control	Wider Stride Width

In summary, NP-C patients showed signs of abnormal gait in most of their gait parameters compared to control group even when not all of the parameters have a significant different between both groups. Table 3.2 showed that NP-C patients results had shown that their stride lengths were shorter, stance % were higher, single support % were significantly lower compared to the control group. Moreover, they took fewer steps per minute and that why they have lower cadence and their stride width was wider. From these finding in gait parameter, it seems that single support % and cadence were the most affected parameters in NP-C patients, and they were different that control group.

3.2.3.2. Fabry patients:

Stride length:

The control group bootstrap mean was 0.011 and the CI was between -0.42 and 0.49 in stride length data, and the patient bootstrap mean (-0.45) was slightly outside these intervals (Appendix 3 Figure 3.B1). Fabry patients‟ stride lengths were 4.8 cm less than control group stride length. Figure 3.20 showed only one patient was outside the upper and lower cut-off in stride length. By removing one extreme patient value (n = 1), (Appendix 3 Figure 3.B2) showed that the control and the patient means were within 95% CI, so there was no difference between these groups. In general, with extreme value included the Fabry mean is just outside the control range, but very close to the boundary and with extreme value removed the Fabry mean is inside the CI, but still an unusual value for the control distribution. This means that the stride length could be affected in Fabry patients.

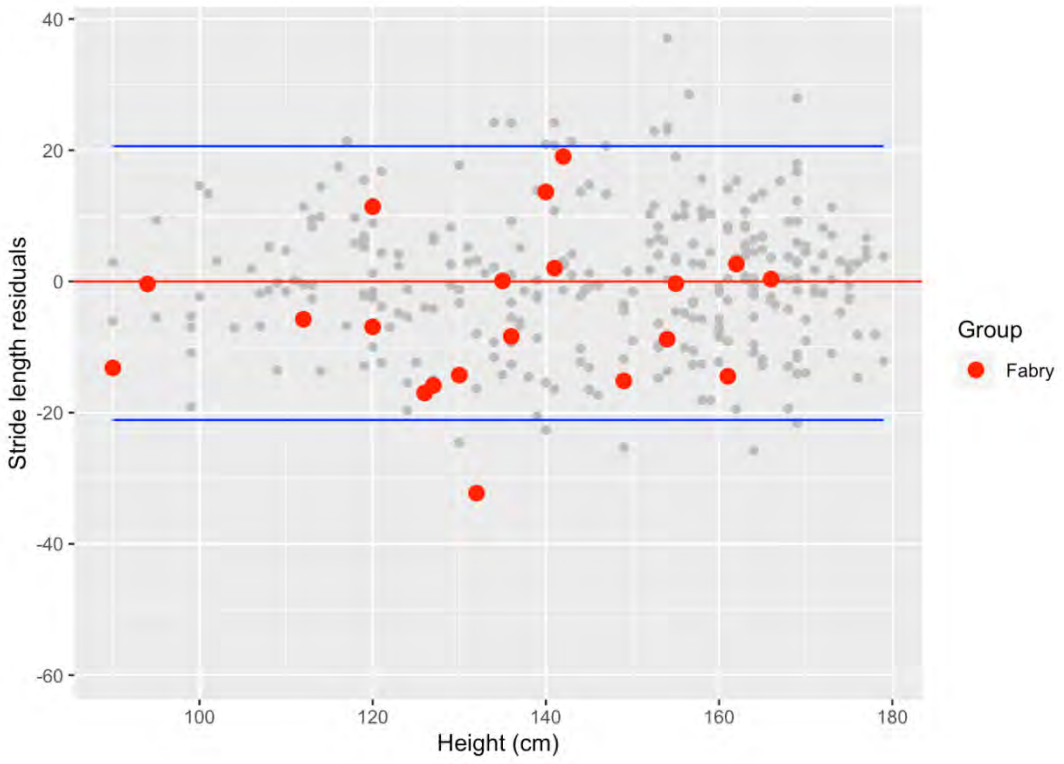


Figure 3.20: Stride length residuals as a function of height. The red line is the control mean. The blue lines are the upper and lower cut-offs for the 95% prediction intervals for controls. Grey dots are the control data and the red dots are the Fabry patient‟s data.

Stance percentage (%):

With regards to the stance %, the control group bootstrap mean was -0.009 and the CI ranged between -0.44 to 0.34, and the patient bootstrap mean (1.15) was outside this interval (Appendix 3 Figure 3.B3). So, there was a significant different between both groups in stance %. Fabry patients spent 1.36% more in the stance phase of the GC than the control group. After removing the extreme patients‟ values (n = 2) which was shown in Figure 3.21, the patient mean remained outside the control 95% CI (Appendix 3 Figure 3.B4).

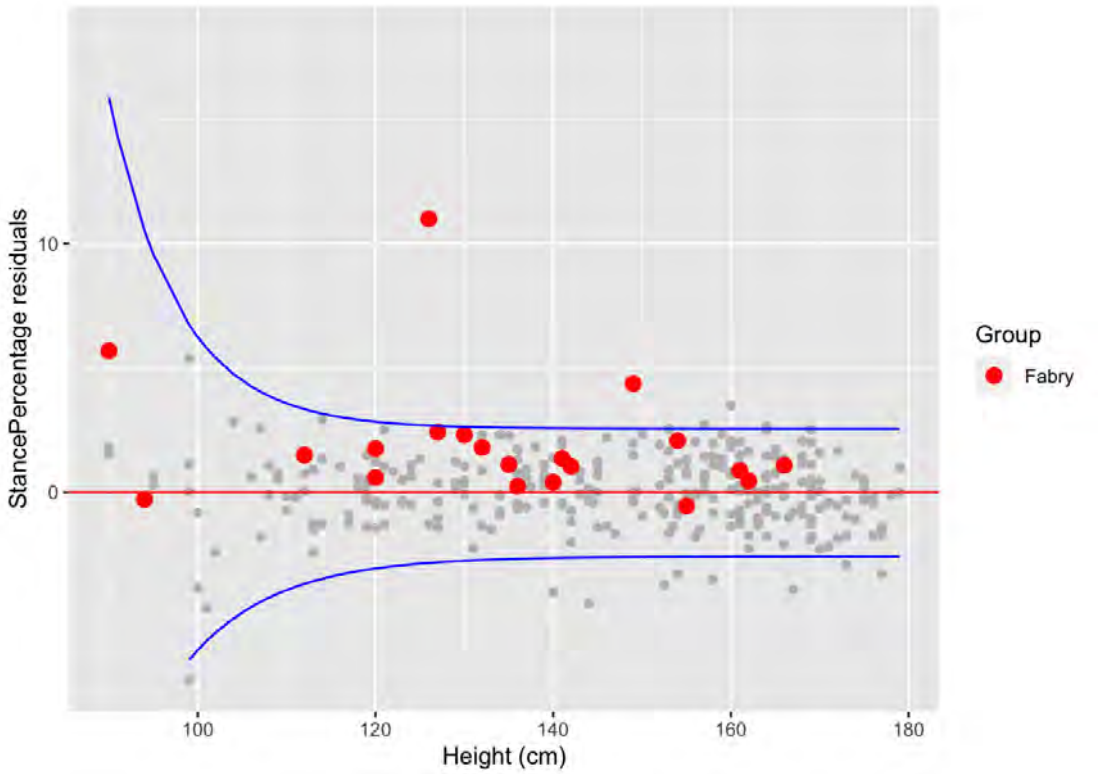


Figure 3.21: Stance percentage residuals as a function of height. The red line is the control mean. The blue lines are upper and lower cut-offs for the 95% prediction intervals for controls. Grey dots are control data, red dots are the Fabry patient‟s data.

Single support percentage (%):

(Appendix 3 Figure 3.B5) revealed that control group had a bootstrap mean (-0.002) and a CI between -0.43 and 0.47. In this figure, the patient bootstrap mean (-0.72) was outside these intervals. This indicates for a difference between Fabry patients and control group.

Comparing both groups with regards to single support %, Fabry patients spend 0.49% less single support % in GC compared to control group.

After removing the extreme patient value (n = 1) which was shown in Figure 3.22, still there was a difference between Fabry patients and control group in single support % (Appendix 3 Figure 3.B6).

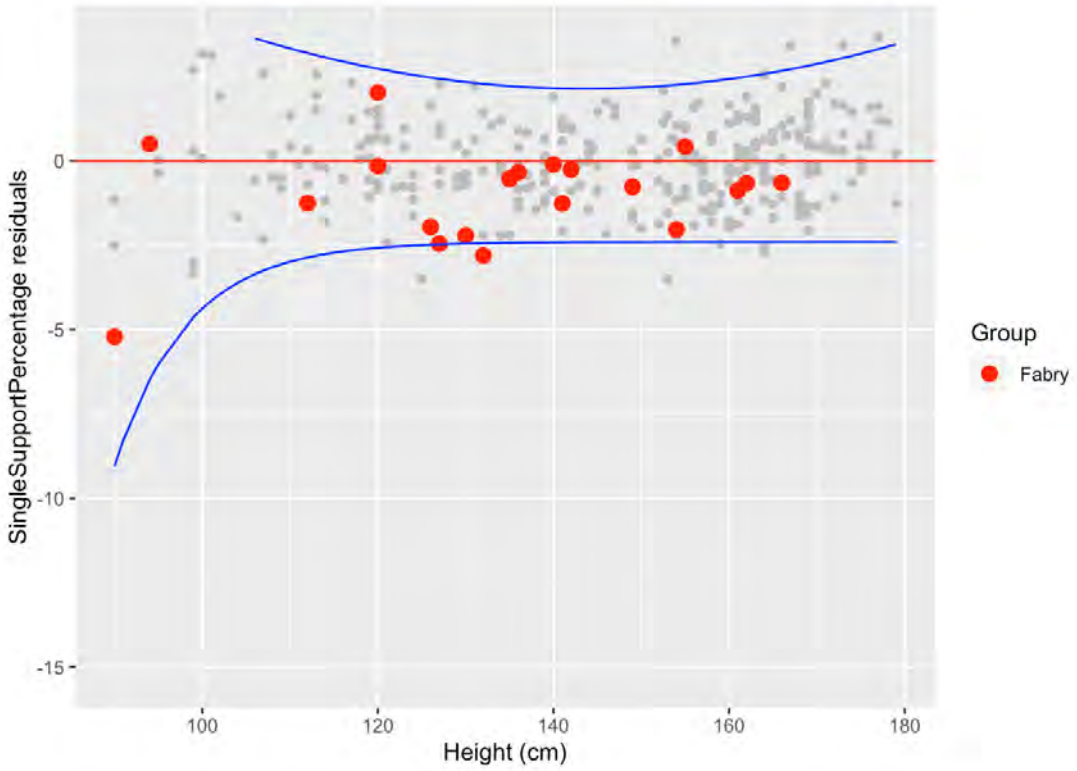


Figure 3.22: Single support percentage residuals as a function of height. The red line is the control mean. The blue lines are the upper and lower cut-offs for the 95% prediction intervals for controls. Grey dots are control group data, red dots are Fabry patient‟s data.

Cadence:

In cadence, the control group bootstrap mean was -0.001 and the CI were between -0.38 to 0.36. The Fabry bootstrap mean was -0.42 and it was outside these intervals (Appendix 3 Figure 3.B7). This revealed that there was a significant difference between Fabry patients and control group. Comparing both groups in cadence, Fabry patients were 4.7 steps/min less than control group. In cadence, there was no extreme patient value for Fabry patients‟ group.

Stride width:

The stride width data in (Appendix 3 Figure 3.B8) showed that control group bootstrap mean was 0.002 and the CI were (-0.41, 0.44), and the control and the patient bootstrap mean (-0.17) were within these intervals. This revealed that there was no difference between Fabry patients and control group. The stride width for Fabry patients showed that they have 0.47 cm less stride width compared to control group data. Like the cadence parameter, there was no extreme patient value for Fabry patient in stride width.

Table 3.3: Summary of Fabry patient group gait results.

Gait Parameters	Data with Extreme values	Data without Extreme values	The Direction
Stride Length	Different than control	Not different than control	Less stride length
Stance %	Different than control	Different than control	More stance %
Single support %	Different than control	Different than control	Less single support %
Cadence	Different than control/no extreme values	N/A	Less Cadence
Stride Width	Not different than control/no extreme values	N/A	Less Stride Width

In conclusion, Fabry patients showed less signs of abnormal gait data in some of their gait parameters. Some of these parameters were not significantly different than control group. However, these parameters showed dissimilar results compared to control group (Table 3.3). This included stride length which was shorter than control group. Moreover, it‟s included, a stride width which was little bit less wide than control group.

On the other hand, there were other parameters showed more significant different than control group. These parameters had shown that Fabry‟s patients spent more % in stance %, less % in single support percentage, and lower cadence in GC compared to control group. In general, stance %, single support %, and cadence were the most affected gait parameters in Fabry patients.

3.2.3.3. Hurler (MPS I):

There were a small number of patients in the Hurler‟s group. The results from Hurler patients should be treated with some caution. This is because the small number (n = 6) of Hurler participants who were available to test compared to the other patient groups.

Stride length:

Control group had shown that the bootstrap mean was 0.014 and the CI was between -1.03 to 1.13 in stride length data, and the patient bootstrap mean (-1.01) was just on the border of these intervals (Appendix 3 Figure 3.C1). In this case it is difficult to state is there a different or not between Hurler patients and control group in stride length. However, figure 3.23 presented that most of Hurler patients‟ data were below the control mean, which indicate shorter stride length in Hurler patient compared to control group. In a comparison to control group, Hurler patients‟ stride length was 12.5 cm shorter.

By removing the extreme value (n = 1), the control and the patient means were within the 95% CI (Appendix 3 Figure 3.C2). Therefore, there was no different between both groups in stride length after eliminating the extreme patient value.

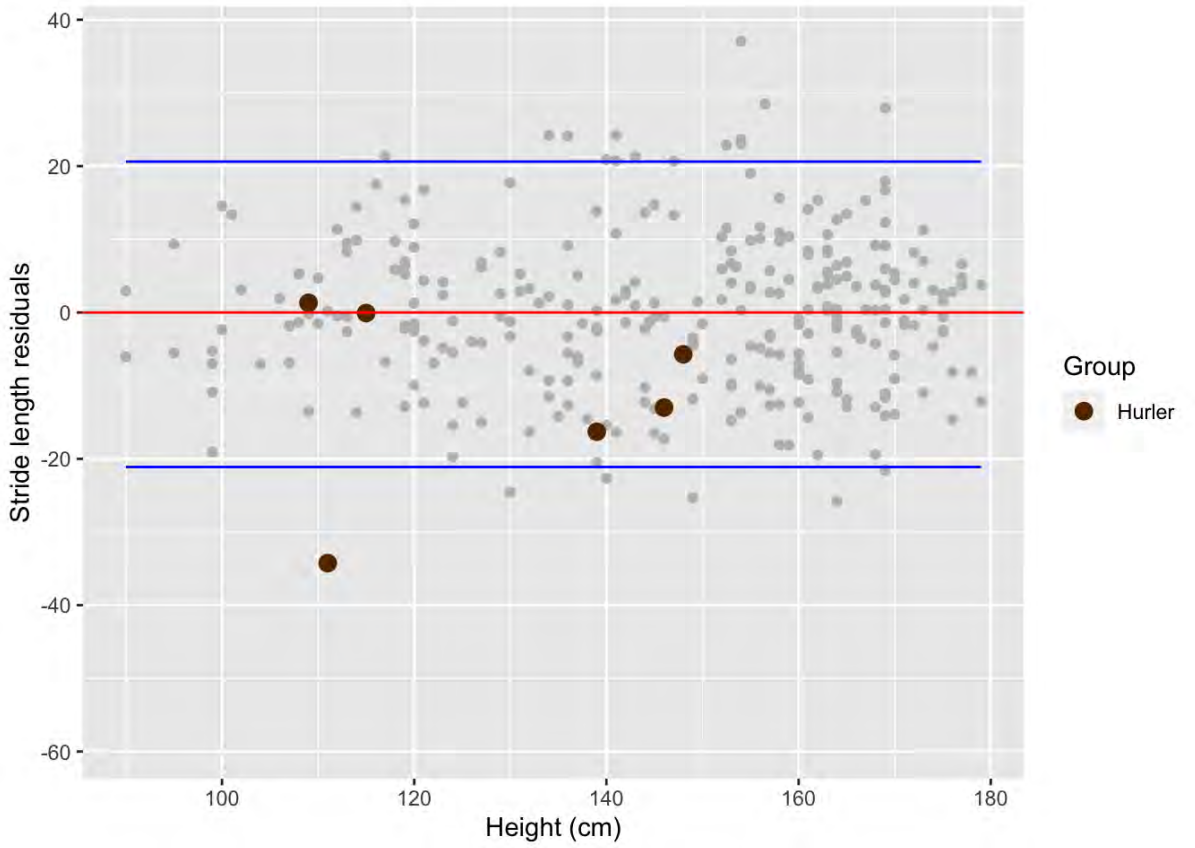


Figure 3.23: Stride length residuals as a function of height. The red line is the control mean. The blue lines are the upper and lower cut-offs for the 95% prediction intervals for controls. Grey dots are the control data and the brown dots are the Hurler patient"s data.

Stance percentage (%):

With regards to the stance %, control group bootstrap CI were ranged between -1.01 to 0.70 (Appendix 3 Figure 3.C3). In this figure, the control group bootstrap mean was -0.014 and the patient bootstrap mean (0.02) were within these intervals and very close to the patients mean. As a result of this, there was no significant different between Hurler patients and control group. This could be interpreted by two reasons. Firstly, one of the Hurler patients had less stance % than control range (Figure 3.24). While, the other reason was due to one of the Hurler patient who had high stance % than control range. In general, Hurler patients were 0.6% more than control group in stance %.

After removing the extreme value (n = 2), the control and patient means were also within the 95% CI (Appendix 3 Figure 3.C4). Consequently, still the stance % data showed there was no difference between both groups.

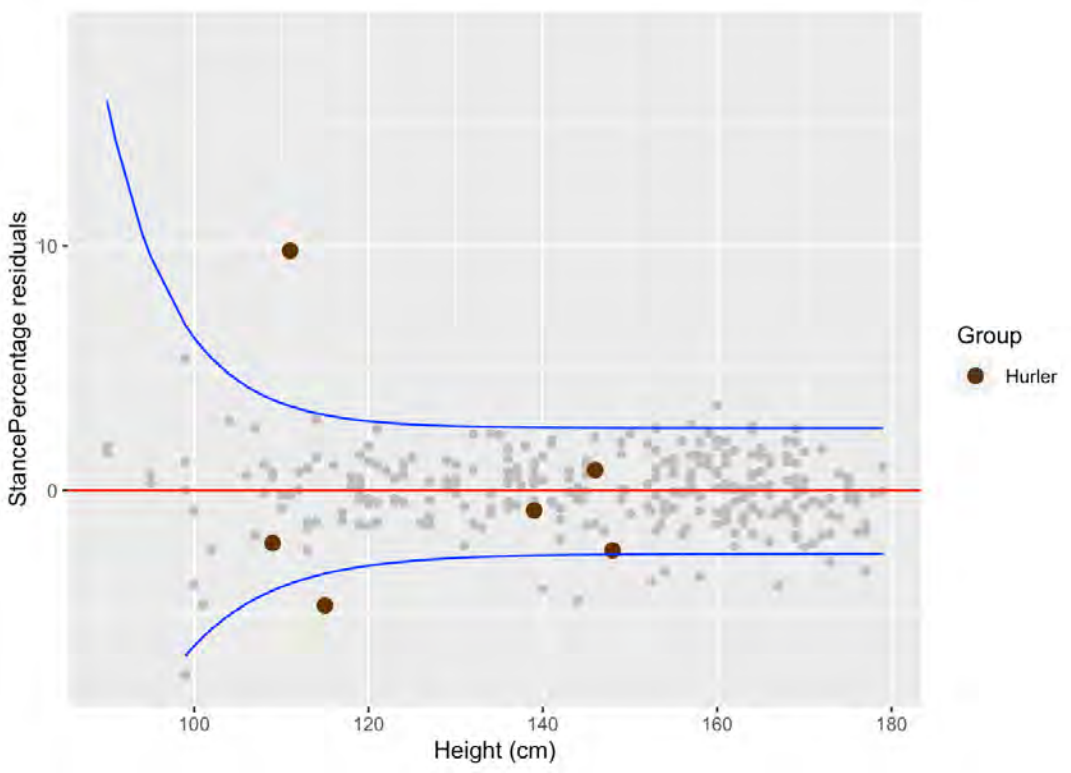


Figure 3.24: Stance percentage residuals as a function of height. The red line is the control mean. The blue lines are upper and lower cut-offs for the 95% prediction intervals for controls. Grey dots are control data, brown dots are the Hurler patient's data.

Single support percentage (%):

The CI for the control group in single support % was ranged from -0.91 to 1.01 and the control bootstrap was -0.003. Appendix 3 Figure 3.C5 showed that the patients bootstrap mean (-2.14) was outside these intervals. As a result, there was a significant different between Hurler patients and control group. By comparing Hurler patients with control group in the single support %, Hurler patients were 2.4% less than control group.

Eliminating the extreme value of the Hurler patient ($n = 2$) which was shown in Figure 3.25, revealed that the patient mean was still outside the 95% CI (Appendix 3 Figure 3.C6). This indicates that there was a difference between both groups in single support %.

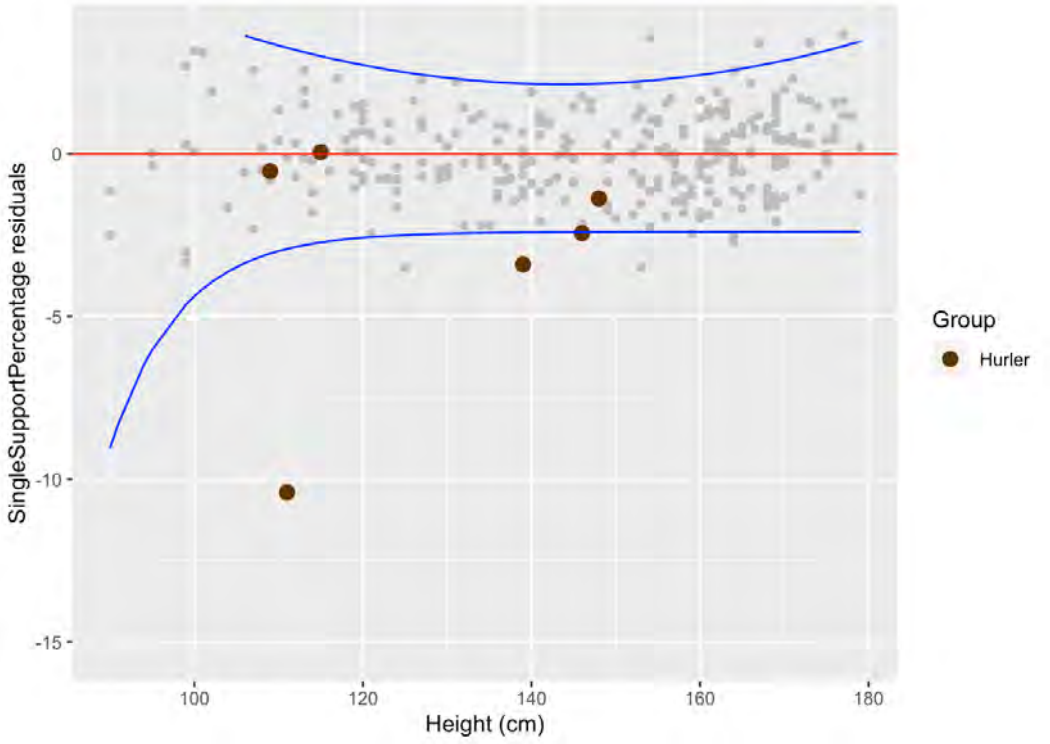


Figure 3.25: Single support percentage residuals as a function of height. The red line is the control mean. The blue lines are the upper and lower cut-offs for the 95% prediction intervals for controls. Grey dots are control group data, brown dots are Hurler patient‟s data.

Cadence:

Figure 3.C7 (Appendix 3) showed the result for Hurler patients in cadence. The control group CI were ranged between -0.98 to 0.82. In this figure, the control bootstrap mean (0.001), and the patient bootstrap mean (-0.87) were within these intervals. Thus, there was no significant different between Hurler patients and control group in cadence. Comparing both groups‟ cadence data had shown that Hurler patients were 9.7 steps/min less than control group. In the cadence data, there was no extreme value for Hurler patients.

Stride width:

For the Hurler patients, the control group bootstrap mean was (-0.0009) and the CI in stride width were between -0.83 to 1.33 (Appendix 3 Figure 3.C8). The patient bootstrap mean was 2.24 and it was outside these intervals as it showed in the figure. Accordingly, there was a significant different between Hurler patients and control group in the stride width. In comparison to the control group, Hurler patients have 2.3 cm wide stride width during the gait.

Figure 3.26 showed the Hurler patient stride width data with extreme values (n = 4). In general, Stride width had more patients outside the control range, but the same patients were not outside the range on other measures, so these patients are not always extreme. This makes stride width look more abnormal (the patients inside the control range are at the top of the range as the bootstrap with extreme values removed shows). Appendix 3 Figure 3.C9 showed that patients mean was at the border of the control range. So based on these data, we can say that there is a difference between both groups in stride width.

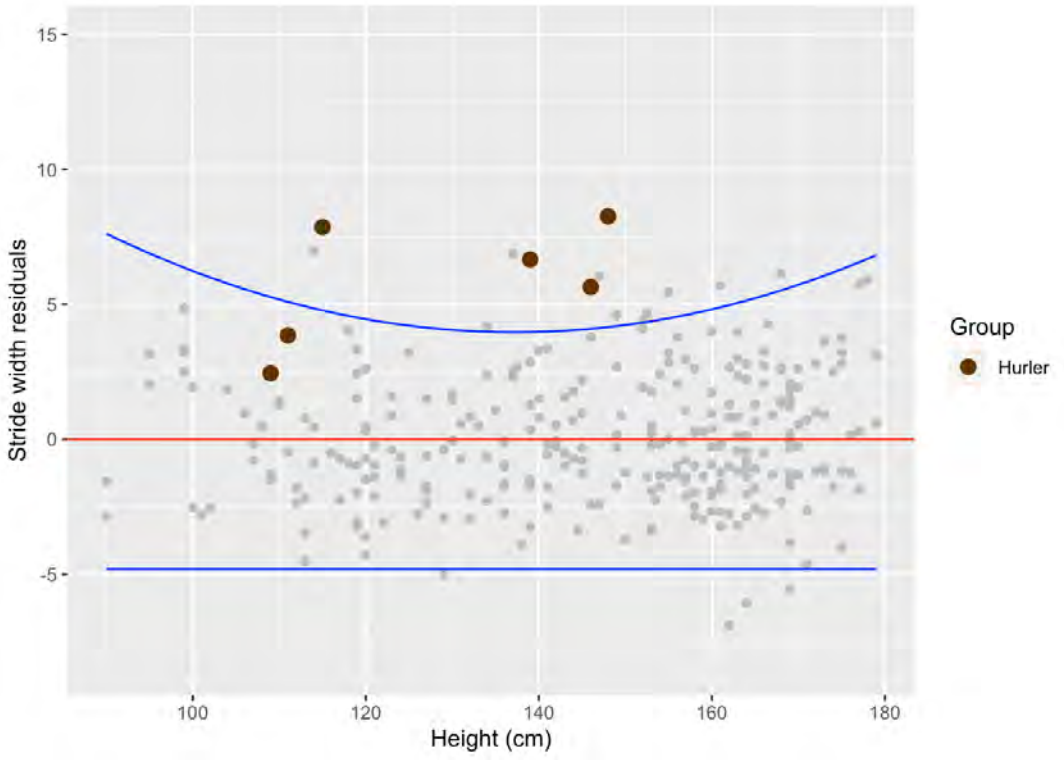


Figure 3.26: Stride width residuals as a function of height. The red line is the control mean. The blue lines are the upper and lower cut-offs for the 95% prediction intervals for controls. Grey dots are control data, brown dots are Hurler patient‟s data.

Table 3.4: Summary of Hurler patient group gait results.

Gait Parameters	Data with Extreme values	Data without Extreme values	The Direction
Stride Length	Not different than control	Not different than control	Less stride length
Stance %	Not different than control	Not different than control	More stance %
Single support %	Different than control	Different than control	Less single support %
Cadence	Not Different than control/no extreme values	N/A	Less Cadence
Stride Width	Different than control	Different than control	Wider Stride Width

In summary, Hurler patients showed different signs of gait abnormalities in their gait parameters compared to control group. Some of these gait abnormalities were not significantly different while the other parameters were different from the control group. For instance, shorter stride length, significantly less single support % and lower cadence were observed within Hurler patient‟s gait. Stance % was not significantly different due to two odds values. One patient had a high stance % and the other patient had a very low stance %. Stride width in Hurler patients had more patients outside the control range and it was wider than control group. Overall, single support % and stride width were the most affected gait parameters in Hurler patients.

3.2.3.4. Morquio (MPS IV), Maroteaux-Lamy (MPS VI), and Pompe:

The other patient groups (Morquio, Maroteaux-Lamy and Pompe) have less than or equal to four patients in each group. Consequently, it is difficult to compare them with the control group. Instead, an S-score for each patient from all the patients‟ groups was calculated, which was based on the cut-off values for controls residuals. This tells us if each patient is inside or outside the control range that includes 95% of control individuals.

Stride length:

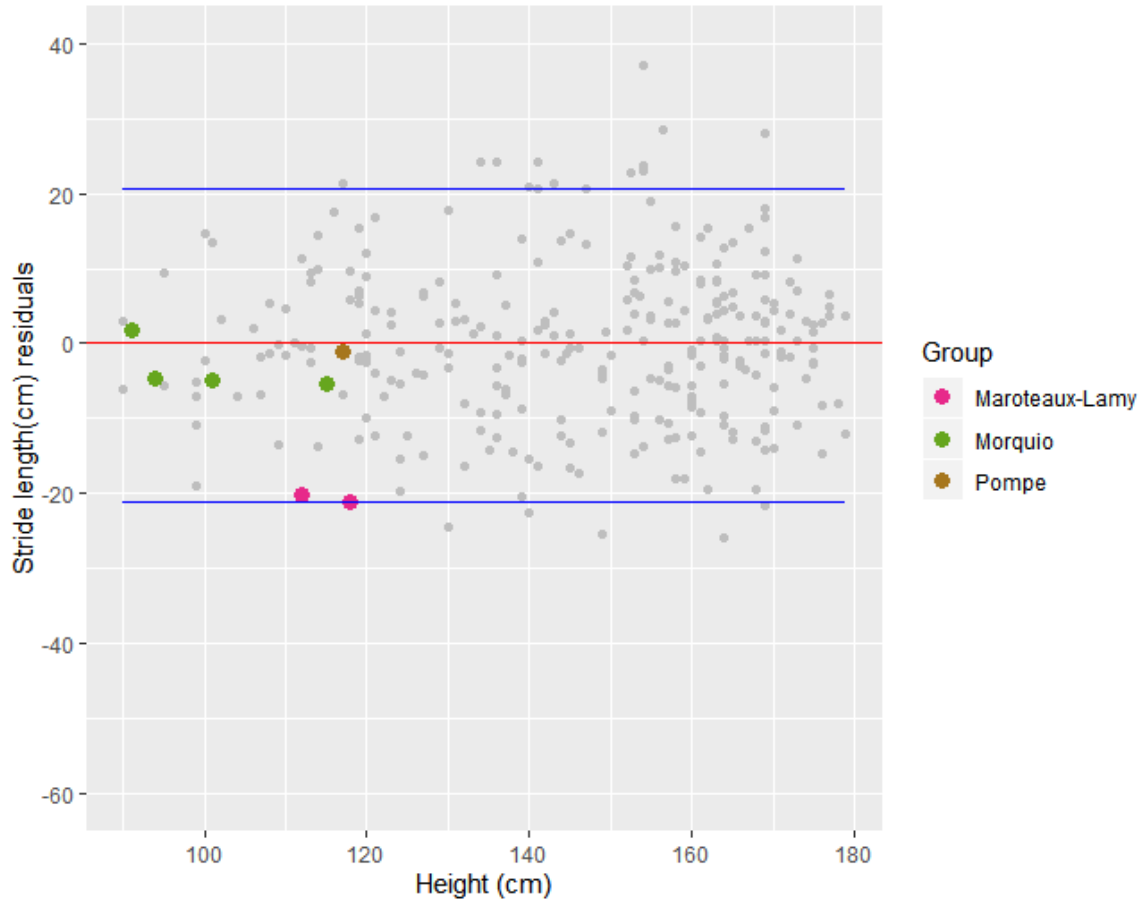


Figure 3.27: The residual data for Maroteaux-Lamy, Morquio, and Pompe patients and controls as a function of height. Blue lines are the upper and lower 95% prediction intervals for controls. Red line is the control mean. Mean stride length residuals on Y-axis and the Height on the X-axis.

In general, these patients were within the control range. However, figure 3.27 showed that Morquio and Pompe were very close to the control means, but Maroteaux-Lamy have shorter stride lengths that were on the border of the control range, so unusual for controls.

Maroteaux-Lamy patients had the shortest stride length from these patients‟ groups. Table 3.5 showed all the patients (including those from larger groups) who were outside the control range in stride length.

Table 3.5: S-score for all the patients outside the control range in stride length.

PID	Group	Age (Years)	Height (cm)	S-Score
Fabry-50014	Fabry	8	132	-3.00
MPSI-10005	Hurler	6	111	-3.18
MPSVI-16002	Maroteaux-Lamy	8	118	-1.96
NPC03	NP-C	10	145	-3.09
NPC04	NP-C	8	120	-5.05
NPC13	NP-C	9	136	2.01

Hurler: MPS I, Maroteaux-Lamy: MPS VI, NP-C: Niemman pick type C, PID: participant identification.

Stance percentage (%):

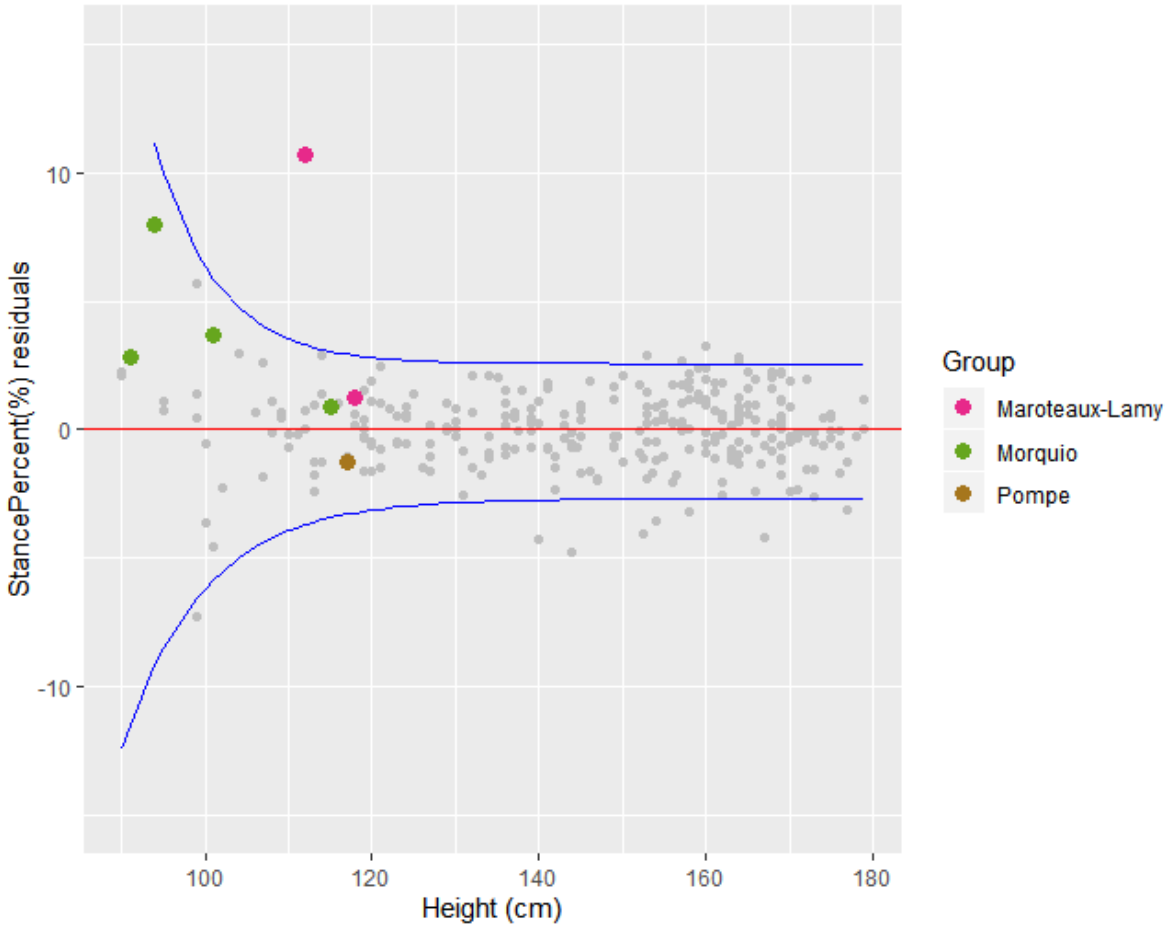


Figure 3.28: The residual data for Maroteaux-Lamy, Morquio, and Pompe patients and controls as a function of height. Blue lines are the upper and lower 95% prediction intervals for controls. Red line is the control mean. Mean stance percentage residuals on Y-axis and the Height on the X-axis.

Figure 3.28 showed that most of the patient‟s stance % data were distributed within the control range and most of them were above the control mean. However, it‟s showed that there was one of the Maroteaux-Lamy patient was outside the control range and had more stance % than the other patients. Moreover, there was one Morquio patient with a high stance percentage, but young controls have higher variance and there was less data available in this range. So, there is quite a lot of uncertainty about where the control boundary is at this height and age. Table 3.6. showed all the patients outside the control range in stance percentage.

Table 3.6: S-score for all the patients outside the control range in stance percentage.

PID	Group	Age (Years)	Height (cm)	S-Score
Fabry-50006	Fabry	8	126	8.09
Fabry-50018	Fabry	10	149	3.37
MPSI-10005	Hurler	6	111	5.51
MPSI-10009	Hurler	7	115	-2.71
MPSVI-16001	Maroteaux-Lamy	6	112	6.21
NPC01	NP-C	12	151	12.02
NPC04	NP-C	8	120	13.44

Hurler: MPS I, Maroteaux-Lamy: MPS VI, NP-C: Niemman pick type C, PID: participant identification.

Single support percentage (%):

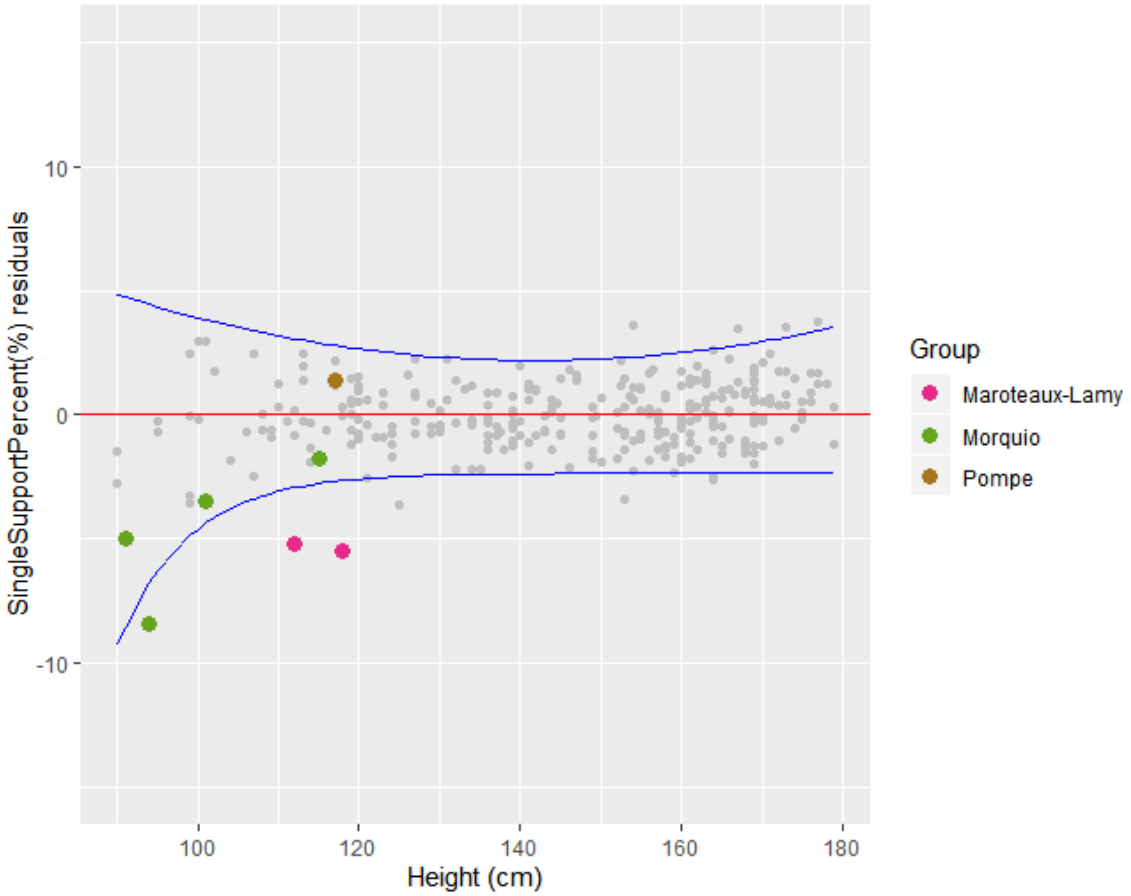


Figure 3.29: The residual data for Maroteaux-Lamy, Morquio, and Pompe patients and controls as a function of height. Blue lines are the upper and lower 95% prediction intervals for controls. Red line is the control mean. Mean single support % residuals on Y-axis and the Height on the X-axis.

The single support % results showed that 3 out of 7 patients in these groups were outside the lower control range (Figure 3.29). However, Pompe patient single support % data was within the control range, and the only one was above the controls mean. While all of the Maroteaux-Lamy and Morquio (1 out 4) have lower single support % and were below the control rage. All patients outside the control range (including those from larger groups) are listed in Table 3.7.

Table 3.7: S-score for all the patients outside the control range in single support percentage.

PID	Group	Age (Years)	Height (cm)	S-Score
Fabry-50010	Fabry	8	127	-1.98
Fabry-50014	Fabry	8	132	-2.31
MPSI-10005	Hurler	6	111	-6.87
MPSI-10006	Hurler	12	139	-2.74
MPSVI-16001	Maroteaux-Lamy	6	112	-3.46
MPSVI-16002	Maroteaux-Lamy	8	118	-4.04
MPSIV-30010	Morquio	17	94	-2.43
NPC03	NP-C	10	145	-2.09
NPC04	NP-C	8	120	-11.14
NPC09	NP-C	6	115	-2.18

Hurler: MPS I, Morquio: MPS IV, Maroteaux-Lamy: MPS VI, NP-C: Niemman pick type C,
PID: participant identification.

Cadence:

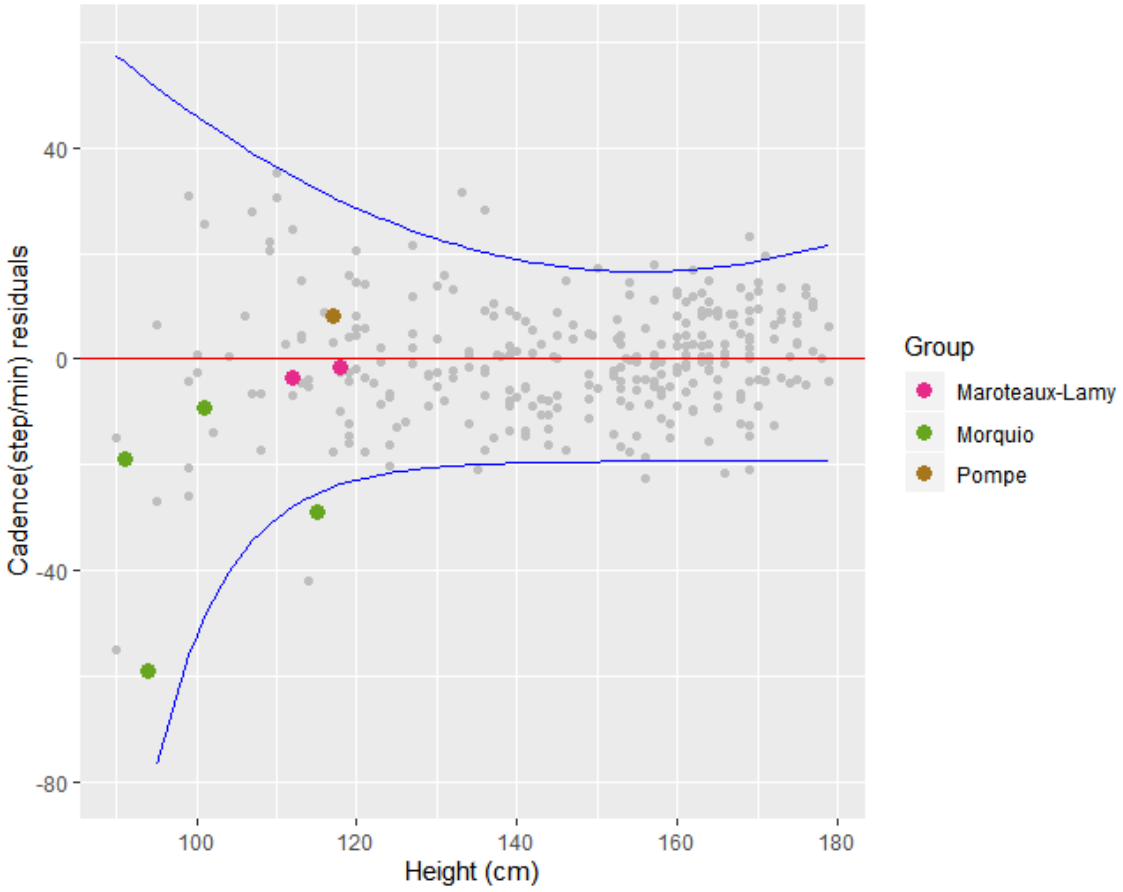


Figure 3.30: The residual data for Maroteaux-Lamy, Morquio, and Pompe patients and controls as a function of height. Blue lines are the upper and lower 95% prediction intervals for controls. Red line is the control mean. Mean cadence residuals on Y-axis and the Height on the X-axis.

Figure 3.30 showed that most of the patients in this group of diseases were below the controls mean, except the Pompe which was above the control mean in cadence. Only one Morquio patient was outside the lower control range. This means that this patient had a fewer steps per minute than the control group. Table 3.8 lists all patients who were outside the control range in cadence.

Table 3.8: S-score for all the patients outside the control range in cadence.

PID	Group	Age (Years)	Height (cm)	S-Score
Fabry-50019	Fabry	8	135	-2.46
MPSI-10006	Hurler	12	139	-2.69
MPSIV-30016	Morquio	9	115	-2.23
NPC03	NP-C	10	145	-3.86
NPC04	NP-C	8	120	-6.15
NPC11	NP-C	8	119	-2.00

Hurler: MPS I, Morquio: MPS IV, NP-C: Niemman pick type C, PID: participant identification.

Stride width:

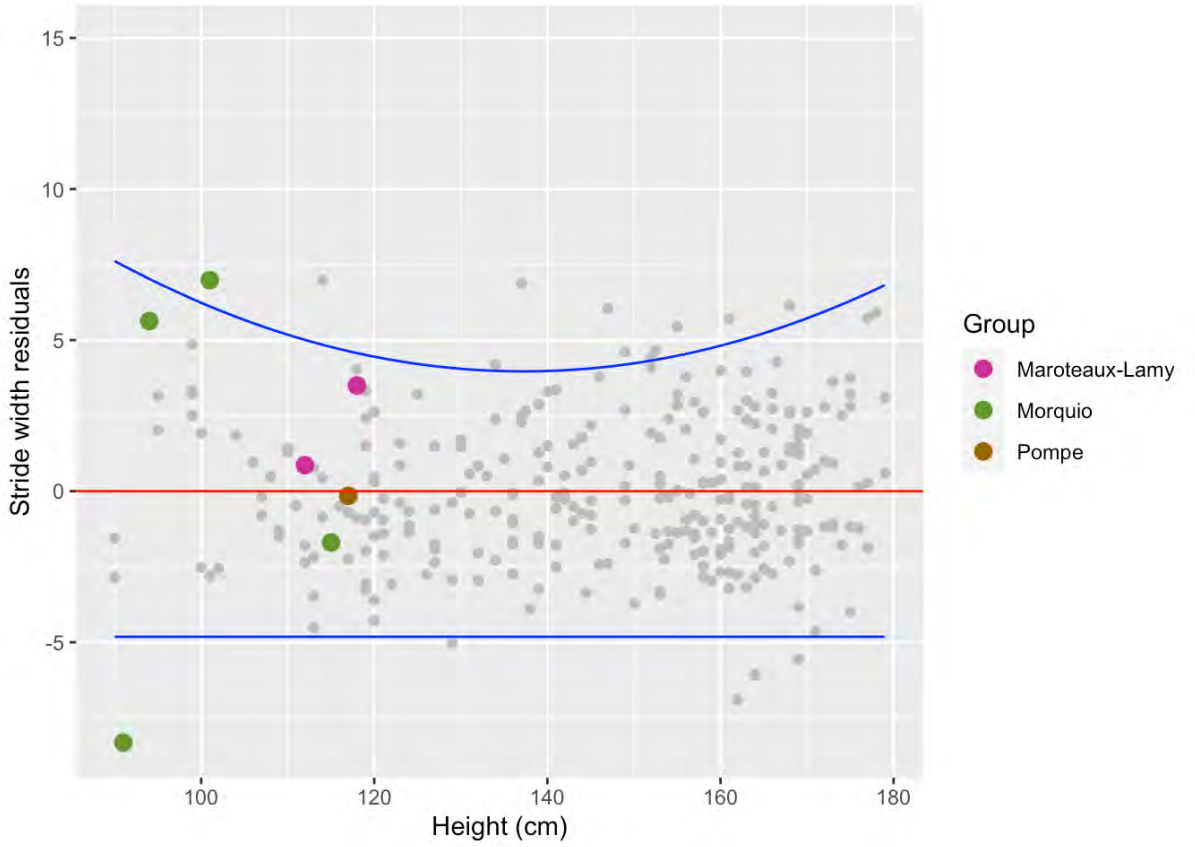


Figure 3.31: The residual data for Maroteaux-Lamy, Morquio, and Pompe patients and controls as a function of height. Blue lines are the upper and lower 95% prediction intervals for controls. Red line is the control mean. Mean stride width residuals on Y-axis and the Height on the X-axis.

Three of four Morquio patients (2 out of 4) were outside the stride width control range (Figure 3.31). One of them had a narrower stride width, while the other one had a wider stride width. In general, irregular stride width (wider or narrower) is linked to lateral instability and can be related to postural control problems (Hoogkamer et al., 2015). On the other hand, the rest of the patients were within the control range in the stride width. S-score calculation was made for all patients who were outside the control range in the stride width (Table 3.9).

Table 3.9: S-score for all the patients outside the control range in stride width.

PID	Group	Age (Years)	Height (cm)	S-Score
Fabry-50016	Fabry	9	155	-2.33
MPSI-10006	Hurler	12	139	2.60
MPSI-10007	Hurler	11	148	3.23
MPSI-10008	Hurler	14	146	2.23
MPSI-10009	Hurler	7	115	3.00
MPSIV-30009	Morquio	14	101	2.71
MPSIV-30015	Morquio	7	91	-3.41
NPC04	NP-C	8	120	5.72
NPC09	NP-C	6	115	3.44
NPC11	NP-C	8	119	2.65

Hurler: MPS I, Morquio: MPS IV, NP-C: Niemman pick type C, PID: participant identification.

In summary, these 3 patient groups have shown gait abnormalities in some parameters compared to control group. Data from Maroteaux-Lamy patients showed that stance % and single support % were the most affected gait parameters. These patients have lower single support % and higher stance % compared to control group. In practice this means that they spent more time with both feet in contact with the floor and walked more slowly. While, data from Morquio patients revealed that single support %, cadence, and stride width were the most affected gait parameters. These patients spent more % were both feet in contact with the floor than with one foot in contact with floor. However, Pompe patient did not have any significant affected gait parameters compared to control group. In general, for the Morquio and Maroteaux-Lamy they seem quite variable across individual and gait measurement and not always the ones outside the control range were the same.

3.2.4. Patient groups discussion:

Some of the neurodegenerative disease patient known to have abnormal gait pattern especially NP-C, Hurler, Morquio, Maroteaux-Lamy. While, Fabry and Pompe are not known to have any abnormal gait pattern. In general, these abnormalities in gait have not been studied before, or not studied in depth in these groups. This is because these diseases are rare. The current thesis aimed to explore the gait developmental changes within these patients. This was achieved firstly, by investigating the changes in gait parameters with neurodegenerative disease patients (mentioned earlier) and compares these changes with healthy control individuals in order to identify the most affected gait parameters. We have used the Zeno mat to identify affected parameters, as the Zeno mat is considered to be a very suitable assessment tool for measuring gait parameters in control and neurodegenerative disease children (Lim, 2014).

This, in turn, could help to understand the gait developmental changes with these patients, and systematically follow them in order to detect early neurological symptoms or quantify changes as the diseases progress. In general, most of the patient groups who have abnormal gait pattern or parameter, showed abnormalities in their muscles or joints, and some of them presented with developmental delay.

Overall, very few researchers have explored changes in gait and postural control for children with neurodegenerative diseases and compared them to normal development children by using the Zeno or GAITRite mat (Alderson et al., 2019; Dusing et al., 2007; Wood et al., 2009).

A) NP-C:

Table 3.10: Demographics data of the NP-C patients.

Patient ID	Age at diagnosis (years)	Joint stiffness	Muscle weakness	Developmental delay	On medication
NPC01	2	none	mild	none	yes, at age 4
NPC02	0.5	none	none	none	no
NPC03	4	mild	mild	mild	yes, at age of 6
NPC04	3	moderate	moderate	moderate	yes, at age of 5
NPC09	2	none	mild	none	no
NPC10	6	moderate	mild	moderate	yes, at age of 7
NPC11	1	none	mild	mild	yes, at age of 5
NPC12	3	mild	none	mild	no
NPC13	4	mild	none	mild	yes, at age of 5

It is well documented that NP-C patients mainly have abnormal unsteady ataxic gait with wide-base of support which lead to frequent falls (Sansare et al., 2018). In this thesis most of the gait parameters have one or two outlier patients (NPC04 and NPC10). Table 3.10 showed that these two patients have moderate joint stiffness, muscle weakness, and developmental delay which, in turn, affect their gait performance and parameters.

In the present study, NP-C patients data showed there was no significant different between them and controls in **stride length** after removing the extreme values. However, even if it was not significant, NP-C have a shorter stride length than controls especially the ones with moderate joint stiffness, spasticity and developmental delay and this was usually caused by cerebellar defects which was found in these patients (Aprigliano et al., 2019). There is only one study in the literature (yet) was found that examine gait and balance in NP-C patients done by Sansare et al. (2018). However, this study examine the step length instead of stride length, which is consider to be normally 2 steps length (Perry & Davids, 1992; Wall & Kirtley, 2001). Sansare et al. (2018) reported that there was no significant difference between NP-C patients (n = 10) and control group (n = 15) in step length by using GAITRite mat and

Vicon Motion System. From the Sansare‟s observation, it can be suggested that also there is no significant difference between the NP-C and control group in stride length, as it is equal to 2 step length.

In regard to the **stance %**, there was also no significant different between NP-C and control group. This is because some patients were really affected, while the other were similar to control. However, NP-C patients spent more percentage in stance (~ 3.7 %) than swing in the total GC percent. Up to date, yet, there is no study investigated the stance % in NP-C patient and compared it with normal group, except the present thesis, which provide novel findings. On the other hand, stance time was examined in NP-C patients only by Paciorkowski et al. (2008). They found that stance time was increasing in NP-C patient, which in turn affected their instability. This finding also was observed in the present study with stance %, as it was increasing with NP-C patients. Increasing in the stance time and/or stance % with NP-C patient resulted an increase in instability. These changes in the gait development in NP-C patient can be due to decrease in the cerebellar white and grey matter volume, which in turn affects motor control and saccadic gain (Walterfang, Abel, et al., 2013).

In contrast with previous parameters, there was a significant difference between **single support %** in NP-C patient and control group. In general, NP-C patients spent less percentage of the GC (3.2 %) with only one foot in contact with the ground than control group. The data obtained from this study agreed with previous study done by Sansare et al., 2018, who found that NP-C patients walk significantly slower than healthy participants and they spent more time in double support than single support to reimburse for their postural instability. Their result confirmed that single support percentage showed a tendency to a reduction in NP-C patients.

NP-C patients showed a significant decrease in **cadence** than control group, which was about 25 steps/min. This finding is in agreement with Paciorkowski et al. (2008) who reported that cadence was significantly decrease with NP-C patient.

These findings from the present study and Paciorkowski et al do not support with Sansare et al., 2018 finding. They found that NP-C cadence did not reach statistical significance, though there were few patients differ from controls. This could be because of the increased variability in the control cadence and some patients did not vary much from controls. In general, cadence is one of the parameters that need to be checked in a larger sample.

Stride width increased significantly in NP-C patients compared with controls. However, after eliminating the extreme values, there was no difference between both groups in stride width (Figure 3.28). In this parameter, the NP-C patients reported to have wider stride width (~ 4.4 cm) compared to control group. Interestingly, Sansare et al. (2018) reported the same results in step width (instead of stride width). They found that step width in NP-C patient was not significantly different from the control group. Moreover, they reported that few NP-C patients had a wider step width compared to control group.

This conclusion about no significant difference between both groups in stride width (present study) or step width (Sansare et al.) could be interpreted as due to variability in patient data. On the other side, both studies had shown that NP-C patients have wider stride or step width. This could be explaining as due to the influence of the patients, who have joint stiffness especially in the hip joint. This was observe in increasing hip abduction, which in turn resulting in increased stride or step width leading to reduce stability (Romano et al., 2019). Moreover, due to the affected of cerebellum in these patients, which have an influence on the step and stride width (Mihara, Miyai, Hatakenaka, Kubota, & Sakoda, 2008; Miyai et al., 2013).

In conclusion, from table 3.2 all gait measurements with extreme values were different than control group. While, for the data without extreme values only single support % and cadence were different than control group. These two parameters were the most affected parameters in NP-C patients. Therefore, they could be used for monitoring gait changes in this group.

B) Fabry:

Table 3.11: Demographics data of Fabry patients.

Patient ID	Age at diagnosis (years)	Joint stiffness	Muscle weakness	Developmental delay	On medication
50001	2	none	none	none	Yes, at 5 years
50002	4	none	none	none	no
50003	5	none	none	none	no
50004	3	none	none	none	no
50005	3	mild	none	mild	Yes, at 4 years
50006	7	mild	mild	moderate	Yes, at 8 years
50007	3	none	none	none	no
50008	5	none	none	none	no
50009	1	none	none	none	no
50010	2	none	none	none	no
50011	6	mild	none	none	Yes, at 9 years
50012	8	mild	none	mild	Yes, at 10 years
50013	2	none	none	none	no
50014	4	none	mild	none	Yes, at 5 years
50015	5	none	none	none	no
50016	3	none	mild	none	Yes, at 7 years
50017	8	mild	none	none	Yes, at 9 years
50018	4	none	none	none	Yes, at 6 years
50019	5	none	mild	none	Yes, at 7 years
50020	6	none	none	none	no

Fabry patients usually characterised with lower gait and transfer speed (Löhle et al., 2015). In the present study, there was no significant different between Fabry patients and control group in **stride length.** However, the patient mean was nearly at the edge of the control CI even when the extreme patient value removed. Moreover, the present results reported that Fabrys‟ patients tend to have shorter stride length than controls participants. There is shortage in the literature regarding examining the gait parameter with Fabry patient. Löhle et al. (2015) consider the only study, who examines the clinical gait feature of Fabry patients with aged-matched control group. They found that Fabry patients featured with slower gait and transfer speed compared to control group. Although their findings did not describe which part of gait parameter can be affected in the Fabry patient, a general idea based on their findings can be build up that slower gait could result abnormities in the gait parameter. This was actually found in the present study findings, where the **stance %** in Fabry patient was significantly higher than control group during walking. Moreover, it was observed in **single support %** and **cadence** parameters, which were significantly different from the control group. With regards to these two parameters, the present study revealed that patient with Fabry disease spent less % in single support (1.07%) and lower cadence (11.6 steps/min) compared to control group. These findings could be interpreted due to the involvement of the primary motor cortex, which showed an increase of excitatory neurotransmission in motor cortex circuit with Fabry patients (Cocozza et al., 2018).

On the other hand, the **stride width** finding revealed that there was no significant different between the Fabry patient and control group. This is because the participants whom recruited in the present study were mainly young, and the motor function becomes worsened with increasing age (Löhle et al., 2015). This in turn showed why the stride width did not reach the statically significant different between Fabry patient and control group.

In addition, it can be explained that many Fabry‟s patients stride width mean were clustered around zero (controls mean), while there were only two to three further away from the mean. Also, there was quite a lot of variability within patients‟ data that was scattered around zero. This individual‟s variability in the data means that the smallish different between Fabry and control means was not reliable to a comparison (could result from individual values which were noisy).

To sum up, it could be concluded from the Fabrys‟ gait data without extreme values that stance % and single support % were different than control and the most affected parameters in Fabry patients (see table 3.3).

C) Hurler (MPS I):

Table 3.12: Demographics data of Hurler (MPS I) patients.

Patient ID	Age at diagnosis (years)	Joint stiffness	Muscle weakness	Developmental delay	On medication
MPSI1005	2	moderate	moderate	moderate	yes, at age 3
MPSI1006	3	moderate	mild	moderate	yes, at age 5
MPSI1007	3	mild	mild	mild	no
MPSI1008	4	moderate	moderate	moderate	yes, at age 6
MPSI1009	5	mild	moderate	moderate	yes, at age 7
MPSI1010	4	mild	moderate	moderate	yes, at age 5

It is well established that Hurler patients have delayed locomotor abilities, vestibular dysfunction, and hydrocephalus which could affect and reduced gait and balance efficiency (Bjoraker et al., 2006). The present study findings showed that there was a significant difference between Hurler patients and control group in **stride length**. With removing the extreme value (n =1), there was no significant difference between both groups in stride length. However, the study presents a good finding that Hurler patients were 12.5 cm shorter

in stride length compared to the control group. These findings are in contradiction with earlier findings by Dusing et al. (2007). They found that there was a significant difference in the step length data between the Hurler patients (*n* =18) and control group. Moreover, they reported that Hurler patients had a shorter step length compared to control group. The differences between the present study and Dusing"s et al study is the number of the sample size of Hurler patients (5 and 18 patients, respectively), which is in turn affect the significance of stride length results of the present study. Both of the present study and Dusing"s et al study agreed that Hurler had a shorter stride or step length compared to the control group. This could be explained as due to generalized muscle weakness, limited ROM and developmental delay in these patients (Aldenhoven et al., 2008).

Stance % findings in the present study revealed there was no significant difference between the Hurler patient and control group before and after eliminating the extreme data (Figure 3.43 and 3.45). Moreover, **Cadence** data was not significantly different between the Hurler patients and control group. However, Hurler patients had fewer steps than control group (less 9.7 steps/ min).

In general, these two parameters were different from controls but did not reached significant level, this might be because the limited number of Hurler patients (*n*=6) in the present study. The present study has confirmed the earlier finding by Dusing et al., (2007) on cadence. They found that there was no significant different in normalized cadence of Hurler patients compared to control group. That was because the changes in cadence with gait maturation were small in normal developing children.

Moreover, there was a significant decrease in **single support %** in Hurler patients compared to control group. This is due to lower limb muscle wasting and decrease ROM of the hips,

knee, and ankle in Hurler patients (Bjoraker et al., 2006). In general, decreased ROM has an influence on the swing movement through part of the GC, which is seen by shorter step length. While muscle imbalance has an impact on heel strike and base of support (Wood et al., 2009). This could explain why the Hurler patient had a wider **stride width** compared to control group in the present study. These present findings in single support % and stride width in patients with Hurler disease consider to be a new finding, as no study in the literature examine these parameters, yet.

In conclusion, single support % gait data with and without extreme values and stride width were different than control group and the most affected parameters in Hurler patients‟ groups.

D) Other three patient groups:

These three other patient groups (Morquio, Maroteaux-Lamy and Pompe) have less than five patients in each group. Consequently, it was difficult to compare them with control group. Due to the small group size and the clinical heterogeneity of the patients, prevented statistical analysis and the results presented from these three patients‟ groups are qualitative rather than quantitative. Therefore, all group results should be treated with some caution because of the small number of patients who were available to test. The analysis was more focused on individual patient performance, looking at whether differences can be recognised in their gait.

Morquio (MPS IV):

Table 3.13: Demographics data of Morquio (MPS IV) patients.

Patient ID	Age at diagnosis (years)	Joint stiffness	Muscle weakness	Developmental delay	On medication
MPSIV3009	1	mild	mild	mild	yes, at age 2
MPSIV3010	2	moderate	mild	moderate	yes, at age 4
MPSIV3015	3	moderate	mild	moderate	yes, at age 4
MPSIV3016	5	moderate	moderate	moderate	yes, at age 6

In general, Children with Morquio disease have impairments in ROM and muscle strength, which contribute to impairments in postural control and gait (Algahim & Almassi, 2013). The finding of the present study showed that all patients were within the control range in the **stride length.** While some (3 out 4) Morquio patients were within the control range in **cadence.** Dhawale et al. (2013) examined the gait kinetics and kinematics with Morquio children (n = 9) and compared them with control group. They found that Morquio patients significantly reduce stride length and cadence compared to control group. Although the present findings differ in significance from those of Dhawale et al (2013), it could nevertheless argue that is due to the small sample size of this rare disease in the present study. Decrease in stride length and cadence in the Morquio patient were interpreted due to lower limb deformities which include increase hip flexion and adduction, increase knee flexion and genu valgus (Dhawale et al., 2013; Dhawale et al., 2012). These lower limbs deformities not only can affect the stride length and cadence, but it could affect other gait parameters (such as **stance %, single support%** and **stride width**). Up to date of writing this these, there are no study in the literature examine the rest of gait parameters (**stance %, single support % and stride width**) in patient with Morquio disease, yet. The present study findings with regards to stance %, single support% and stride width consider to be novel. Finding of the **stance %**

showed that the data were within the control range. While the **single support %** data 3 out of 4 Morquio patients were within the control range.

Regarding the **stride width**, only two patients were within the control range. However, for the other two patients; one patient have a wider stride width from control group, while the other one (MPS IV 15) have a very shorter stride width from controls. That was because this patient have a severe joint stiffness in the hip extension and adduction and ankle dorsiflexion, and this could affect on the stride width range. Ankle contracture was the primary musculoskeletal malformation to show and influence on the walking ability (Romano et al., 2019). The data found from the present study agreed with earlier study (Dhawale et al., 2013) which confirmed that hip and ankle joint range and muscle strength were abnormal in Morquio patients and this affect on their gait pattern. Overall, although the presents study findings in gait parameter consider to be new, it should be interpreted with caution due to small size sample of Morquio patients.

Maroteaux-Lamy (MPS VI):

Table 3.14: Demographics data of Maroteaux-Lamy (MPS VI) patients.

Patient ID	Age at diagnosis (years)	Joint stiffness	Muscle weakness	Developmental delay	On medication
MPSVI1601	2	moderate	moderate	moderate	yes, at age 4
MPSVI1602	6	moderate	moderate	moderate	yes, at age 7

The findings of **stride length** in the present study showed that both Maroteaux-Lamy patients were at the lower range of the control"s range which indicates the normality of the stride length compare to control group. While, for the **stance %** one of them (MPS VI 1601) have a

very high stance % than control group. In the **single support %**, both Maroteaux-Lamy patients spend less percentage in than control group.

On the other hand, Maroteaux-Lamy patients have no different in both **cadence** and **stride width**. These outcomes could be as a result of joint stiffness and bone deformities which were found in patients with Maroteaux-Lamy disease (Giugliani et al., 2007; Quirino de Almeida-Barros et al., 2012).

Pompe:

Table 3.15: Demographics data of Pompe patient.

Patient ID	Age at diagnosis (years)	Joint stiffness	Muscle weakness	Developmental delay	On medication
14001	1	none	mild	none	yes, at age 2

In all the gait parameters, this patient was within the normal control range and mainly around the controls mean. This means that the patient was not different from healthy participants. That was because he started ERT in a very early stage and he didn‟t develop all of the Pompe patients‟ complications, yet. Moreover, ERT significantly improves motor development and it produces better outcomes (Chien et al., 2013). Although, one patient was participant in the present study, it is not enough to build a full argument or conclusion on it. However, it does approve that an earlier treatment intervention could help to achieve better results in Pompe patient. Without any early treatment intervention, could results in muscle imbalance. This in turn can influence on the gait pattern (Wood et al., 2009).

CHAPTER 4: BALANCE

4. Balance:

This chapter will present the methodology, results and discussion of balance data from patients with neurodegenerative disease and healthy controls. Firstly, I will explain the methodology used to measure balance in both groups. Then the results will be reported in 5 sections. The first section will report the balance results for controls only. The second, third and fourth sections will report the balance results for NP-C, Fabry and Hurler patients. The fifth section will report individual results from groups with limited numbers (Morquio, Maroteaux-Lamy and Pompe). Finally, these results will be discussed.

4.1. Balance Methodology:

4.1.1. Balance test procedure:

Our normal perception of balance during quiet standing is that no bodily movements occur. However, the postural system is continually making small adjustments to maintain the body‟s center of gravity over its base of support to prevent falling. Looking at a person who is standing quietly in view of a vertical background marker (e.g. the edge of a doorway) will show that they are constantly swaying slightly forward and backward (or left and right). The postural control system must sense when changes to posture are moving the body to an unstable position. Then, the system must program an effective response in order to bring the body back to a stable position. This can be divided into two stage: one senses when the body is in a stable or unstable position. The second stage adjusts, making any effective changes necessary to bring the body back to a stable position.

Body position is sensed using three primary systems. The first system is the visual system. This system works on sensing changes to optical flow based on nearby surfaces (Assländer & Peterka, 2014). The second system depends on a proprioceptive signal from muscle tension. The muscles in the back of the legs, for example will experience increased tension when the body sways forward. The increase in tension produces a proprioceptive signal, in the initial sensing stage, to adjust body posture. In the adjustment stage a response increases the tension of the back muscles of the thigh or calf and decreasing tension in the muscles at the front to tilt the body backward and bring it into upright alignment. The third system is the vestibular system, where signals from the inner ear senses changes to body position by using the semi-circular canals and otolith organs (Manor et al., 2010). The three systems sense changes independently, but their signals must be combined to produce a single effective response.

Signals from these three systems are combined by weighting. Weightings from each system can change in response to signal efficacy. If one system is impaired, it will provide inconsistent or insensitive input. This in turn will affect the weighting system by reducing it (Assländer & Peterks, 2014). Impairment to signals and re-weighting can be measured by removing a signal (e.g. by wearing a blindfold). This leaves the remaining combination of systems (including a system that may have been down-weighted because it is impaired) less able to compensate for the removal of a good signal. There will be a disproportionate effect of removing an upweighted signal in the impaired group. This allows changes to signal weightings to be measured (Assländer & Peterka, 2014).

In this study, the participants‟ balance during quiet standing was measured using accelerometers (APDM, Inc, ©2014) (see section 2.6.4, page 56). Briefly, accelerometers measure parameters related to sensing and control. In the present study, only RMS and jerk parameters were analyzed. RMS of the acceleration signal was measured as a proxy for sway area. The sway area is usually measured as the area spanned by movements around the COP.

An increase in the sway area is associated with instability and risk of falling (Mancini et al., 2011; Chen et al., 2018). Mancini et al. (2012) has established that RMS and sway area can both be used as an index of stability and are highly correlated.

The second parameter obtained was jerk. Jerk measures the smoothness of postural adjustments. A higher value of jerk indicates that adjustments are less smooth. In the present study, a time-normalized signal of jerk was used. That was done in order to compare data from participants who were engaged in quiet standing for different amounts of time. Sway and jerk were independent and associated with the two aspects of the control system that have been described: sensing the body‟s position and adjusting it to maintain stability.

In this study, the placement of the sensor was done by specialist physiotherapist. One sensor was applied to the participant‟s middle of the lower back at L5. Participants were asked to take off their shoes and stand still for 30 seconds with arms folded and feet apart at approximately shoulder width. While holding this position, 6 measurements were taken. Three measurements were taken with eyes open (EO; allowing visual, proprioceptive and vestibular signals) and three with eyes closed (EC) using a blindfold (allowing proprioceptive and vestibular, but no visual feedback). These test conditions were used to eliminate the contribution of visual system on balance control and, therefore, measure any impairment to the proprioceptive and/or vestibular signals. An impairment to the remaining signals is indicated by an abnormal difference between EO and EC conditions, which shows that the visual signal has been up-weighted in relationship to the other two. When participants‟ eyes were open, they were required to stare at a picture in front of them placed at approximately head level. All trials were videotaped for later analysis.

In the present study, overall RMS and jerk data were compared to the anterior-posterior and medio-lateral RMS and jerk data. Pilot testing showed that the anterior-posterior and medio-

lateral movements did not make different contributions to overall RMS and jerk data. Therefore, the present study reported only the overall RMS and jerk values.

4.1.2. Balance statistical analysis:

RMS and jerk for both conditions (EO and EC) were first cleaned and then filtered. Cleaning was done by using the video in combination with the accelerometer record, to check for any deviations from quiet standing (e.g. voluntary movement). For example, any clearly identifiable movement in the video record or clear corresponding spike in the acceleration record which could be identified as an extraneous movement in the video when it was checked, was cleaned and cut. This removes changes from the accelerometer signal that were large, but not due to postural adjustments. Examples of voluntary movement included participant moving their head to the side, shrugging their shoulders, moving their arms or hands in any direction, moving their legs or their feet or tapping their feet on the floor.

Similar to previous studies, acceleration signals were collected with a 50 Hz sampling frequency and filtered with a high pass butterworth filter with a cut-off frequency of 0.3 Hz (Barter, Castro, Sukharnikova, Rossi, & Yin, 2014; Martinez-Mendez, Sekine, & Tamura, 2012; Yelshyna et al., 2016). This was done to remove slow changes due to sensor drift, and a savitsky-golay filter with a polynomial of 3 and widow size of 11 to smooth fast changes (e.g. from tremor at rest) (Crenna, Rossi, Belotti, & Palazzo, 2015; Kosse, Caljouw, Vervoort, Vuillerme, & Lamoth, 2015; Press & Teukolsky, 1990). Filtering was done separately on sections where quiet standing was maintained, and parameters were calculated independently for each section before being combined into a time-weighted average.

The effect of group and condition were analyzed using linear mixed models. Main effects of group, condition and the group X condition interaction were assessed using likelihood ratios. A likelihood ratio chi-square egl af (G^2) and *p*-value were used to walh e w oead h e r l mo h er fe a crucial effect.

Other statistical analysis details related to identifying outliers, computing residuals, bootstrapping confidence intervals and calculating prediction intervals were described earlier in the method chapter (Chapter 2, section 2.7, p: 58).

4.2. Balance results and discussions:

In the following section, results from two balance parameters (RMS and Jerk) will be reported for the controls and the neurodegenerative disease patient groups. The numbers of the participants recruited are listed in Table 4.1.

Table 4.1: The number of controls and patients in both eye conditions:

Group	EC	EO
control	296	299
NP-C	12	13
Fabry	19	19
Hurler (MPS I)	5	6
Morquio (MPS IV)	1	1
Maroteaux-Lamy (MPS VI)	2	2
Pompe	1	1

4.2.1. Control group results:

RMS:

There were 36 outliers out of 1835 control RMS data (Figure 4.1). The best model for the mean as a function of height was asymptotic (constant ΔAIC = 970.63, linear ΔAIC = 384.8, quadratic ΔAIC = 178.31). Figure 4.1 shows that there was a high sway in younger control participants, which then decreases until participants reach 130 cm of height, after which RMS remains relatively stable.

There was a significant effect of age after the effect of height was accounted for (F value = 3.9; $p = 0.01$). An asymptotic function was the best function for age (constant ΔAIC = 4.15,

linear ΔAIC = 0.93, quadratic ΔAIC = 2.86). Residuals were calculated after effects of both height and age had been removed.

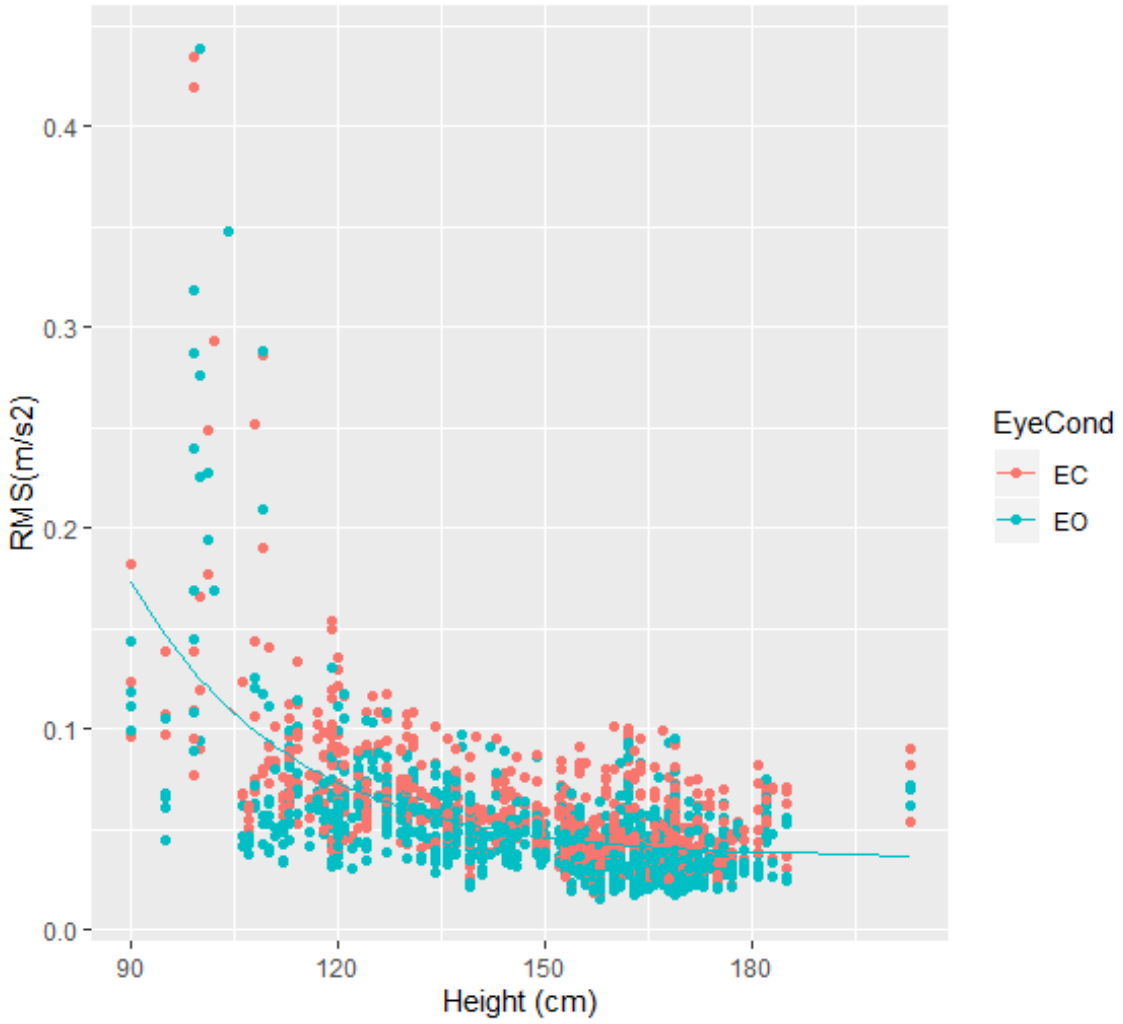


Figure 4.1: Control data without outliers for raw RMS in both eye conditions as a function of height. Green line is the fitted mean.

There was a significant effect of eye condition in control group ($G^2 = 164.7$; $p < 0.001$). RMS was higher in the EC condition (0.0045) than in EO condition (-0.0044), as expected. The CI for the EC/EO difference was between 0.006 and 0.011. The CI for the EC condition was between 0.002 and 0.009, and for the EO condition was between -0.006 and -0.0008.

Control predication intervals were calculated for each condition, so that patient values outside the control range could be identified. An asymptotic function was best for both the upper

cutoff (constant ΔAIC = 26.37, linear ΔAIC = 20.96, quadratic ΔAIC = 8.91) and the lower cutoff (constant ΔAIC = 24.71, linear ΔAIC = 18.16, quadratic ΔAIC = 6.25) in the EC condition (Figure 4.2).

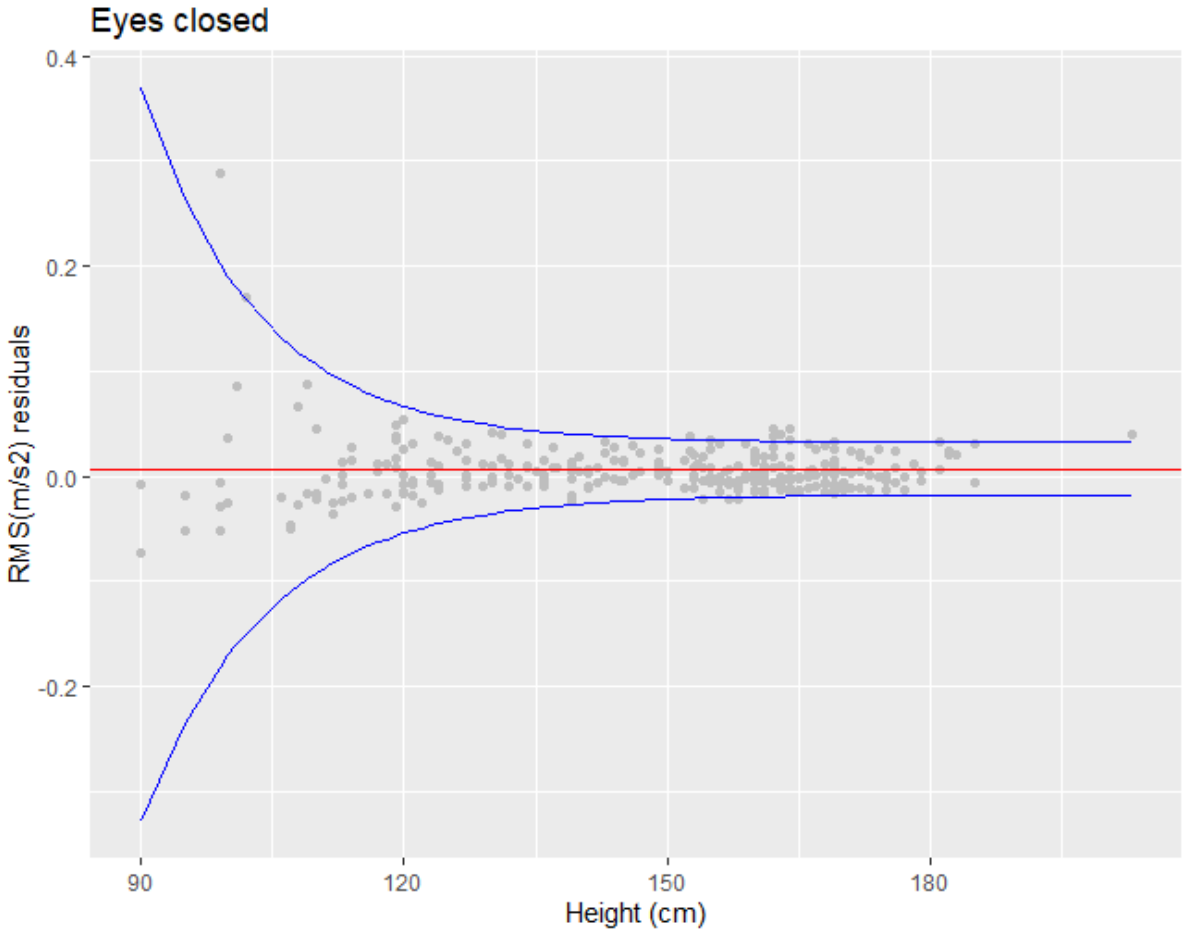


Figure 4.2: The upper and lower cut-offs (in blue) of 95% prediction intervals of control participant residuals in the EC condition.

Figure 4.3 showed an asymptotic function was also best for both the upper cut-off (constant ΔAIC = 20.93, linear ΔAIC = 15.57, quadratic ΔAIC = 5.3) and lower cut-off (constant ΔAIC = 18.27, linear ΔAIC = 12.87, quadratic ΔAIC = 1.14) in the EO condition.

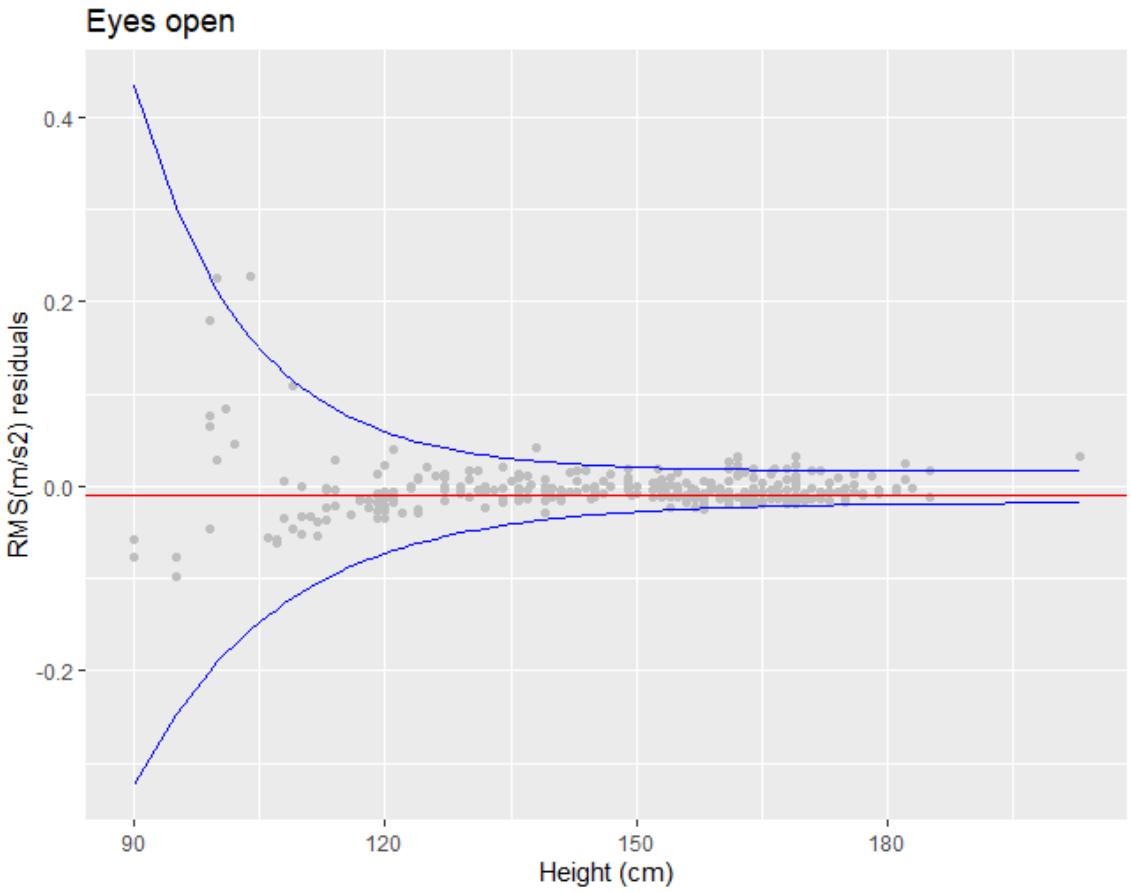


Figure 4.3: The upper and lower cut-offs (in blue) of 95% prediction intervals of control participant residuals in the EO condition.

Jerk:

There were 26 outliers out of 1835 control jerk data (Figure 4.4). The best function for the jerk mean was an asymptotic function of height (constant ΔAIC = 609.51, linear ΔAIC = 326.48, quadratic ΔAIC = 217.98). Figure 4.4 revealed that jerk was increased in younger participants, decreases until participants reach a height of about 130 cm, and then becomes more stable.

There was a significant effect of age after the effect of height was accounted for (F value = 5.1; p = 0.001). A quadratic function was the best function for age (constant ΔAIC = 6.26,

linear ΔAIC = 3.56, asymptotic ΔAIC = 4.13). The rest of the analysis was done using residuals after effects of height and age had been removed.

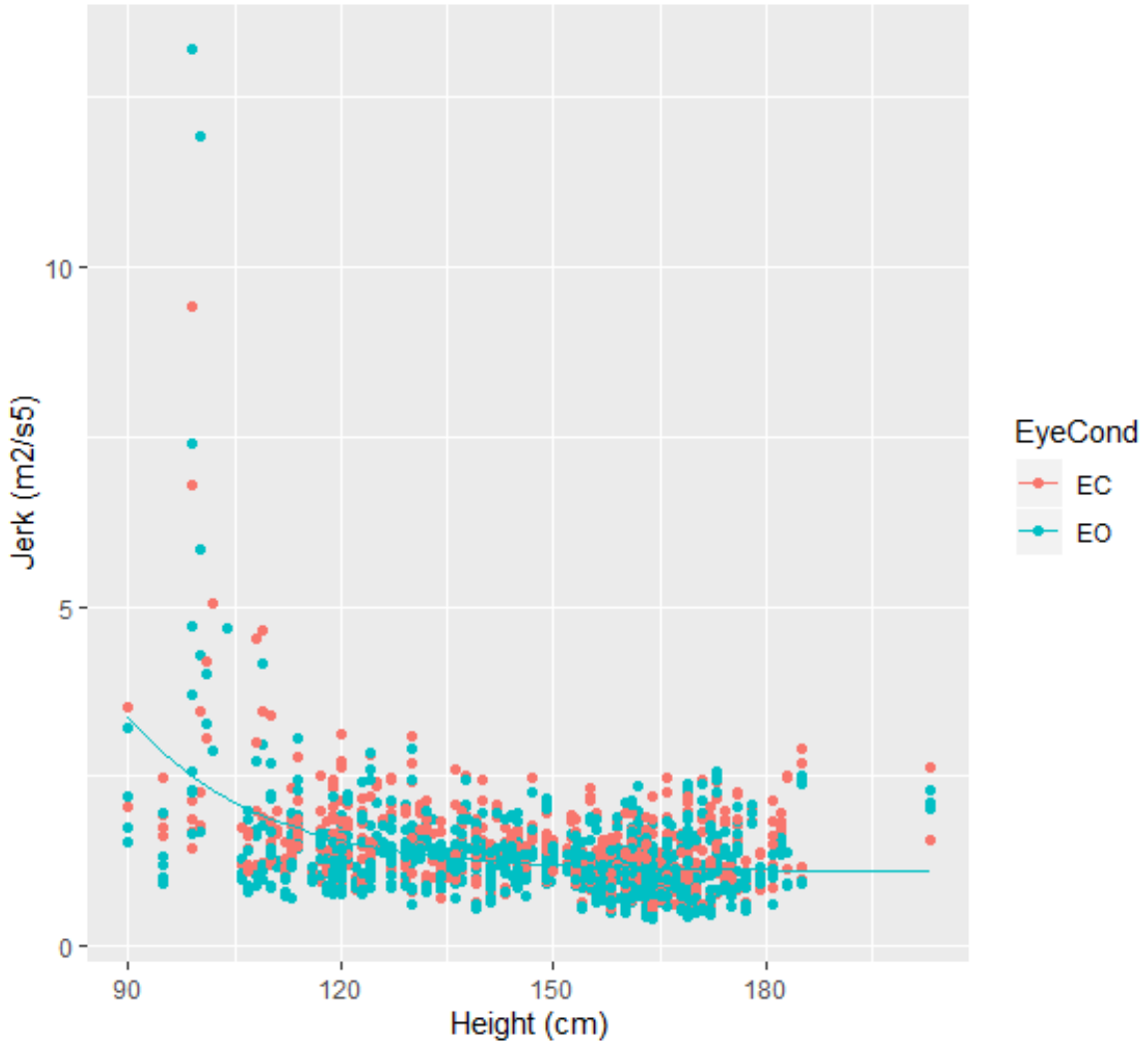


Figure 4.4: Control data without outliers for raw jerk in both eye conditions as a function of height. Green line is the fitted mean.

There was a significant effect of eye condition on jerk in the control group ($G^2 = 44.5$; $p < 0.001$). Jerk mean was higher in the EC condition (0.052) compared to the EO condition (-0.050). The CI for the EC/EO difference ranged between 0.02 and 0.13. The CI for the EC condition was between 0.007 and 0.1431, and for the EO condition between -0.10 and 0.11.

Prediction intervals were calculated for each condition, so that patient values outside the control range could be identified. For the EC condition, an asymptotic function was best for

both the upper cutoff (constant ΔAIC = 22.59, linear ΔAIC = 18.56, quadratic ΔAIC = 6.35), and the lower cutoff (constant ΔAIC = 23.43, linear ΔAIC = 19.03, quadratic ΔAIC = 3.92) (Figure 4.5).

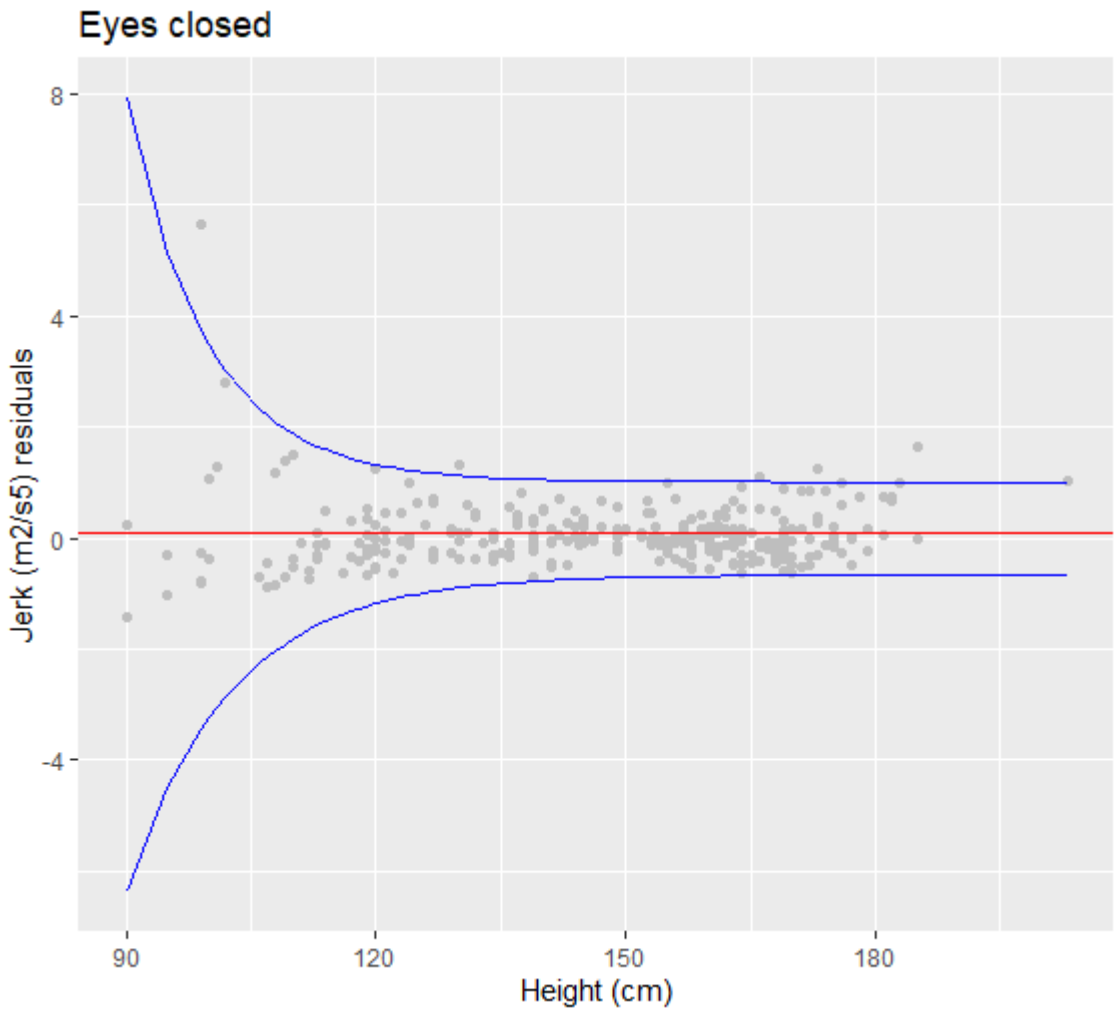


Figure 4.5: The upper and lower cut-offs (in blue) of 95% prediction intervals of control participant residuals in the EC condition.

For the EO condition, an asymptotic function was also best for both the upper cutoff (constant ΔAIC = 36.49, linear ΔAIC = 34.33, quadratic ΔAIC = 27.55) and the lower cutoff (constant ΔAIC = 36.01, linear ΔAIC = 32.59, quadratic ΔAIC = 22.21; Figure 4.6).

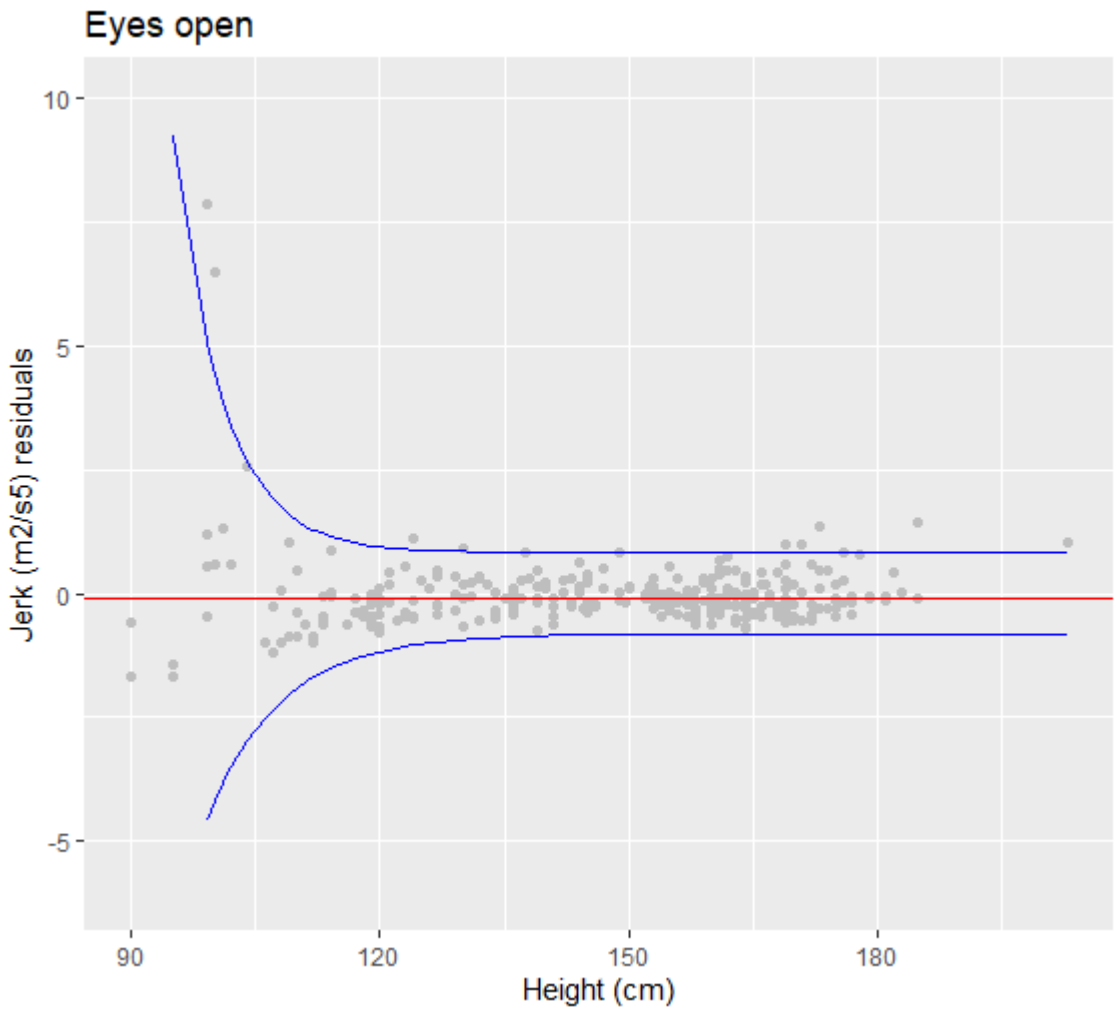


Figure 4.6: The upper and lower cut-offs (in blue) of 95% prediction intervals of control participant residuals in the EO condition.

4.2.2. Control group discussion:

To effectively measure balance changes in patients, it was necessary to characterize normal balance in a large group of healthy controls. I found that there was a significant effect of age and height in **RMS** data, with height and age increase, RMS data decrease. As expected, there was also a significant effect of asking participants to close their eyes on RMS. When participants close their eyes, this removes one source of information about subtle changes to body position during standing. Eyes closed participants have to depend only on the remaining proprioceptive and vestibular inputs and become more unstable. RMS values were higher in the EC condition compared to the EO condition. My findings were consistent with previous findings from Silfies et al.(2003) which were collected using a force plate. They examined the RMS during EC and EO in thirteen healthy participants. They found that RMS was increased significantly during the EC condition. Nolan et al. (2005) also reported that the RMS was significantly increased in an EC condition compared to an EO condition, specifically in boys (n = 90) compared to girls (n = 90) aged 9 to 16 years old. They found that during EO condition boys are using similar control strategy to girls to monitor sway, while during EC condition, they use different strategy to monitor sway (e.g. high sway velocity which is considered a ballistic corrections of COP). This indicates that visual system (normal weighting) has great impact on postural control. In general, Visual, vestibular and proprioceptive signals need to be combined to produce a reliable measure of when sway movements threaten to exceed the area where balance is maintained. Each signal is weighted to produce an overall signal and the change when one signal is removed is a measure of its influence on the combined signal (Assländer & Peterka, 2014).

Similar to RMS, jerk data had showed that there was an effect of age and height. Where the jerk decrease when age and height increase. There was also a significant effect of eye

condition in healthy participants, with higher jerk values in the EC condition compared to the EO condition. Jerk reflects the smoothness of adjustments to postural sway and the magnitude of the active postural correction. However, in previous studies jerk has been a measure that discriminates between patients and controls. One of these studies was done by Chen et al.(2018) with Parkinson‟s disease and compared them to healthy control group. They reported a small increase in jerk in their healthy controls in the EC condition compared to the EO condition (n = 23). However, this increase did not reach significance. Although the jerk data tend to be increase during EC condition in both of present study and Chen et al. (2018) study, the increase only reached significance in the present study. This is maybe due to the difference of the sample size in the present study (n = 296) and Chen et al study (n = 23). Nevertheless, both study findings agreed that jerk increase with EC condition compared to EO condition in healthy individual. This increase in jerk during EC condition was compensating the loss of the visual inputs in the static balance. In general, jerk has to do with the response to correct position. Clearly sensing position will change with EC condition. That is because people get closer to the "falling over" point due to sensing being poor and then have to correct more quickly. When that is happening higher jerk and higher sway go together. It is also possible, however, that the correction itself is controlled by feedback from vision and if this feedback is take away (in the EC condition) you could get higher jerk in the EC condition without higher jerk in the EO condition (Collins & De Luca, 1995; Lee & Aronson, 1974).

Generally, RMS and Jerk data obtain from accelerometers with healthy individuals in the present study are consistent with previous findings. In this study, however, there is a large group of controls from a range of ages, data are normalized for developmental changes and confidence and prediction intervals take into account changes in variance during

development, making our sample particularly useful for comparison with a sample from a patient population.

4.2.3. Patient groups results:

Similar to gait, we used a linear mixed model with a random term for participant to predict residuals from a model with an interaction between height and group. In balance, NP-C RMS EC showed more change with increasing height than controls. Therefore, there was some evidence of progression over time, but the change was from *more* stable performance than controls in shorter patients to around average performance in taller participants.
However, for all other parameters and in all other patient groups the interaction was not significant (all $p > 0.1$).

4.2.3.1. NP-C patients:

RMS:

In this section, the RMS data were tested in three conditions (group X eye condition interaction, group, and eye conditions) to determine the differences between the NP-C patients and the control group (Figure 4.7). There was no significant interaction between eye condition and group ($G^2 = 2.04$; $p = 0.15$). There was also no significant effect of group ($G^2 = 0.27$; $p = 0.59$). However, there was a significant effect of eye condition ($G^2 = 165.65$; $p < 0.001$) driven primarily by the control data. However NP-C patients were, on their own, still more unstable in the EC than the EO condition ($p = 0.019$).

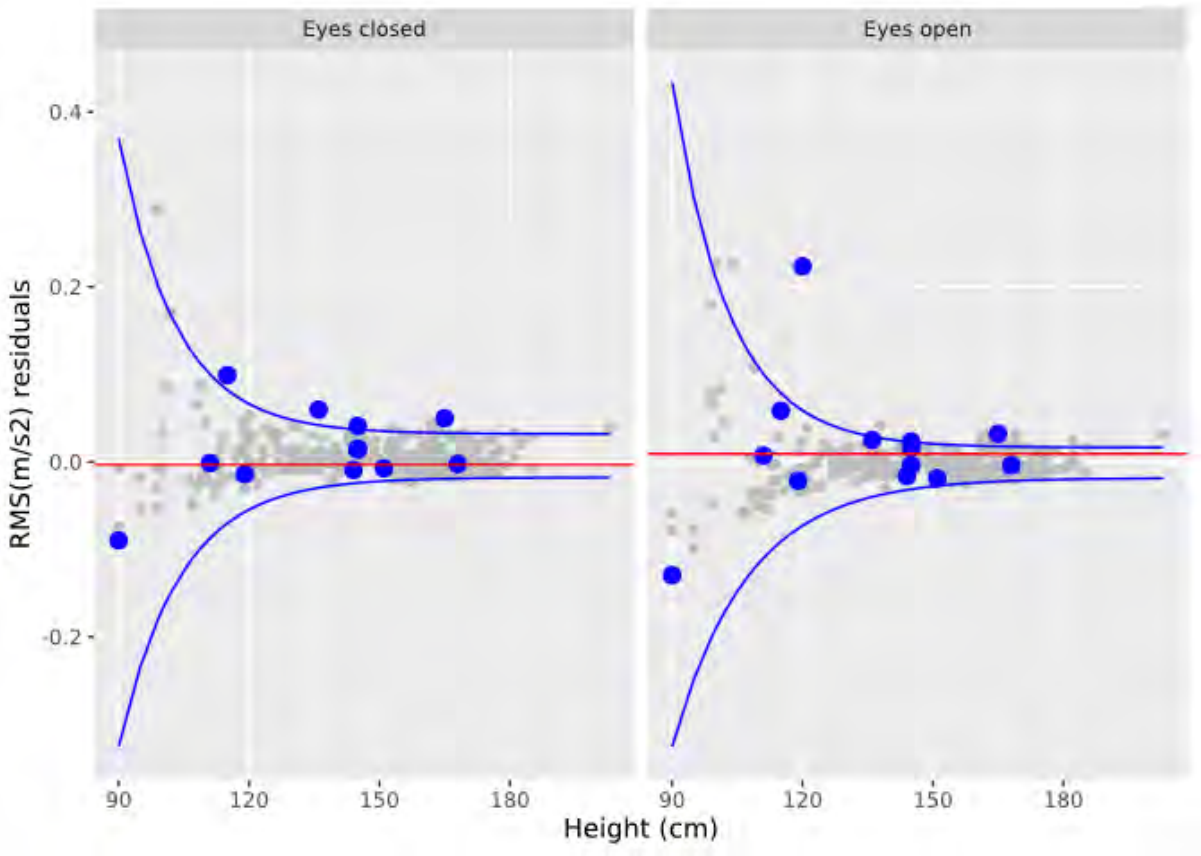


Figure 4.7: The upper and lower cut-offs (blue lines) of 95% prediction intervals of control participant residuals (grey dots) and NP-C patients (blue dots) in RMS EC and EO conditions.

Bootstrap samples of control data that were of the same size as the patient sample were used to set a control confidence interval that could be used to evaluate the patient mean. The patient mean for the EC/EO difference was within the 95% CI from controls (-0.002 - 0.025; Figure 4.8). The bootstrap analysis supports the earlier mixed model analysis that found no interaction between eye condition and group (bootstrap mean difference for patients = 0.016, and bootstrap mean difference for controls = 0.010). In the EC condition, the CI was between -0.006 and 0.033 (Figure 4.9). While in the EO condition, the CI was between -0.014 and 0.019 (Figure 4.10). Patient means were within these two control confidence intervals. Overall, there was no indication that RMS was abnormal in the NP-C group.

Table 4.2: Mean RMS residuals for controls and NP-C patients.

Eye Condition	Control	NP-C
EO	-0.0036	-0.0025
EC	0.005	0.013

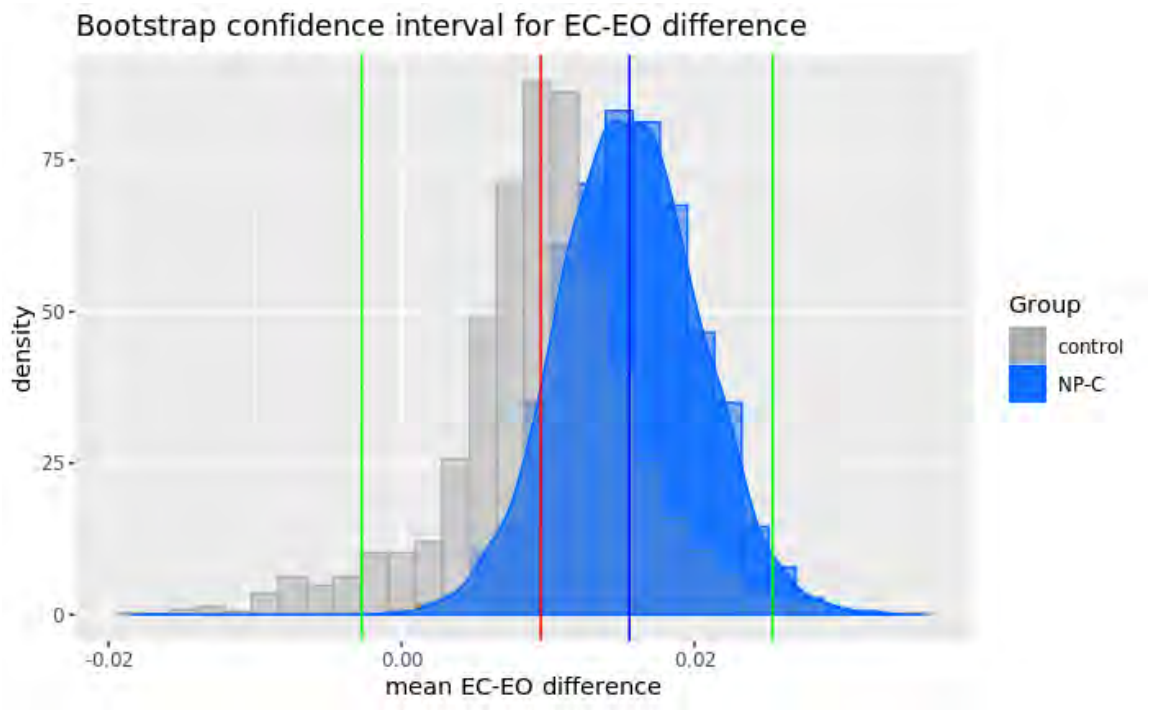


Figure 4.8: The distribution of bootstrap means for NP-C patients and controls in RMS EC/EO difference. Green lines are the control 95% confidence intervals. Red line is the control mean. Blue line is the patients mean.

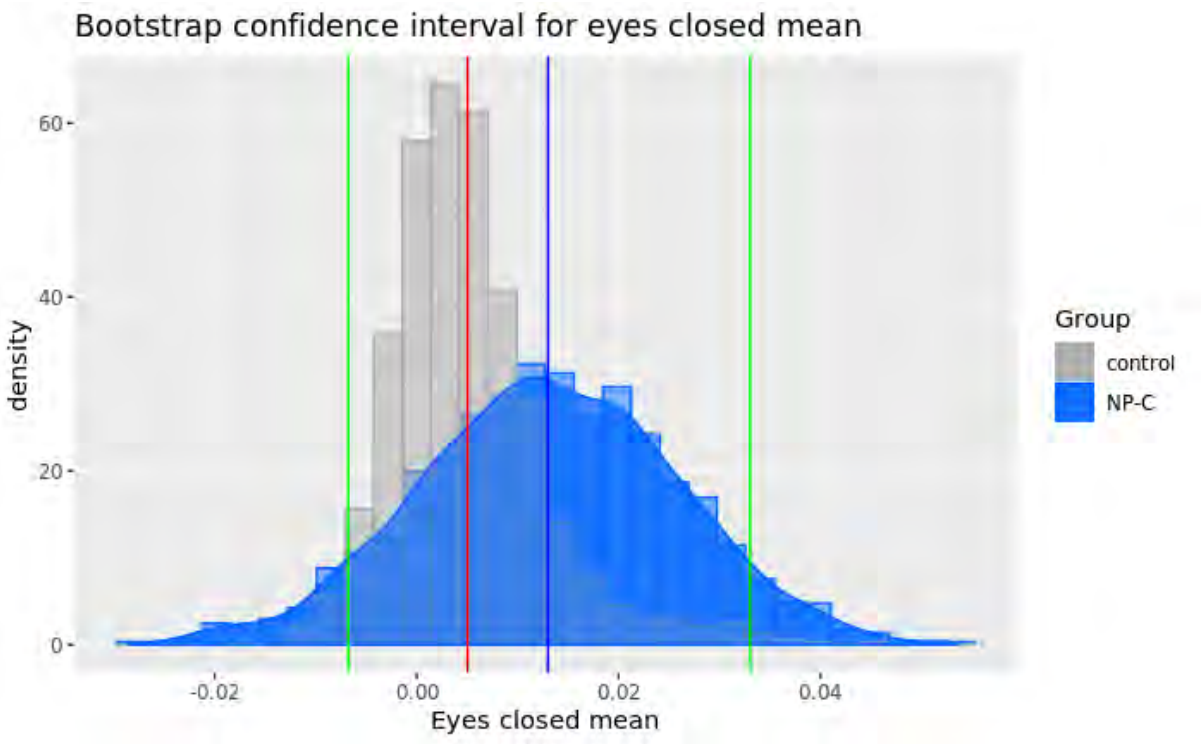


Figure 4.9: The distribution of bootstrap means for NP-C patients and controls in RMS EC condition. Green lines are the control 95% confidence intervals. Red line is the control mean. Blue line is the patients mean.

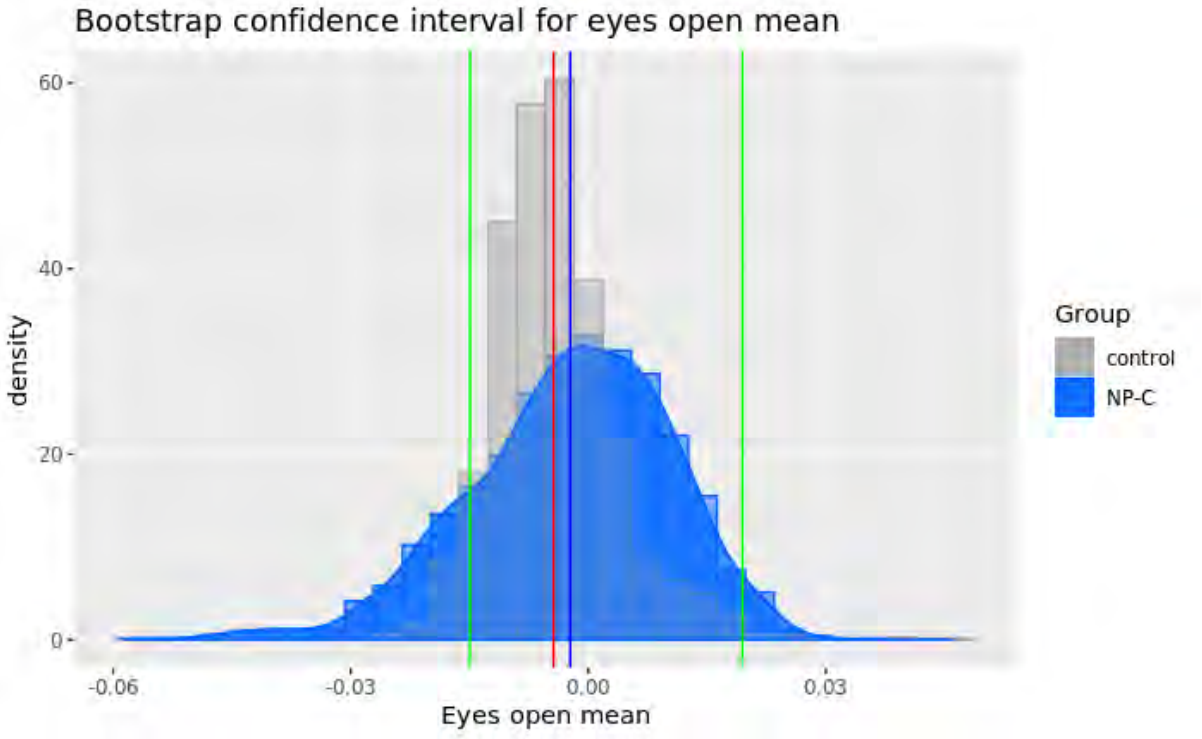


Figure 4.10: The distribution of bootstrap means for NP-C patients and controls in RMS EO condition. Green lines are the control 95% confidence intervals. Red line is the control mean. Blue line is the patients mean.

Jerk:

Jerk data showed that there was an interaction between group and eye condition ($G^2 = 5.3$; $p = 0.02$), and there was a main effect of eye condition ($G^2 = 50.7$; $p < 0.001$) (Figure 4.11). There was no significant effect of group ($G^2 = 0.73$; $p = 0.39$). NP-C patients showed a larger EC/EO difference than control group ($p < 0.001$), and they were more unstable in EC than in EO conditions (Table 4.3).

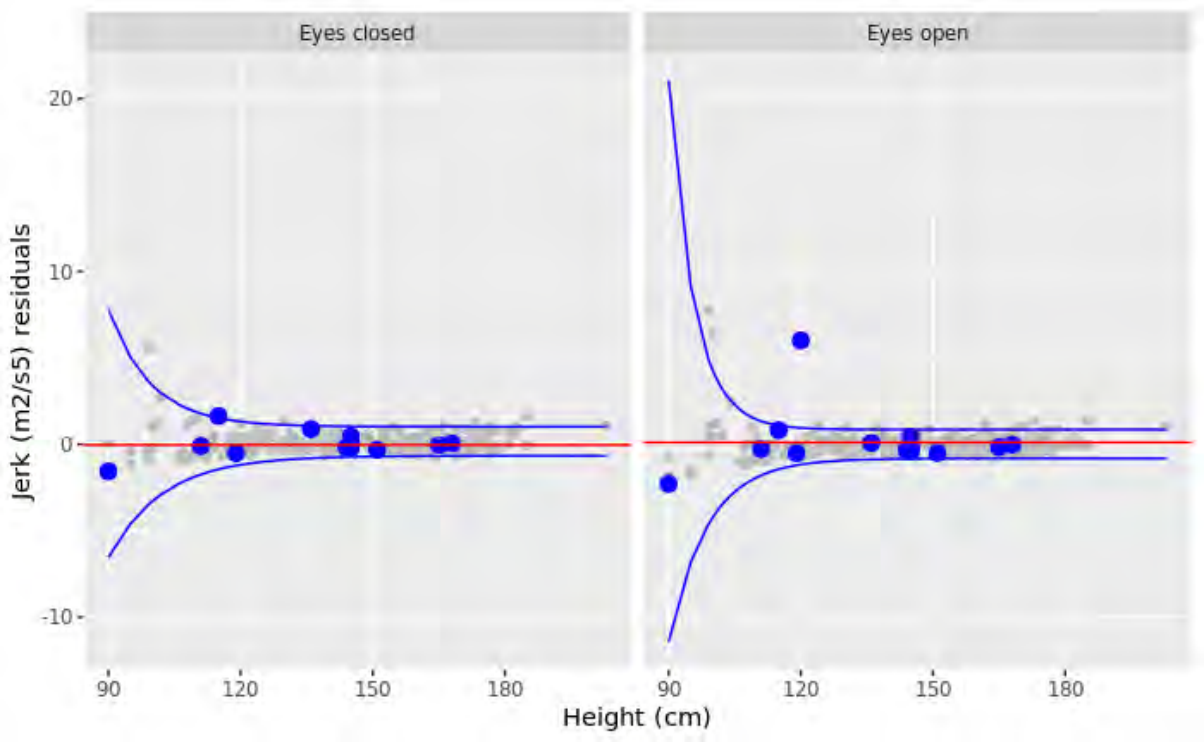


Figure 4.11: The upper and lower cut-offs (blue lines) of 95% prediction intervals of control participant residuals (grey dots) and NP-C patients (blue dots) in jerk EC and EO conditions.

Based on the bootstrap analysis, the 95% CI for the EC/EO difference in controls was between -0.262 and 0.289. The NP-C mean was outside these intervals (Appendix 4 Figure 4.A1). Therefore, there was a significant different between NP-C patients and control group in EC/EO difference, which it was higher in NP-C patients. The bootstrap mean difference for patients was 0.310, and bootstrap mean difference for controls was 0.099.

In the EC condition, the control CI was between -0.212 and 0.631 (Appendix 4 Figure 4.A2). While, the CI for the EO condition was between -0.315 and 0.705 (Appendix 4 Figure 4.A3). The bootstrap patient means were within these two confidence intervals. However, in EO the patient bootstrap mean (-0.28) was near to the lower boundary of the control CI, while in EC the patient bootstrap mean (0.017) was very similar to the control mean. This means that there was less jerk in patients than controls in the EO condition and about the same level of jerk in the EC condition, leading to a larger EO/EC difference, but not because of increased jerk in either of the eye conditions on their own. NP-C patients generally start off a bit more stable than controls with their eyes open, but then their stability increases abnormally when they close their eyes.

Table 4.3: Mean jerk residuals for controls and NP-C patients.

Eye Condition	Control	NP-C
EO	-0.041	-0.295
EC	0.034	0.016

In summary, NP-C balance results showed that for the RMS there was no interaction between group and eye condition. While, in jerk there was a significant interaction between the group and eye condition. Both RMS and jerk had a main effect of the eye conditions, and no significant main effect of group. With regards to eye conditions, RMS and jerk values showed that they were higher in EC than in EO condition in NP-C patients. There was no evidence that NP-C affected RMS, but the EC/EO difference in jerk was larger for NP-C patients, based on starting from a more stable EO baseline. This could indicate an impaired response to balance changes in NP-C without impairment to sensing the changes themselves.

4.2.3.2. Fabry patients:

RMS:

RMS data showed that there was no significant interaction between group and eye condition in Fabry patients ($G^2 = 0.31$; $p = 0.57$) (Figure 4.12). Moreover, there was no main effect of group ($G^2 = 0.002$; $p = 0.96$). However, there was a main effect of eye conditions ($G^2 = 179.15$; $p < 0.001$). Both groups have higher RMS in the EC condition compared to EO condition (Table 4.4).

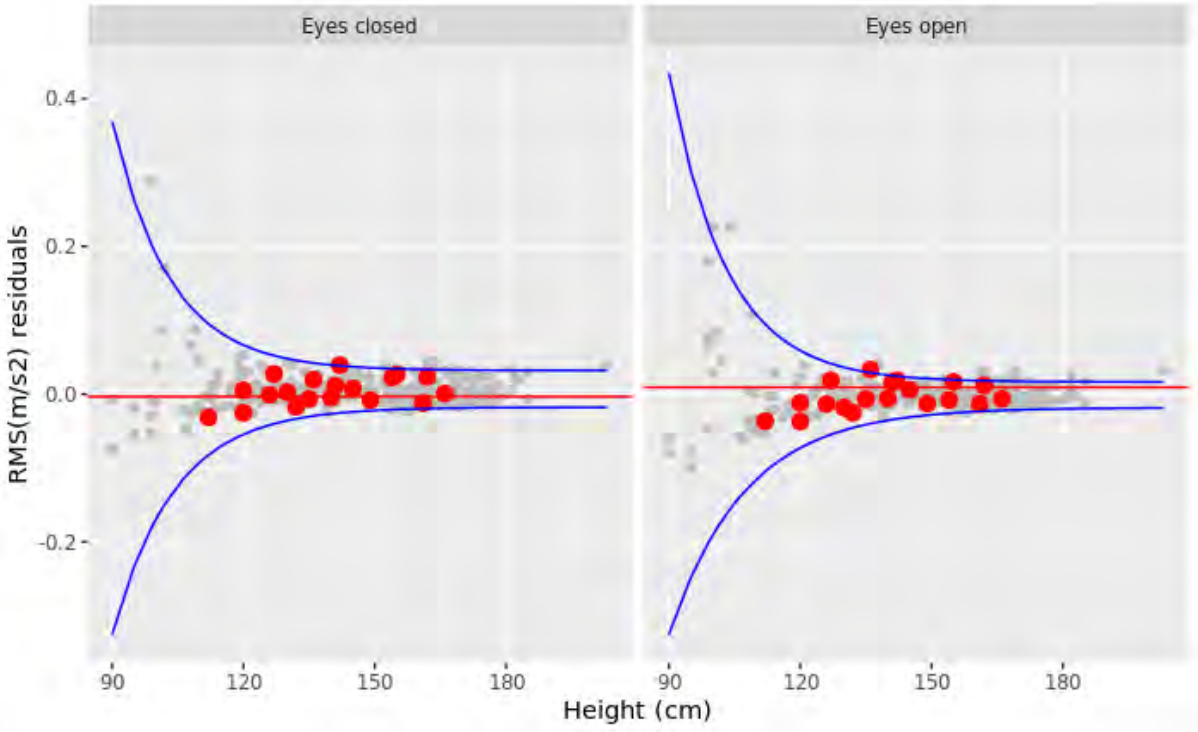


Figure 4.12: The upper and lower cut-offs (blue lines) of 95% prediction intervals of control participant residuals (grey dots) and Fabry patients (red dots) in RMS EC and EO conditions.

The control group 95% confidence interval for the EO/EC difference was between -0.005 and 0.018. The bootstrap mean difference for patients was 0.008, and bootstrap mean difference for controls was 0.009. Bootstrap and mixed model analyses agreed that there was no abnormal EC/EO difference in Fabry patients (Appendix 4 Figure 4.B1). The CI for the EO

condition was -0.013 - 0.011 and the CI for the EC condition was -0.003 - 0.027. Fabry bootstrap means for EO was (-0.004) and for EC was (0.0039) and they were always within the control confidence intervals. There was no evidence that RMS was different in the Fabry group (Appendix 4 Figure 4.B2 and 4.B3).

Table 4.4: Mean RMS residuals for controls and Fabry patients.

Eye Condition	**Control**	**Fabry**
EO	-0.0042	-0.0038
EC	0.0047	0.0042

Jerk:

Jerk data revealed that there was no significant interaction between group and eye condition ($G^2 = 0.12$; $p = 0.72$) (Figure 4.13). Moreover, there was no effect of group ($G^2 = 0.43$; $p = 0.51$). There was, however, a main effect of eye condition ($G^2 = 48.15$; $p < 0.001$). Table 4.5 shows that Fabry values in EC condition were numerically lower, not higher, than controls, but these were not statistically reliable differences. The Fabry EC/EO difference was similar to controls ($p = 0.08$), and both groups showed larger jerk in EC compared to EO.

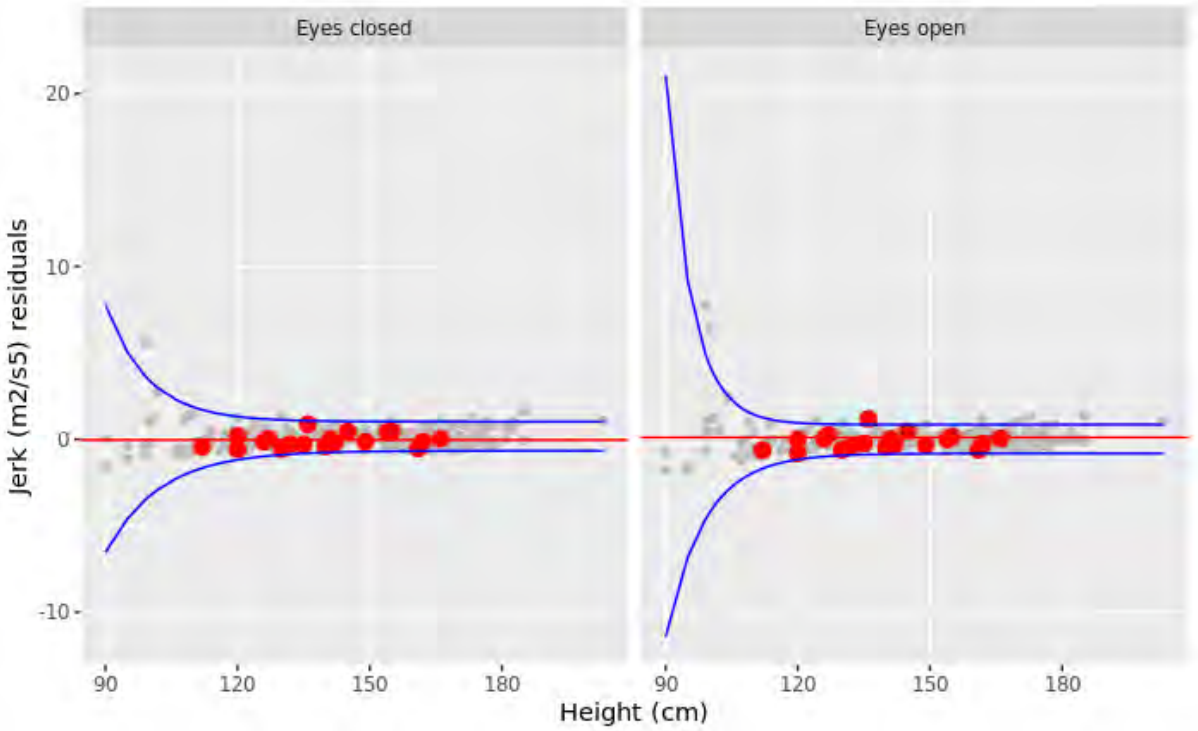


Figure 4.13: The upper and lower cut-offs (blue lines) of 95% prediction intervals of control participant residuals (grey dots) and Fabry patients (red dots) in jerk EC and EO conditions.

The control bootstrap CI for the EC/EO difference was -0.19 - 0.24, and the patient mean was within this interval (Appendix 4 Figure 4.B4) indicating no abnormality in EO/EC differences. The bootstrap mean difference for Fabry patients was 0.08 and bootstrap mean difference for controls was 0.100. Regarding the eye conditions, the CI for the EC condition was -0.14 - 0.45(Appendix 4 Figure 4.B5), and the CI for the EO condition was -0.26 - 0.53

(Appendix 4 Figure 4.B6). Fabry bootstrap means in EC was (-0.07) and in EO was (-0.12) and they were always inside the control confidence intervals, indicating that there were no significant differences between Fabry patients and controls in jerk values.

Table 4.5: Mean jerk residuals for controls and Fabry patients.

Eye Condition	Controls	Fabry
EO	-0.041	-0.185
EC	0.085	-0.054

In general, Fabry patients‟ data in both RMS and jerk have the same results. These data showed there was no interaction between group and eye condition nor any main effect of group. There was, instead, a normal main effect of eye condition. Overall, these results showed that balance did not differ from controls in Fabry patients.

4.2.3.3. Hurler patients (MPS I):

RMS:

RMS data showed no interaction between group and eye condition ($G^2 = 0.71$; $p = 0.39$) in Hurler patients compared to controls. There was, however, a main effect of group ($G^2 = 63.99$; $p < 0.001$), and a main effect of eye condition ($G^2 = 87.56$; $p < 0.001$) (Figure 4.14). In general, Hurler patients were more unstable than controls (Table 4.6). However, there was no evidence that Hurler patients had a greater EC/EO difference ($p = 0.34$). Interpretation of these effects, however, should be cautious because of the small number of patients (note jagged patient distributions in the bootstrap analyses).

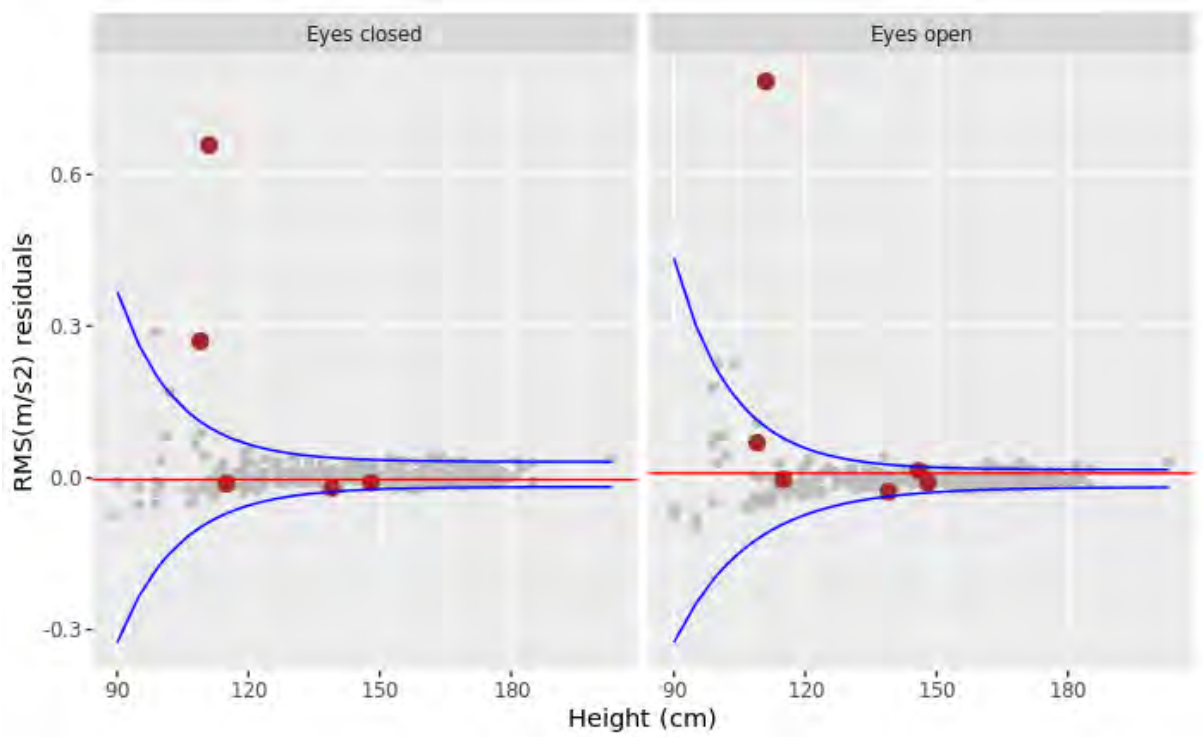


Figure 4.14: The upper and lower cut-offs (blue lines) of 95% prediction intervals of control participant residuals (grey dots) and Hurler patients (brown dots) in RMS EC and EO conditions.

In the bootstrap analysis, the control group CI for the EC/EO difference ranged between -0.009 to 0.053, and the control and patient means were within these intervals. The bootstrap mean difference for Hurler patients was 0.016, and bootstrap mean difference for control

group was 0.009. In the eye conditions, the CI for the EO condition was (-0.023 – 0.036) and the CI for the EC condition was (-0.015 - 0.083). Although, there were very limited sample in this group, these intervals showed that there was no indication that EC/EO difference was abnormal (Appendix 4 Figure 4.C1). However, EC values (Appendix 4 Figure 4.C2), and EO values (Appendix 4 Figure 4.C3) were significantly different (both of their CI were wide to be meaningful).

Table 4.6: Mean RMS residuals for controls and Hurler patients.

Eye Condition	Control	Hurler
EO	-0.0041	0.176
EC	0.0051	0.185

Jerk:

In the mixed model analysis was a significant interaction between group and eye condition ($G^2 = 8.68$; $p = 0.003$). There was also a significant effect of group ($G^2 = 69.26$; $p < 0.001$), and a main effect of eye condition ($G^2 = 14.85$; $p < 0.001$). Table 4.7 showed that Hurler patients‟ EC/EO difference was larger than controls, but there were a small number of patients and results were dominated by one high value (Figure 4.15). Therefore, there was no significant EC/EO difference ($p = 0.10$).

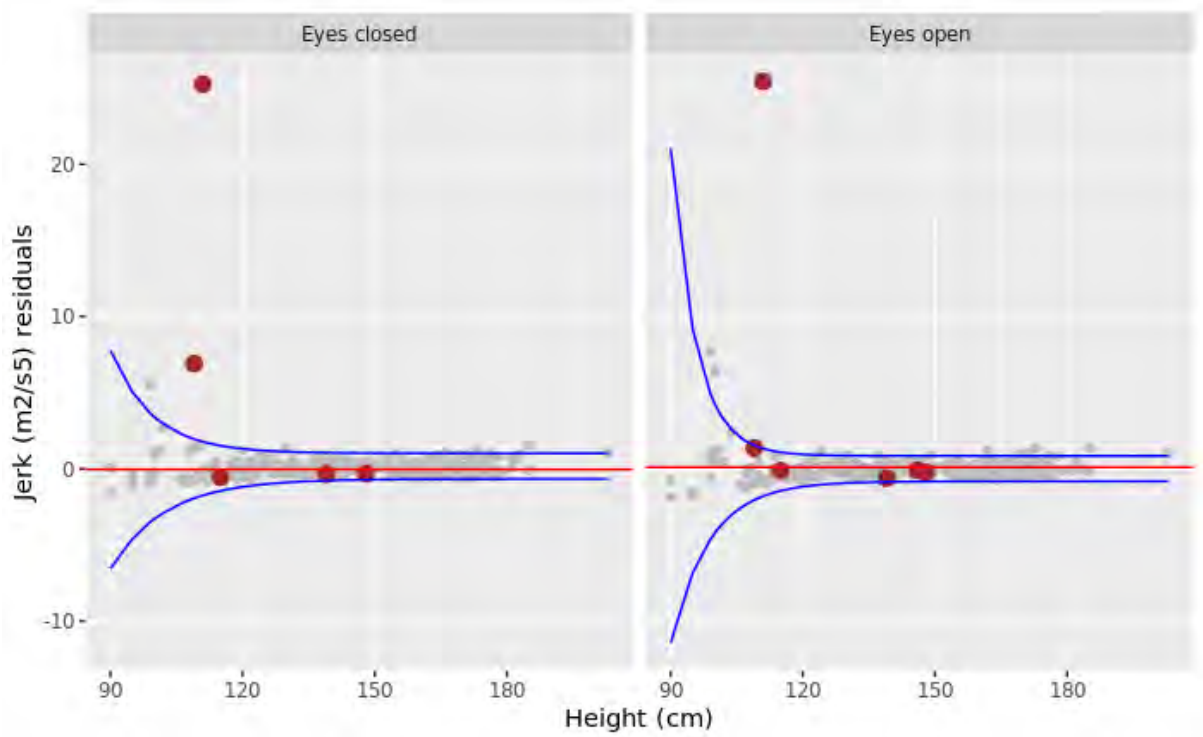


Figure 4.15: The upper and lower cut-offs (blue lines) of 95% prediction intervals of control participant residuals (grey dots) and Hurler patients (brown dots) in jerk EC and EO conditions.

With regards to the EC/EO difference, the control group CI ranged from -0.53 to 0.57 (Appendix 4 Figure 4.C4). The patient mean was outside this interval. The bootstrap mean difference for Hurler patients was 1.083, while the bootstrap mean difference for the control group was 0.091. The control CI for the EC condition was -0.36 – 1.22 (Appendix 4 Figure 4.C5), and the CI for the EO condition was -0.53 – 1.54 (Appendix 4 Figure 4.C6). Patients

means for the EC was (6) and for the EO was (5.1) and they were outside these intervals. As for RMS, jerk was higher in patients. This time, however, there was also a larger EO/EC difference. The same caution about interpreting these effects due to the small number of Hurler patients applies to the jerk result and is amplified by some extreme values. Results from more patients would be necessary to have stable estimates for the Hurler group as a whole. In a larger sample the extreme values might occur relatively rarely or more frequently to change the interpretation of how Hurler affects balance mechanisms.

Table 4.7: Mean jerk residuals for controls and Hurler patients.

Eye Condition	Control	Hurler
EO	-0.031	5.16
EC	0.024	6.19

In conclusion, Hurler patients had higher RMS than controls, but no abnormal weighting of the visual signal. Jerk values higher in both eye conditions but the difference between conditions was also larger. On the surface, this suggests more instability but no change in weighting and an exaggerated response to sway that does depend more on a visual signal. Generally, however, there is substantial uncertainty about how these values represent the Hurler population as a whole. Three patients were similar to controls and two had higher jerk. One patient had an exaggerated EC\EO difference and this patient was also much more unstable in the EC condition. In such a small sample, extreme points, which may not be representative in the population have an exaggerated influence. We have a preliminary indication that balance is affected in at least some Hurler patients, but a good understanding of whether these changes are widespread will require data from more participants.

4.2.3.4. Morquio (MPS IV), Maroteaux- Lamy (MPS VI), and Pompe:

RMS:

There were only few patients tested in each of the groups Morquio, Maroteaux-Lamy and Pompe. Therefore, no group comparisons were possible. The S-score was measured to check how many patients were outside the control 95% prediction interval for the EC condition (Table 4.8 and 4.9) and the EO (Table 4.10 and 4.11) condition. A number of patients did not want to complete the EC condition. The patients reported that it was difficult, and they were afraid to perform it. Figure 4.25 shows the RMS data from both eye conditions. The Morquio and Pompe patients had RMS values outside the control range in both eye conditions and the RMS value was even more extreme in the EC condition than the EO condition. Maroteaux-Lamy patients were closer to the control range. One of the Maroteaux-Lamy patients was within the control range, while the other patient was just outside the control range in both eye conditions.

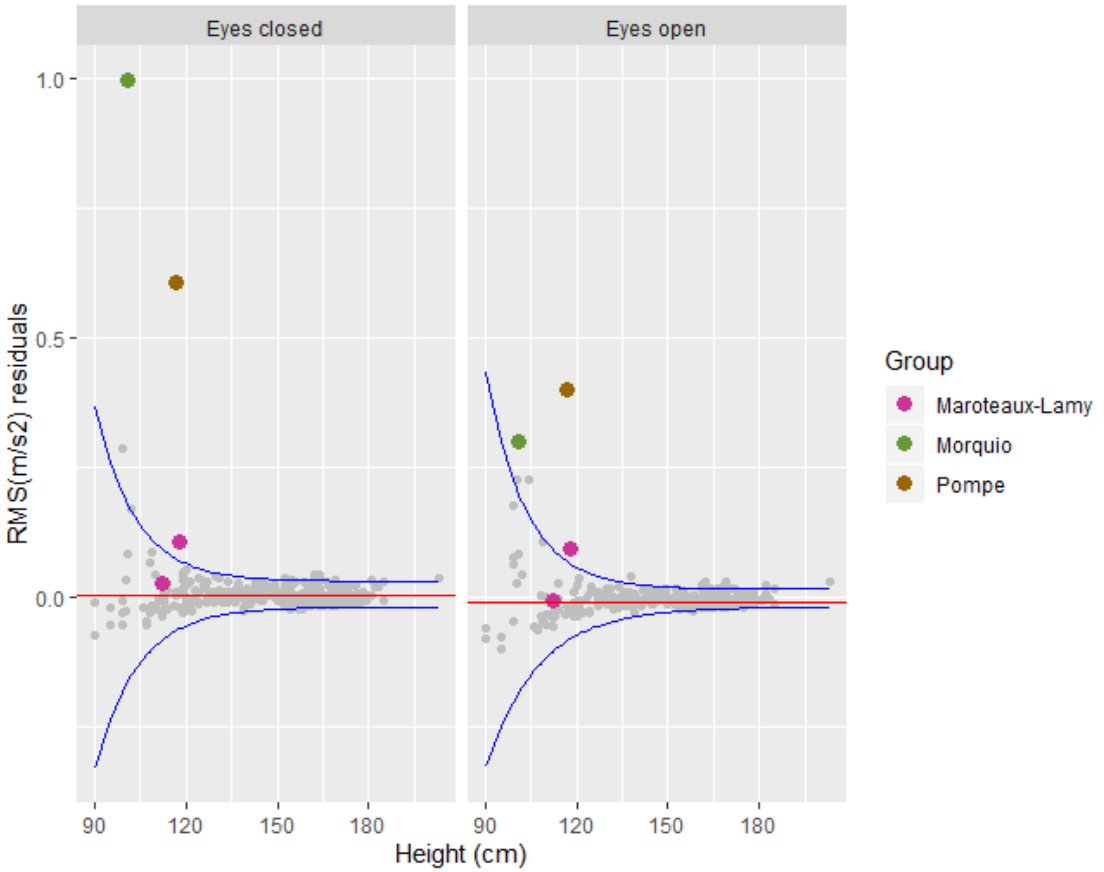


Figure 4.16: RMS residuals for Morquio, Maroteaux-Lamy and Pompe patients and control group (grey dots) in EO and EC conditions. Blue lines are the upper and lower cut-offs for 95% prediction intervals for controls.

Table 4.8: The S-score for all the patients outside the control range in RMS EC condition.

PID	Group	Age (Years)	Height (cm)	S-score
Fabry_50003	Fabry	9	142	2.004508
MPSI_10005	Hurler	6	111	12.84339
MPSI_10010	Hurler	6	109	4.750127
MPSVI_16002	Maroteaux-Lamy	8	118	2.931256
MPSIV_30009	Morquio	14	101	10.9558
NPC_NPC06	NP-C	12	145	2.173042
NPC_NPC07	NP-C	17	165	2.973151
NPC_NPC09	NP-C	6	115	2.355673
NPC_NPC13	NP-C	9	136	2.777047
Pompe_14001	Pompe	6	117	15.83208

Hurler: MPS I, Maroteaux-Lamy: MPS VI, Morquio: MPS IV, NP-C: Niemman pick type C, PID: participant identification.

Table 4.9: The number of patients outside and inside the control range in RMS EC condition.

Patients group	Number of patients (outside/inside)
NP-C	4/12 patients
Fabry	1/19 patients
Hurler	2/5 patients
Morquio	1/1 patient
Maroteaux-Lamy	1/2 patients
Pompe	1/1 patient

Table 4.10: The S-score for all the patients outside the control range in RMS EO condition.

PID	Group	Age (Years)	Height (cm)	S-score
Fabry_50007	Fabry	9	136	2.241326
MPSI_10005	Hurler	6	111	15.23655
MPSVI_16002	Maroteaux-Lamy	8	118	2.812246
MPSIV_30009	Morquio	14	101	2.976484
NPC_NPC03	NP-C	10	145	2.839155
NPC_NPC04	NP-C	8	120	7.433488
NPC_NPC07	NP-C	17	165	3.579524
Pompe_14001	Pompe	6	117	11.26309

Hurler: MPS I, Maroteaux-Lamy: MPS VI, Morquio: MPS IV, NP-C: Niemman pick type C, PID: participant identification.

Table 4.11: The number of patients outside and inside the control range in RMS EO condition.

Patients group	Number of patients (outside/inside)
NP-C	3/13 patients
Fabry	1/19 patients
Hurler	1/6 patients
Morquio	1/1 patient
Maroteaux-Lamy	1/2 patients
Pompe	1/1 patient

Jerk:

The pattern for jerk data was similar to RMS (Figure 4.26). S-scores are reported for the EC condition in Table 4.12 and 4.13 and, for the EO condition in Table 4.13 and 4.14. Both the Morquio patient and the Pompe patient have higher jerk values than controls and EC is more different than EO condition. Maroteaux-Lamy values were less different, with one jerk value within the control range, and the other just above the border of the control range.

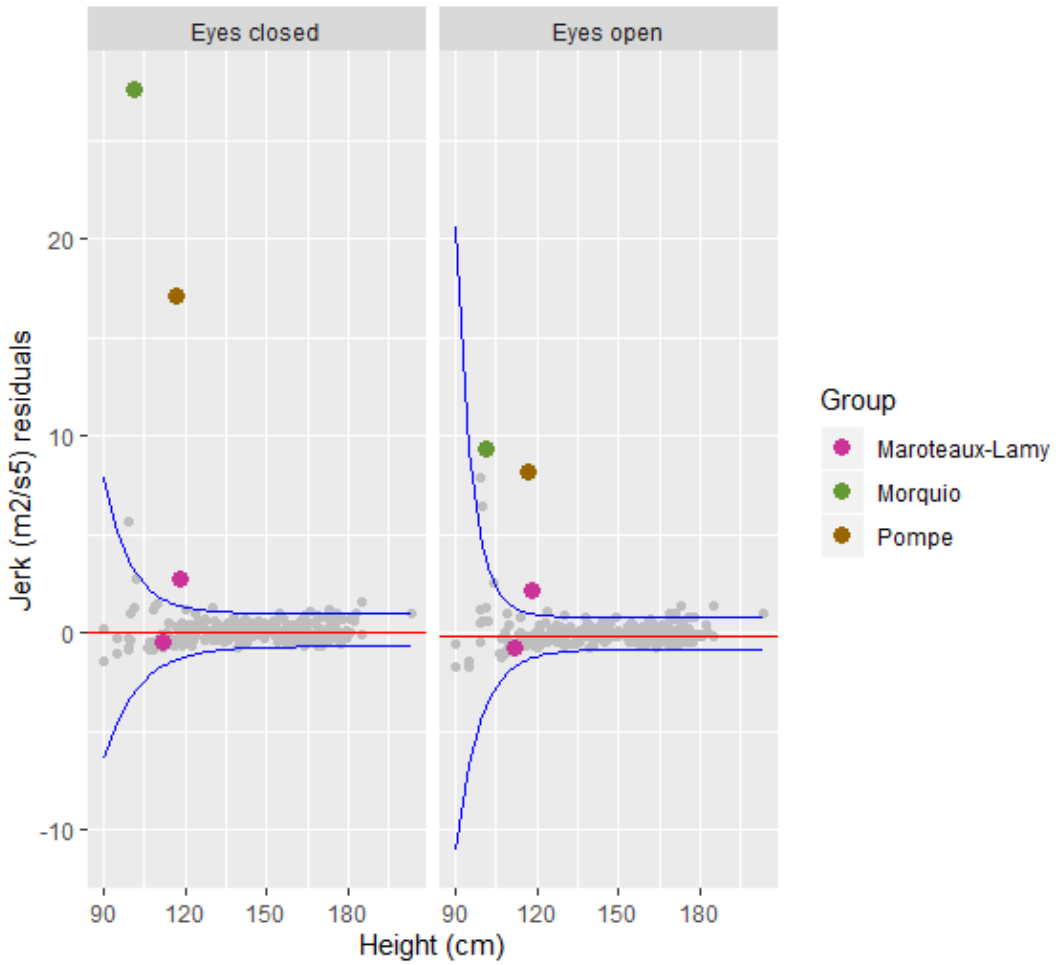


Figure 4.17: Jerk residuals for Morquio, Maroteaux-Lamy and Pompe patients and control group (grey dots) in EO and EC conditions. Blue lines are the upper and lower cut-offs for 95% prediction intervals for controls.

Table 4.12: The S-score for all the patients outside the control range in jerk EC condition.

PID	Group	Age (Years)	Height (cm)	S-score
MPSI_10005	Hurler	6	111	27.43916
MPSI_10010	Hurler	6	109	6.844048
MPSVI_16002	Maroteaux-Lamy	8	118	3.836891
MPSIV_30009	Morquio	14	101	16.68683
NPC_NPC09	NP-C	6	115	2.124223
Pompe_14001	Pompe	6	117	23.27511

Hurler: MPS I, Maroteaux-Lamy: MPS VI, Morquio: MPS IV, NP-C: Niemman pick type C, PID: participant identification.

Table 4.13: The number of patients outside and inside the control range in jerk EC condition.

Patients group	Number of patients (outside/inside)
NP-C	1/12 patients
Hurler	2/5 patients
Morquio	1/1 patient
Maroteaux-Lamy	1/2 patients
Pompe	1/1 patient

Table 4.14: The S-score for all the patients outside the control range in jerk EO condition.

PID	Group	Age (Years)	Height (cm)	S-score
Fabry_50007	Fabry	9	136	2.723268
MPSI_10005	Hurler	6	111	36.29959
MPSVI_16002	Maroteaux-Lamy	8	118	4.271004
MPSIV_30009	Morquio	14	101	4.767226
NPC_NPC04	NP-C	8	120	12.40333
Pompe_14001	Pompe	6	117	15.6215

Hurler: MPS I, Maroteaux-Lamy: MPS VI, Morquio: MPS IV, NP-C: Niemman pick type C, PID: participant identification.

Table 4.15: The number of patients outside and inside the control range in jerk EO condition.

Patients group	Number of patients (outside/inside)
NP-C	1/13 patients
Fabry	1/19 patients
Hurler	1/6 patients
Morquio	1/1 patient
Maroteaux-Lamy	1/2 patients
Pompe	1/1 patient

In summary, RMS and jerk values from a single Morquio patient and a single Pompe patient were higher than control values in both eye conditions. In both cases, the difference from controls was larger in the EC condition than the EO condition. These results suggest increased reliance on the visual signal due to potential sensory reweighting in these patients. On the other hand, Maroteaux-Lamy RMS and jerk values were much closer to the control range. In both eye conditions one patient was within the control range while the other was just above the upper cut-off of the control range.

4.2.4. Patients groups discussion:

Balance is a very vital practical feature for maintaining stability when participants are not moving, but balance control will also influence stability during motion. By tracking variations in participants‟ balance, strong indications about the effectiveness of rehabilitation on physical function can be obtained (Dault, de Haart, Geurts, Arts, & Nienhuis, 2003). It is well established that some patients with neurodegenerative diseases had abnormal balance and postural control. This, in turn, can affect the gait pattern of these patients (Sansare et al., 2018). The balance control has not previously been investigated in these types of disease before. The rarity of these diseases makes it difficult to document changes to balance parameters. This thesis documented balance changes in neurodegenerative patients and compared them to a healthy matched group in order to quantify changes to sway area (via RMS) and changes to postural adjustment mechanisms (via jerk). By comparing EO and EC conditions it was possible to determine whether the visual input to balance control had been given increased importance in comparison to proprioceptive and vestibular inputs due to sensory reweighting.

A) NP-C:

The **RMS** data showed that there was no significant interaction between group and eye condition. Moreover, there was no significant effect of the group. However, in eye conditions, the RMS data showed that there was an effect on sway in NP-C patients. In general, RMS was higher in both eye conditions in NP-C patients compared to control group. This was observed in details in EC condition, where RMS value was higher than EO condition in NP-C patients, but still all sway conditions were within the CI for control group. The present findings are in some parts agreed with Sansare et al. (2018) study, who measured

balance in NP-C (n = 10) and compared it with matched control group (n = 15). They found that, during quiet stance on a firm surface, NP-C patients swayed significantly more than controls in both eye conditions. Also, they found that as disease severity increased, postural instability increased too in both eye conditions. When they compared EC condition to EO condition, they found that the EC condition showed more postural sway than the EO condition. Sansare et al. (2018) suggested this happened due to the impaired use of proprioceptive inputs for postural stability in NP-C patients. Moreover, these findings was also reported by Chen et al. (2018) who found that PD patients had mild increase in RMS compared to control group in both eye conditions. Also, they reported that during EC conditions, the RMS was higher than EO condition in PD patients. Although PD caused traditionally by dysfunction of basal ganglia, recent evidence suggest involvement of cerebellum is pathological in Parkinson (Di Biasio et al., 2015; Mirdamadi, 2016). In NP-C patients the cerebellum is affected (Walterfang, Abel, et al., 2013) (section:1.2.1, p: 4). Dysfunction of the cerebellum is associated with impairment of pure motor control (Blakemore, Frith, & Wolpert, 2001; Miall & Jenkinson, 2005). Moreover, dysfunction of the cerebellum can affect the feedback mechanism that required for maintain and adjust the static and dynamic posture (Yanagihara, 2014).

With regards to **jerk** data, finding of the present study revealed that there was an interaction between group and eye condition, but no main effect of group. There was a significant main effect of eye condition, with EC producing higher jerk. NP-C patients showed a larger difference between EO and EC, without having higher overall jerk. This was because they were less jerky than controls (at the lower margin of the control range) with eyes open and then at the same level as controls with eyes closed, producing a larger difference. Unfortunately, there is no studies investigated jerk in NP-C patients, yet. On the other hand,

there were some studies conducted on patient that share similar disease pathological to NP-C, which is PD. One of these studies done by Chen et al. (2018) examined the balance control with PD and compared them with control group. They found that PD patients had a higher jerk compared to control group in both eye conditions. Furthermore, they reported that jerk was higher in the EC condition compared to EO condition in PD patients and control group. In Chen study Parkinson‟s have higher sway as well, this is consistent with higher jerk resulting from higher sway. Here it looks like higher jerk in the EC condition is the result of depending on visual input to control postural adjustments via feedback. This finding indicate the important role of the cerebellum to compensate for postural equilibrium in PD. While in our study, NP-C increase in jerk is NOT a consequence of increased sway. Jerk itself is not abnormally high, however, the EO/EC difference is abnormally high. In general, NP-C patients are LESS jerky when they have their eyes open, but then change more than control group when they close their eyes, which shows that the visual input is being used to help control corrective movements. A selective effect on corrective movements is consistent with damage to cerebellar mechanisms that are involved in feedback and correction (Yanagihara, 2014).

B) Fabry:

Fabry disease is a disorder of the X-linked lysosomal storage. However, several neuropathological studies suggest that effects of Fabry disease are not only limited to the vasculature. It also involves some neurons in brain regions such as substatia nigra (de Veber et al., 1992; Kaye et al., 1988; Löhle et al., 2015). Substatia nigra play an essential role in regulating the motor movement (Barter et al., 2014; Sonne J, Reddy V, & MR, 2020).

The findings of the present study revealed that there was no significant interaction between group and eye conditions in **RMS** with Fabry patients. There was also no main effect of group in the RMS data. There was a normal main effect of eye condition. Up to date there is limited study in the literature examine and describe the balance control in details with Fabry patients. Löhle et al. (2015) reported that Fabry patients had asymmetrical motor slowing and postural instability compared to control group. In contrast to Löhle et al. findings, the present study findings showed that there was no signficant difference between Fabry patients and the control group in RMS, which indicates good balance control. These findings should be interpreted with caution. Especially given the differences the methods used and the sample size in the present study and the Löhle et al.study (sample size, 19 vs. 110 fabry patients and measurement method, accelerometer vs. TUG). In general, TUG has high error in test retest use (Barry et al., 2014) which make it less accurate than accelerometers. It is well documanted that the substantia nigra is one of the brian regions affected in PD, which, in turn, results in a disruption in the motor movement and control (Hodge & Butcher, 1980; Johns, 2014; Sonne J et al., 2020). Mancini et al. (2012) found that PD patient had increase in the RMS value compared to a control group. Moreover, Chen et al.(2018) reported also a slight increase (but not significant) in RMS values in PD patients compared to a control group in both eye conditions. Furthermore, they found that RMS was increase during EC condition compared to EO condition in PD patients. These findings tends in some parts support the present study findings in RMS with Fabry patients. However, the contrast with Fabry‟s patients probably shows that the damage to the substantial nigra is not severe enough in Fabry patients to cause changes in balance control comparable in PD.

The **jerk** findings of the present study revealed that there was no significant interaction between group and eye conditions in Fabry patients. There was also no main effect of group.

There was a normal main effect of eye condition. Like RMS, jerk was normal in Fabry patients indicating both normal sensing and normal adjustment during postural control.

To our knowledge, this is the first study reporting postural balance measures in Fabry‟s patients using an accelerometer. However, Rose et al., (2002) had the same result when they investigated postural control in CP patients. They found that there was no significant difference in both eye conditions, and this is because CP had normal sensory reweighting to maintain balance. This could be the same reason why Fabry patients were not showing statistically reliable differences in eye conditions between groups. Moreover, study done by Spain et al. (2012) who examined balance control with multiple sclerosis (MS) patients compared to a control group using accelerometers. It is well known that MS disease affects the substantia nigra (S. Chen, Lu, Seeman, & Liu, 2012; Minagar et al., 2013; Pedemonte, Trabucco, Cella, & Solaro, 2013; Shaygannejad, Shirmardi, Dehghani, & Maghzi, 2016). Spain et al. found that during EC condition, jerk value was reduced compared to control group. Interestingly, this finding also was reported in the present study (even it wasn‟t a reliable difference), where EC jerk value was lower in Fabry patients compared to control group. This could be explained as direct results of taking away the visual input or involving other mechanism as compensatory strategy of losing visual input to produce a lower jerk value.

C) Hurler (MPS I):

Briefly, Hurler is a rare disorder of lysosomal storage caused by deficiency of enzyme a-L-iduronidase activity, which in turn leads to glycosaminoglcans accumulation all over the body. This leads to progressive multi-system deterioration and, in particular, in the CNS. It is estimated that this metabolic disorder affects more than 65% of CNS (Neufeld, 2007).

Affecting the CNS leads to secondary musculoskeletal abnormalities (Aldenhoven et al., 2015a). That is because CNS diseases affect the structure and the function of the brain or the spinal cord. If they were affected the communication information from the receptors in the muscle about the body position and the brain will be affect and this result in numerous abnormalities.

It was difficult to interpret Hurler results based on group data due to the small number of the patients. Findings of the present study suggest that there was no interaction between group and eye condition in **RMS** data. However, there was a main effect of the group, and a main effect of the eye condition. Hurler patients had significantly higher RMS in both eye conditions compared to control group, but not an abnormal difference between EO and EC conditions. This might be due to a small number of extreme values. In general, two Hurler patients out of six had RMS and jerk values that were outside the control range in some conditions. This means it is possible that balance is affected by Hurler, but also that a number of patients are not strongly affected. What is typical for the group would need a larger sample to determine. In general, there is lack of studies investigating balance control with Hurler patients. Therefore, the present study findings will be compared to similar disease that share similar features to Hurler, for example CP. CP usually caused by an injury in the immature brain (H. K. Graham & Selber, 2003) resulting a progressive musculoskeletal abnormalities (joint contraction and decrease ROM especially in spine, hips, and knees) that affect muscle control, movement and posture (H. Graham, 2002). J. Rose et al. (2002) reported that CP patient had increase COP value in both eye conditions compared to control group. Furthermore, they found that there was slight increase in ARD in EC condition compared to EO condition with CP patients, but this did not reach significance. ARD is considered an indicator for a postural control deficit. These findings are in agreement with the present study findings.

In the **jerk** data there was a group X eye condition interaction. There was also a main effect of group. Jerk values were higher in Hurler patients compared to the control group and the EO/EC difference was larger. Jerk results, like the RMS results, however, must be interpreted with caution. The differences resulted mainly from a single patient who produced extreme values in a small sample. One other patient also produced some abnormal values. How common abnormalities are in a larger population will be uncertain until a larger group of patients is studied. It remains possible, however, that both RMS and jerk are affected in Hurler.

Instability in Hurler is due to the impaired weight shifting ability and increasing the sway area due to the weakness of the hip abductors (Wood et al., 2009). Moreover, an increase in the base of support and stride width could lead to an increase in the participant‟s instability (Duarte & Freitas, 2010), which was found also in Hurler patients. In general, wider stride width decreases the muscle activity required to rebalance COM movement in standing (Walker, Hyngstrom, & Schmit, 2016). These musculoskeletal factors may lead, in turn, to decrease balance control and postural instability in Hurler patients. The cause may not be abnormal neural control.

D) Other three patient groups:

Similar to the gait section (Chapter 3), the other three patient groups examined in this thesis (Morquio, Maroteaux-Lamy and Pompe) have less than three patients in each disease group. Consequently, it was not possible to make group comparisons. In addition, a number of patients were unable to complete all conditions of the balance test. One Morquio patient, one Pompe patient and two Maroteaux-Lamy patients were able to complete some conditions.

Their results can only be compared to the range of values produced by controls to say whether they produced abnormal values in the conditions they were able to complete.

Morquio (MPS IV):

The RMS findings revealed that the Morquio patient had higher sway values than controls in both eye conditions. Jerk was similar. There was increase in jerk values in both eye conditions. RMS and jerk values could result from joint stiffness and muscle weakness in the lower limbs that characterises Morquio (Dhawale et al., 2012) rather than from changes to the brain. Morquio is caused by an enzyme deficiency (e.g. GALNS and β-galactosidase) (Dvorak-Ewell et al., 2010b; Geer et al., 2010). Only a few studies suggest involvement of CNS, in particular prominent perivascular spaces (Davison et al., 2013). Perivascular spaces are positioned around the cerebral blood vessels, and work on regulating the exchange of the cerebrospinal fluid and the brain interstitial fluid (Iliff, Thrane, & Nedergaard, 2017). It is well established from magnetic resonance imaging (MRI) studies that perivascular spaces are located in the inferolateral basal ganglia, brainstem, thalami and in the white matter of high convexities (Elster & Richardson, 1991; Saeki et al., 2005; Zamani, 2008). Normally, most of these spaces are asymptomatic in their nature. However, injury to these spaces can cause enlargement of perivascular spaces resulting different symptoms (Zamani, 2008). One of these symptoms, is motor weakness (Elster & Richardson, 1991; Saeki et al., 2005), which is seen in MS patients (Ge, Law, Herbert, & Grossman, 2005) and in Morquio patient of the present study were these patient had prominent perivascular spaces. McLoughlin et al. (2015) examined the postural sway in MS patients and compared them with aged matched control group under EC and EO conditions. They found that under both conditions, MS patients swayed more than control group. Moreover, they reported that MS patients had higher sway

in EC condition compared to EO condition. Taking in consideration the differences in the methodology in the McLoughlin et al and the present study, the findings suggested that MS patient and Morquio patient may depend on visual inputs in their balance control in order to compensate for some of the effects of muscle weakness.

Maroteaux-Lamy (MPS VI):

RMS and **jerk** values for Maroteaux-Lamy patients were did not show dramatic changes. One patient‟s RMS and jerk values were just above the upper cut-off control range in both eye conditions. The other patient was within the control range in both conditions. Interestingly, findings showed that there was no difference between EC and EO in RMS and jerk values in Maroteaux-Lamy patients. Although the findings of the balance control in Maroteaux-Lamy patients seem to be normal, one patient had slightly abnormal reading. This could be due to the poor biomechanical alignment occurs with impaired and insufficient postural muscle activity during balance activities in these patients (Harmatz & Shediac, 2017). Maroteaux-Lamy patients are known to have abnormal changes to the CNS, which includes abnormalities in the ventricular system, white matter, perivascular spaces and cerebral atrophy (Azevedo et al., 2013; Vedolin et al., 2007). An early diagnosed and intervention could result a better outcome, and this was observed in the Maroteaux-Lamy patients in this thesis. Both Patients in this thesis started ERT at early ages. The one diagnosed at 2 years started treatment at 4 years old, while the other one diagnosed at 6 years and started the treatment at 7 years.

Pompe:

Although this patient was within the normal control range in all of the gait parameters, in balance parameters the situation was different. This patient had higher **RMS** in both eye conditions than the control group. Furthermore, findings showed that the patient had abnormally higher RMS value in EC condition compared to EO condition. Also, in **jerk** this patient had abnormal higher jerk values in both eye conditions, and more in EC condition than in EO condition. It is well documented that Pompe disease considered as a metabolic muscle disorder affecting the muscular system. However, several studies have also demonstrated the involvement of the CNS. This was demonstrated by the accumulation of the glycogen in the anterior horn cells, cerebellum and cerebral cortex (Gambetti, DiMauro, & Baker, 1971; Hobson-Webb et al., 2012; Mancall, Aponte, & Berry, 1965; Martini et al., 2001; Thurberg et al., 2006), which is associated with motor deficits (Hobson-Webb et al., 2015; Prater et al., 2012). To date, there are no studies examining the balance control in detail in patients with Pompe disease. However, CP, for example, shares some of the causes and the symptoms which are similar to Pompe disease. For example, Rose et al. (2002) demonstrated an increase in COP values with CP patients under both eye conditions. Moreover, their results showed a mild increase in ARD with CP patients in EC compared to EO conditions. In contrast to Rose et al findings, the present study showed a significant increase in RMS and jerk value during EC condition compared to EO. This finding of the present study should be interpreted with caution due to the small sample size (n =1) compared to Rose et al (n =23). The present findings regarding the increase in RMS and jerk values in EC condition could be due to impair sensory reweighting due to take away the visual signals, and muscle imbalance. In general, this Pompe patient has a mild muscle weakness, and this could lead to change in postural tendencies and positioning (Kawakami, Kawakami, Nohara, Tsuji, & Ohara, 2016; Tanida et al., 2017). Moreover, this could let the patient to use a compensatory pattern of

movement to avoid instability, like increasing the correction velocity (jerk) in order to compensate for high sway value or sway back to avoid falling (Kishnani et al., 2006). In order to confirm these present findings in balance control with Pompe patients, further studies should be conducted on a larger sample of patients.

CHAPTER 5: CORRELATION

5. Correlation:

In order to determine whether there was a relationship between variables, a Pearson product moment correlation coefficient (r) was calculated. In this chapter, three main kinds of correlation results will be addressed: correlations among gait variables, correlations among balance variables, and correlations between gait and balance variables.

5.1. Correlation statistical analysis:

In this section, the control bootstrap is based on the size of the patient sample. This allows us to estimate the range of correlations present in the control sample when the sample size is as small as the sample we had available for patients. The control data that was sampled for the bootstrap was restricted to controls with heights less than or equal to the maximum height from the patient group. The control bootstrap was used to set a confidence interval for the range of correlations that normal development would produce. The correlation from the patient sample was compared to the range found in controls. It is worth noting, from the outset, that conclusions allowed by correlations based on small samples are likely to be limited. Small samples mean that real values in the larger population are uncertain.

Figure 5.1 plots the correlation matrix for gait and balance parameters for the whole of the control group. Table 5.1 reports the correlation coefficient (r) values. Based on these values, moderate and strong correlations were identified ($r \geq 0.30$) and analysed for control and patient groups.

In the following section the correlations in patients in comparison to controls will be reported. Only results from NP-C and Fabry patients (the two largest groups) will be reported.

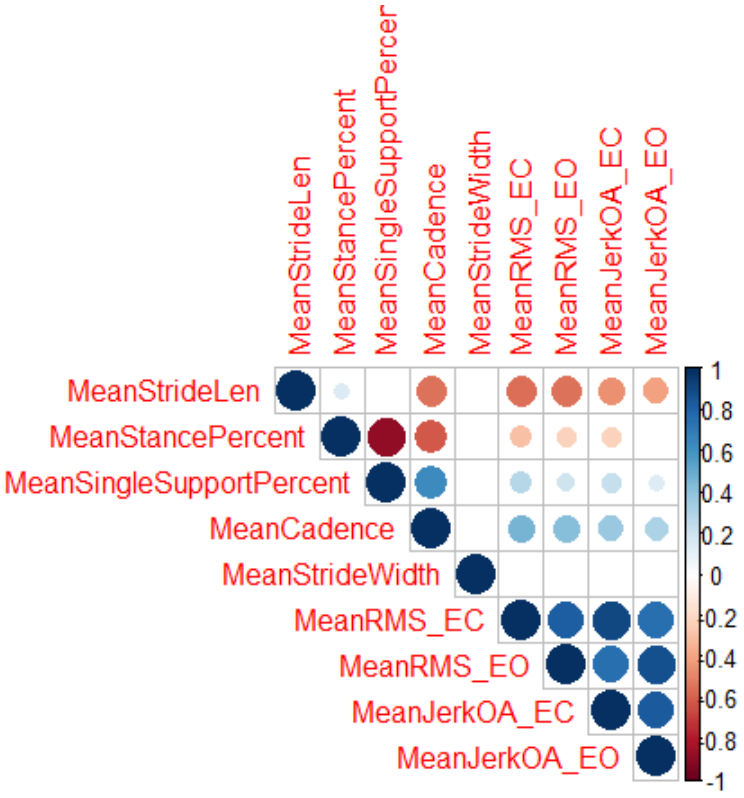


Figure 5.1: Correlation matrix between the gait and balance parameters for control group. Blue colour indicates a positive correlation. Red colour indicates a negative correlation. Size and colour intensity represent the strength of the correlation. The size associated with a correlation of 1 is show on the diagonal. EC=eyes closed; EO=eyes open.

Table 5.1: Correlation coefficient (*r*) for gait and balance parameters.

Variable	Mean Stride Length	Mean Stance %	Mean Single Support %	Mean Cadence	Mean Stride Width	Mean RMS_EC	Mean RMS_EO	Mean Jerk _EC
Mean Stride Length								
Mean Stance %	0.15*							
Mean Single Support %	-0.08	-0.89***						
Mean Cadence	-0.55***	-0.62***	0.63***					
Mean Stride Width	-0.02	0.09	-0.12*	-0.09				
Mean RMS_EC	-0.55***	-0.29***	0.28***	0.47***	0.08			
Mean RMS_EO	-0.54***	-0.22***	0.20***	0.43***	0.09	0.82***		
Mean Jerk _EC	-0.45***	-0.22***	0.23***	0.38***	0.09	0.91***	0.76***	
Mean Jerk _EO	-0.41***	-0.14*	0.15*	0.31***	0.13*	0.76***	0.88***	0.83***

EC=Eyes closed, EO=Eyes open, *: $p < 0.05$, **: $p < 0.01$, ***: $p < .001$

5.2. Gait correlations results:

According to the correlation matrix (Figure 5.1 and Table 5.1), there were four gait parameters had a large positive or negative correlation: Cadence and stride length; Single support percentage and stance percentage; Stance percentage and cadence; Single support percentage and cadence. However, because some parameters considered to be similar but just in the opposite direction, only two gait correlation will be discussed in this thesis: Cadence and stride length and Single support percentage and cadence.

5.2.1. Control group results:

Cadence and Stride length (r = -0.55):

The correlation between the cadence and the stride length is presented in figure 5.2. There was a negative correlation in controls (r = - 0.55, $p < 0.001$) as stride length increased, the cadence reduced. Although cadence and stride length may typically vary together (longer strides mean a slower cadence) these variables are not inevitably linked (short strides can be taken slowly).

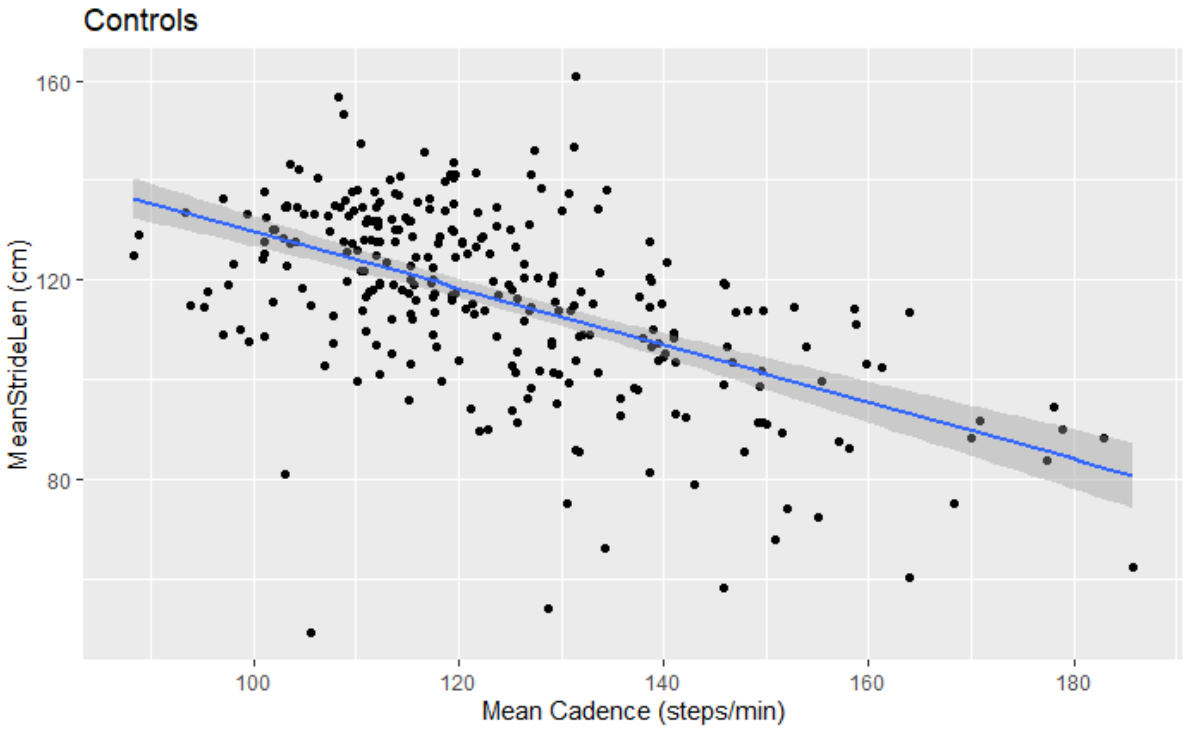


Figure 5.2: Correlation between mean stride length (y-axis) and mean cadence (x-axis) for control group. The blue line plots the slope of the relationship.

Single support percentage and Cadence (r = 0.63):

Single support percentage and cadence were strongly positive correlated in the control group ($r = 0.63$, $p < 0.001$) (Figure 5.3). Those healthy participants who walked faster tended to increase the portion of the gait cycle with only one foot in contact with the ground.

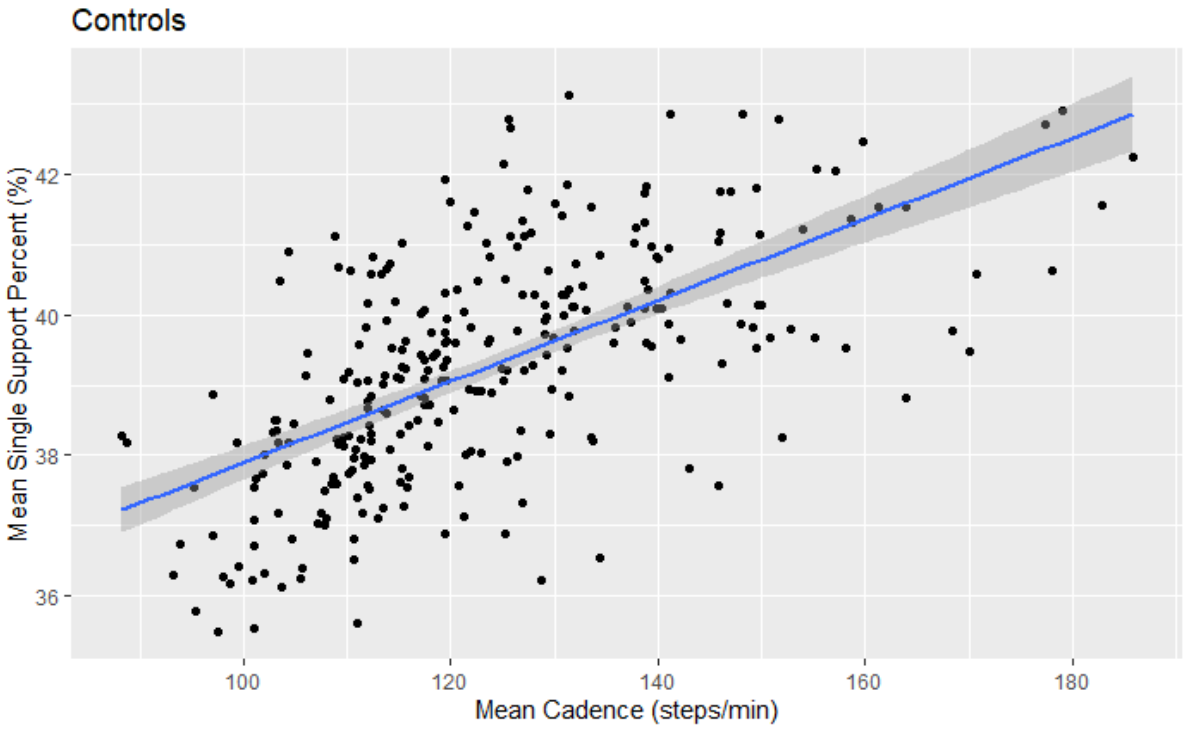


Figure 5.3: Correlation between mean single support % (y-axis) and mean cadence (x-axis) for control group. The blue line plots the slope of the relationship.

5.2.2. Patient groups results:

5.2.2.1. NP-C patients:

Cadence and stride length:

In NP-C patients, findings showed that there was positive relationship (moderate effect) between cadence and stride length (r = 0.38; bootstrap r = 0.37). On the other hand, in the control group, there was negative relationship (large effect) between cadence and stride length (r = -0.52; bootstrap r = -0.57). The CI for the control group that was appropriate to compare to NP-C was between -1.31 to 0.13 and the patient r was outside this interval (Figure 5.4). There was a positive relationship between cadence and stride length in NP-C patients that was uncharacteristic of controls, where the relationship was negative. NP-C patients with a slower cadence generally took shorter steps, in contrast to controls where participants with a slower cadence generally took longer steps.

Note, however, that this difference is primarily created by results from two NP-C patients with abnormally low cadence values (Figure 5.5). After eliminating these extreme values the control and NP-C patient r values were within the control group CI (control CI = -1.45 to 0.26; control bootstrap r = -0.51, NP-C patient bootstrap r = -0.15) (Figure 5.6). There was no evidence of a difference in the relationship between cadence and stride length in NP-C patients after a limited number (2/9) of more extreme patient values had been removed.

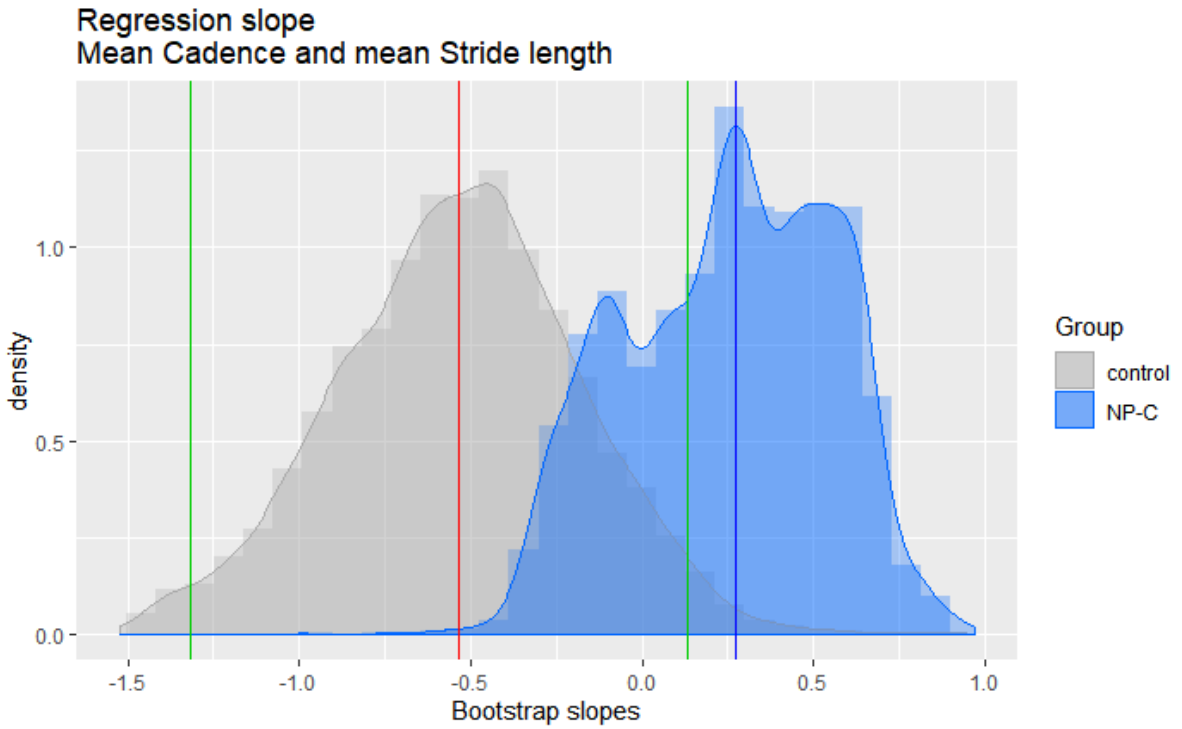


Figure 5.4: The distribution of bootstrap slopes for the relationship between cadence and stride length in NP-C patients and controls. The green lines are the boundaries of the 95% confidence interval for controls. The red line is the control mean. The blue line is the patient mean.

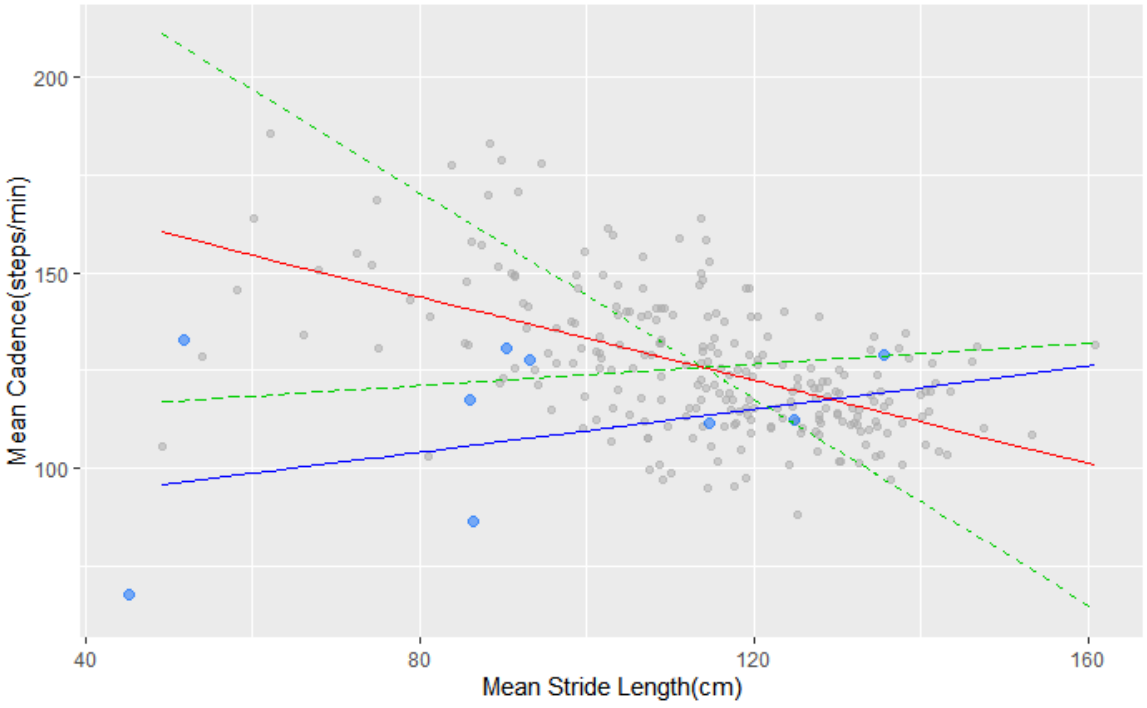


Figure 5.5: Regression slopes for the relationship between cadence (y-axis) and stride length (x-axis) in NP-C patients (blue dots) and controls (grey dots). Dashed green lines are the confidence interval for the slope in controls. The red line is based on the median slope and intercept from the control bootstrap. The blue line is the patients‟ regression line.

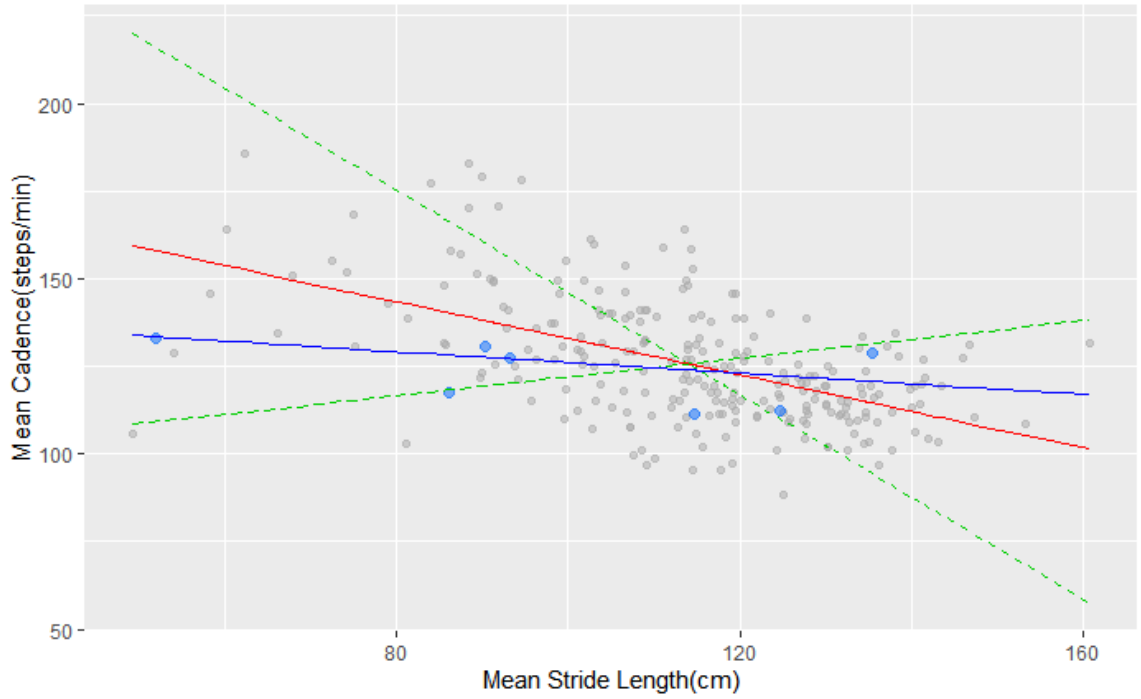


Figure 5.6: Regression slopes for the relationship between mean cadence (y-axis) and mean stride length (x-axis) in NP-C patients (blue dots) and controls (grey dots) after removing extreme patient values. Dashed green lines are the confidence interval for the slope in controls. The red line is based on the median slope and intercept from the control bootstrap. The blue line is the patients‟ regression line.

Single support percentage and cadence:

In NP-C patients, the statistical analysis for the data had shown there was a correlation (large positive effect) between single support % and cadence ($r = 0.74$), and bootstrapping these data confirmed the same results (bootstrap $r = 0.74$). On the other side, in control group, statistical analysis for the single support % and cadence data showed also there was a correlation (large positive effect) ($r = 0.59$). While, bootstrapping these data revealed also large effect correlation between these parameters (bootstrap $r = 0.63$).

The CI for control group were ranged from -0.003 to 0.128, where the patients mean was outside the 95% CI (Appendix 5 Figure 5.A1) indicating there were a significant difference between the single support % and cadence in both groups.

Figure 5.7 shows the NP-C bootstrap slope (0.15) and control group bootstrap slope (0.05). Observation of this figure (5.7), revealed that there was one patient had very low single support % value and was outside the control correlation range, which might have influence on the outcome. Removing this extreme data (Figure 5.8), showed that control and patients means were within the 95% CI. Accordingly, there were no significant difference between NP-C patients and the control group in this correlation. This figure showed that the NP-C patients bootstrap slope (0.0004) and the control group bootstrap slope (0.056).

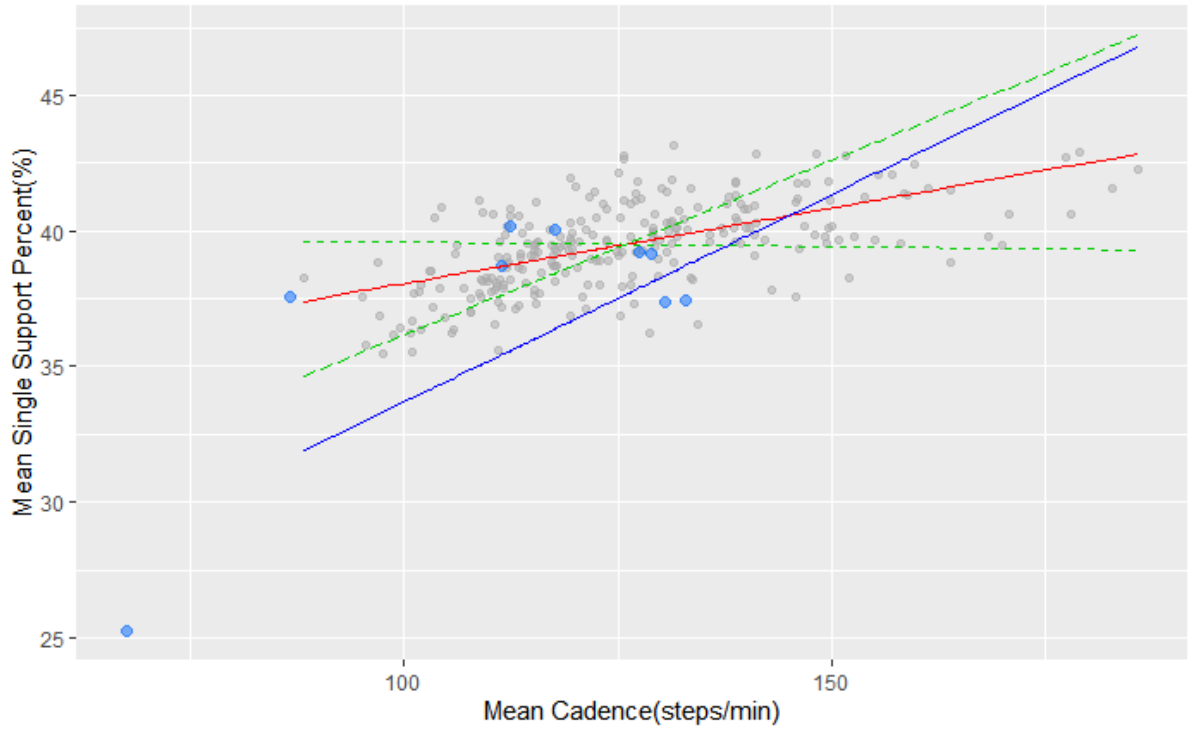


Figure 5.7: Regression slopes for the relationship between single support % (y-axis) and mean cadence (x-axis) in NP-C patients (blue dots) and control group (grey dots). Dashed green lines are the confidence interval for the slope in controls. The red line is based on the median slope and intercept from the control bootstrap. The blue line is the patient‟s regression line.

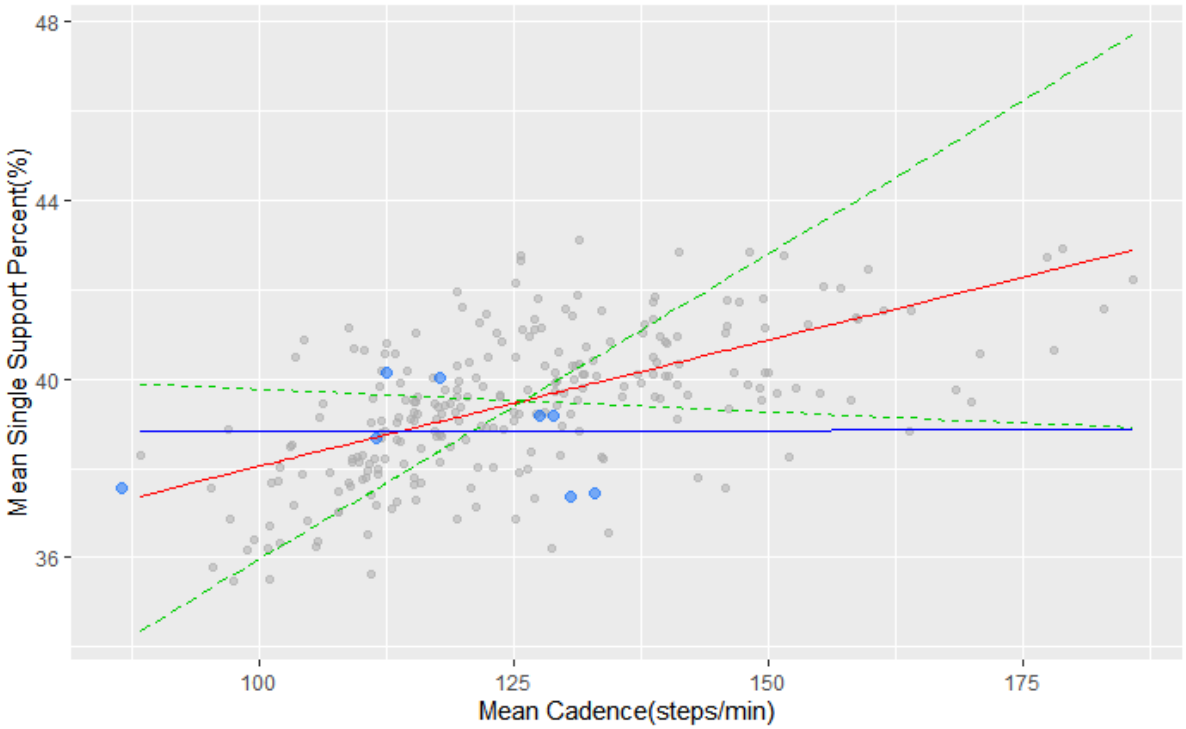


Figure 5.8: Regression slopes for the relationship between single support % (y-axis) and mean cadence (x-axis) in NP-C patients (blue dots) and control group (grey dots) after removing extreme patient values. Dashed green lines are the confidence interval for the slope in controls. The red line is based on the median slope and intercept from the control bootstrap. The blue line is the patient‟s regression line.

5.2.2.2. Fabry patients:

Cadence and stride length:

In Fabry patients there was a large negative relationship between cadence and stride length (Fabry patients original r = -0.59; bootstrap r = -0.60). The control group showed the same large negative effect (Control original r = -0.52; bootstrap r = -0.55). The bootstrap CI for the regression slope in the control sample was between -1.02 and -0.05 and the patient bootstrap slope was within this interval (Appendix 5 Figure 5.B1 and Figure 5.9) control bootstrap slope = -0.5; Fabry bootstrap slope = -0.44). Thus, the relationship between cadence and stride length was not disrupted in Fabry patients.

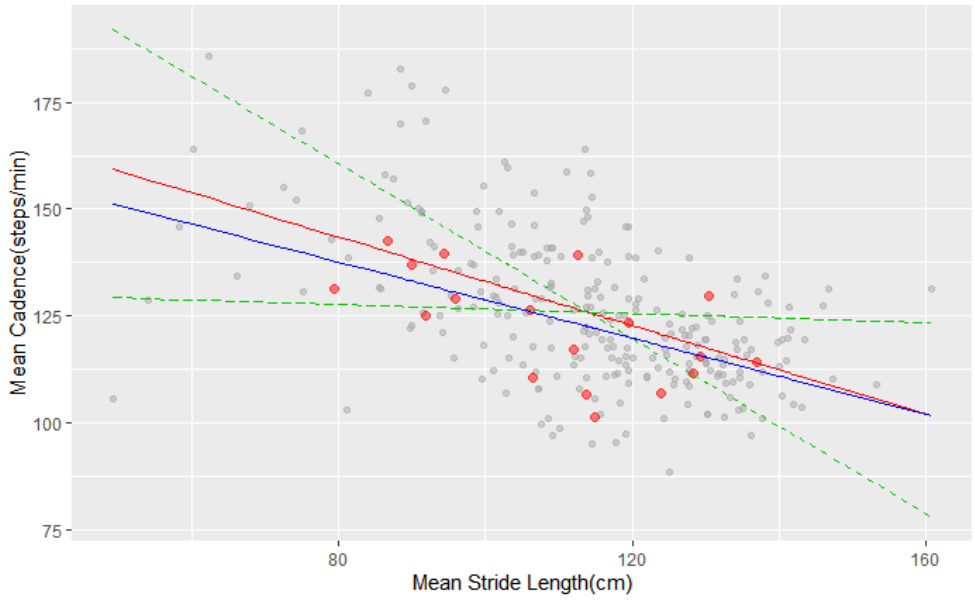


Figure 5.9: Regression slopes for the relationship between cadence (y-axis) and stride length (x-axis) in Fabry patients (red dots) and controls (grey dots). Dashed green lines are the confidence interval for the slope in controls. The red line is based on the median slope and intercept from the control bootstrap. The blue line is the patient regression line.

Single support percentage and cadence:

Statistical analysis revealed that there was a moderate positive relationship between single support percentage and cadence for Fabry patients (original $r = 0.31$; bootstrap $r = 0.32$). In the control group there was a stronger positive relationship between these two parameters (original $r = 0.59$; bootstrap $r = 0.60$). For the control group the bootstrap slope CI was between 0.017 and 0.099 and the bootstrap slope for Fabry group (0.03) was within the CI (Appendix 5 Figure 5.B2 and Figure 10).

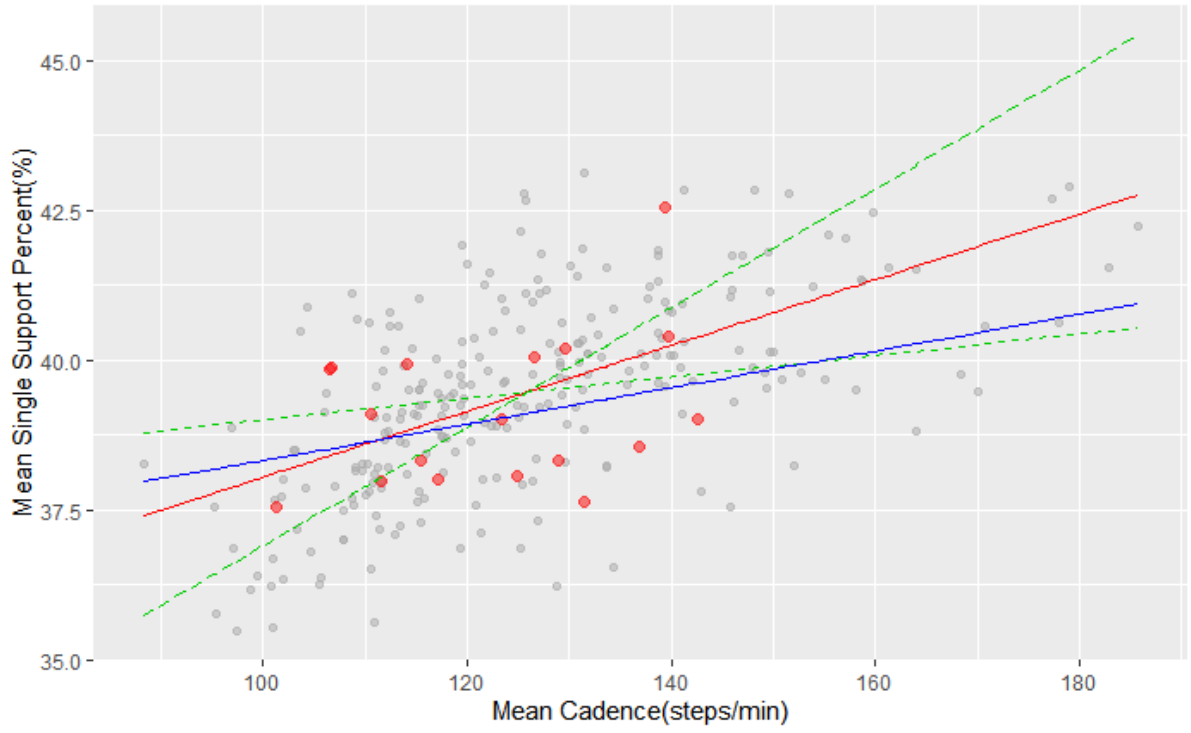


Figure 5.10: Regression slopes for the relationship between single support % (y-axis) and cadence (x-axis) in Fabry patients (red dots) and controls (grey dots). Dashed green lines are the confidence interval for the slope in controls. The red line is based on the median slope and intercept from the control bootstrap. The blue line is the patient regression line.

5.3. Balance correlation results:

Based on the correlation matrix (Figure 5.1) and the *r* values in Table 5.1, there were four strong positive correlation ($r \geq 0.70$) between balance parameters. However, most of these involved correlations between eye conditions for the same measures were highly correlated (e.g. RMS EC and RMS EO). Therefore, here we present the correlation between jerk and RMS for a single eye condition (jerk EC and RMS EC). The resulting correlation between these two balance parameters in control group and patient groups will be addressed in the coming section.

5.3.1. Control group results:

Jerk EC and RMS EC (r = 0.91):

Figure 5.11 showed a strong positive correlation between jerk EC and RMS EC ($r = 0.91$, $p < 0.001$). This means that healthy individual who had an increase in the sway area in EC condition will have higher jerk in EC condition. There were two participants had an extreme value in RMS EC. Removing these extreme values did not affect the final results.

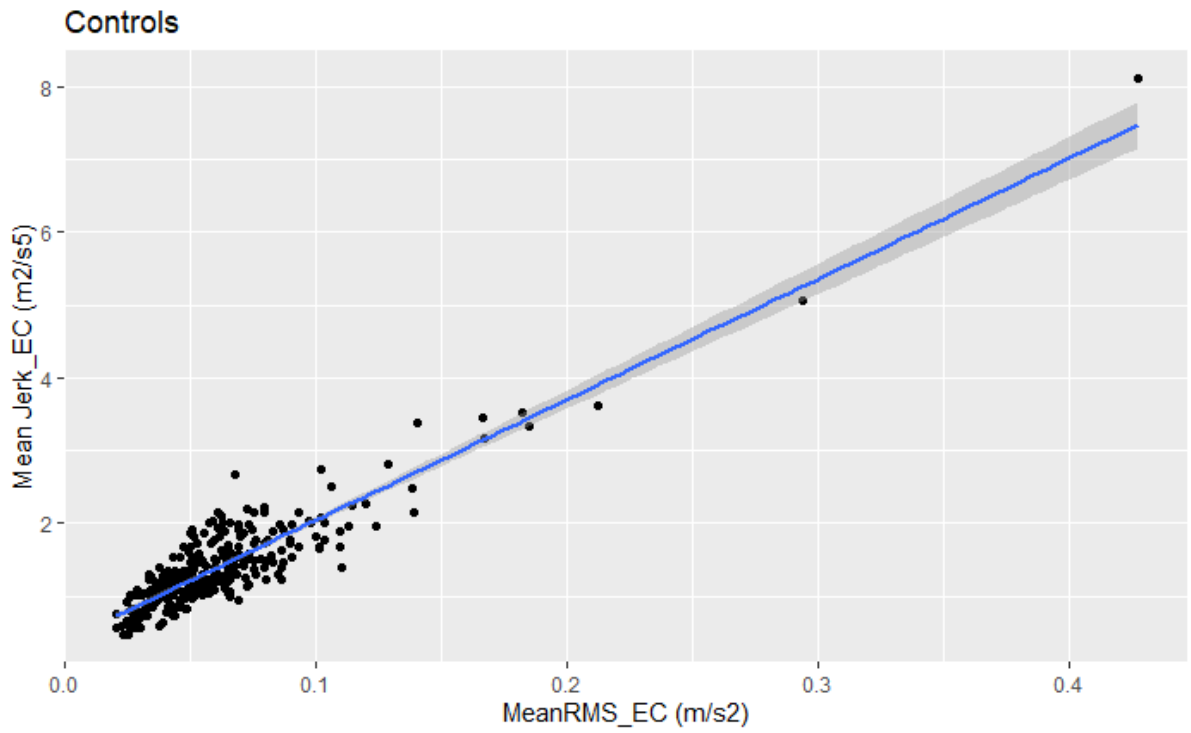


Figure 5.11: Correlation between mean jerk EC (y-axis) and mean RMS EC (x-axis) for control group. The blue line is the correlation line.

5.3.2. Patient groups results:

5.3.2.1. NP-C patients:

There were no significant changes in the correlation among balance parameters for NP-C patients when compared to correlation in controls.

Jerk EC and RMS EC:

In this correlation, NP-C patients had a large positive effect between jerk EC and RMS EC. Their original *r* was 0.91 and their bootstrap *r* was 0.91. Equally, control group had a large positive effect between these two parameters (original *r* = 0.92 and bootstrap *r* = 0.86). The control group CI was between 7.72 to 22.62, where the control and the patient means were within these intervals (Appendix 5 Figure 5.C1). Consequently, there were no significant different between NP-C patients and control group in this correlation. Figure 5.12 showed the bootstrap slopes for both control group (15.5) and NP-C patients (15.5) in this correlation.

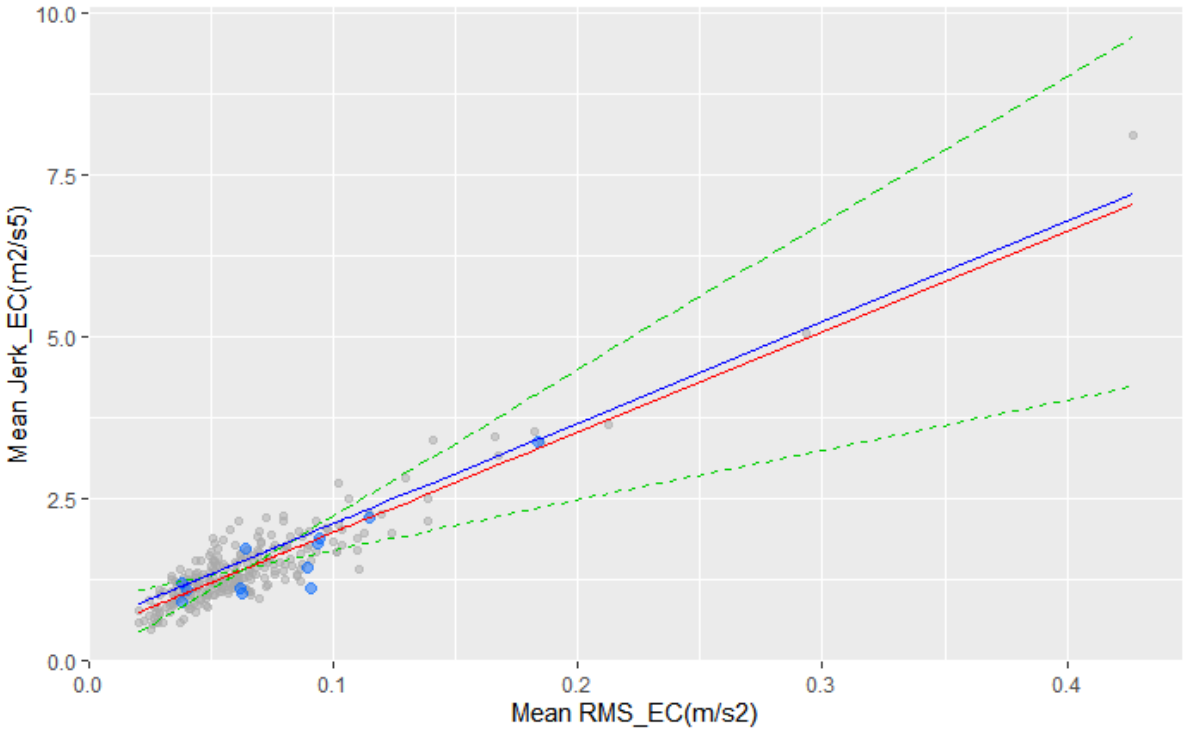


Figure 5.12: Regression slopes for the relationship between mean jerk EC (y-axis) and mean RMS EC (x-axis) in NP-C patients (blue dots) and controls (grey dots). Dashed green lines are the confidence interval for the slope in controls. The red line is based on the median slope and intercept from the control bootstrap. The blue line is the patients‟ regression line.

5.3.2.2. Fabry patients:

Similar to NP-C patients, there were no significant differences in the correlation among balance parameters when comparing correlation in Fabry patients and controls.

Jerk EC and RMS EC:

Statistical analysis revealed that Fabry patients had a large positive effect between jerk EC and RMS EC. Their original *r* was 0.55 and their bootstrap *r* was 0.57. Also, control group had a large positive effect between these two parameters (original $r = 0.92$ and bootstrap $r = 0.87$). The control group CI was between 9.6 to 20.5 and the control and the patient means were within these intervals (Appendix 5 Figure 5.D1). Therefore, there were no significant different between Fabry patients and control group in this correlation. Figure 5.13 showed the bootstrap slopes for control group (15.7) and Fabry patients (12.7) in this correlation.

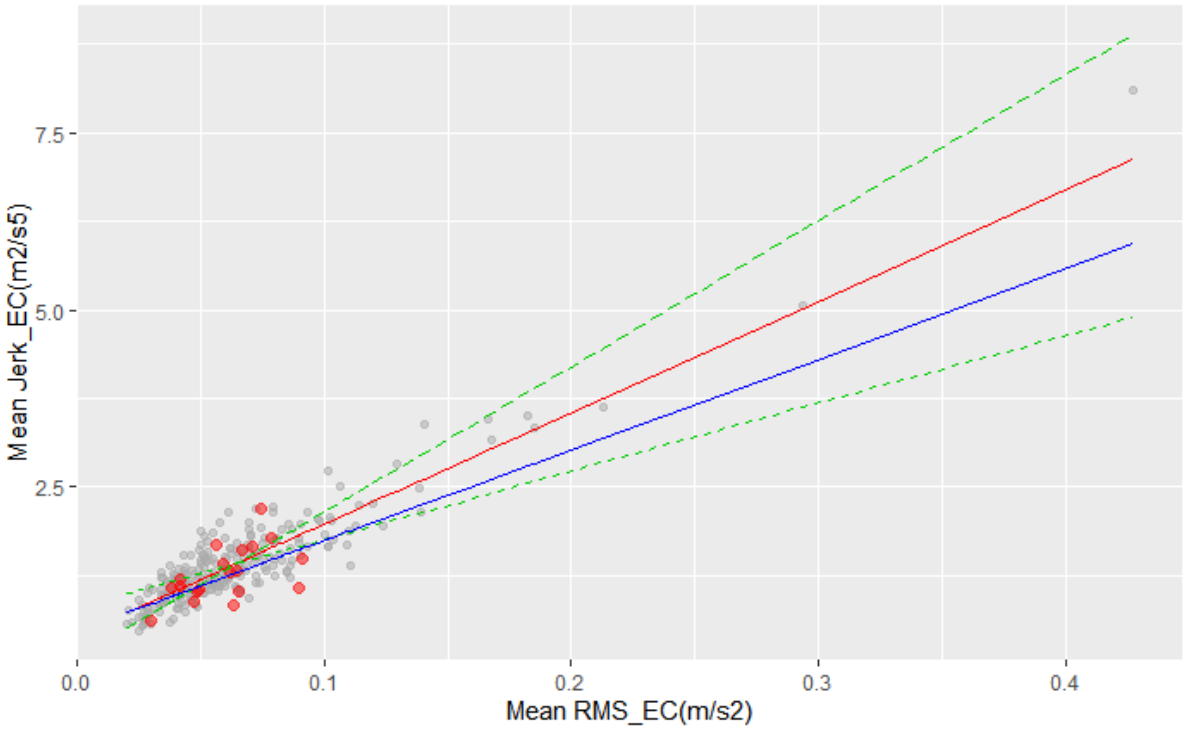


Figure 5.13: Regression slopes for the relationship between mean jerk EC (y-axis) and mean RMS EC (x-axis) in Fabry patients (red dots) and controls (grey dots). Dashed green lines are the confidence interval for the slope in controls. The red line is based on the median slope and intercept from the control bootstrap. The blue line is the patient regression line.

5.4. Gait and balance correlation results:

The correlation matrix (Figure 5.1) and the *r* values table (Table 5.1) list two clear and large effect correlations between gait and balance parameters. One of these was a positive correlation between cadence and all the balance parameters. While, the other was a negative correlation between stride length and all the balance parameters. The reason behind choosing these specific correlations from other correlation between gait and balance parameters is that *r* values were moderate to strong ($r \geq 0.30$). Therefore, only one correlation between cadence and RMS EO were chosen to be tested, and one correlation between stride length and RMS EC were tested because they showed some difference when it was compared to patients‟ groups.

5.4.1. Control group results:

5.4.1.1. Cadence:

Cadence and RMS EO (r = 0.43):

Figure 5.14 presented the relationship between cadence and RMS EC, where there were a positive correlation between these parameters in control group ($r = 0.43$, $p < 0.001$). This finding indicates that increasing in cadence was correlated with increasing in RMS EO.

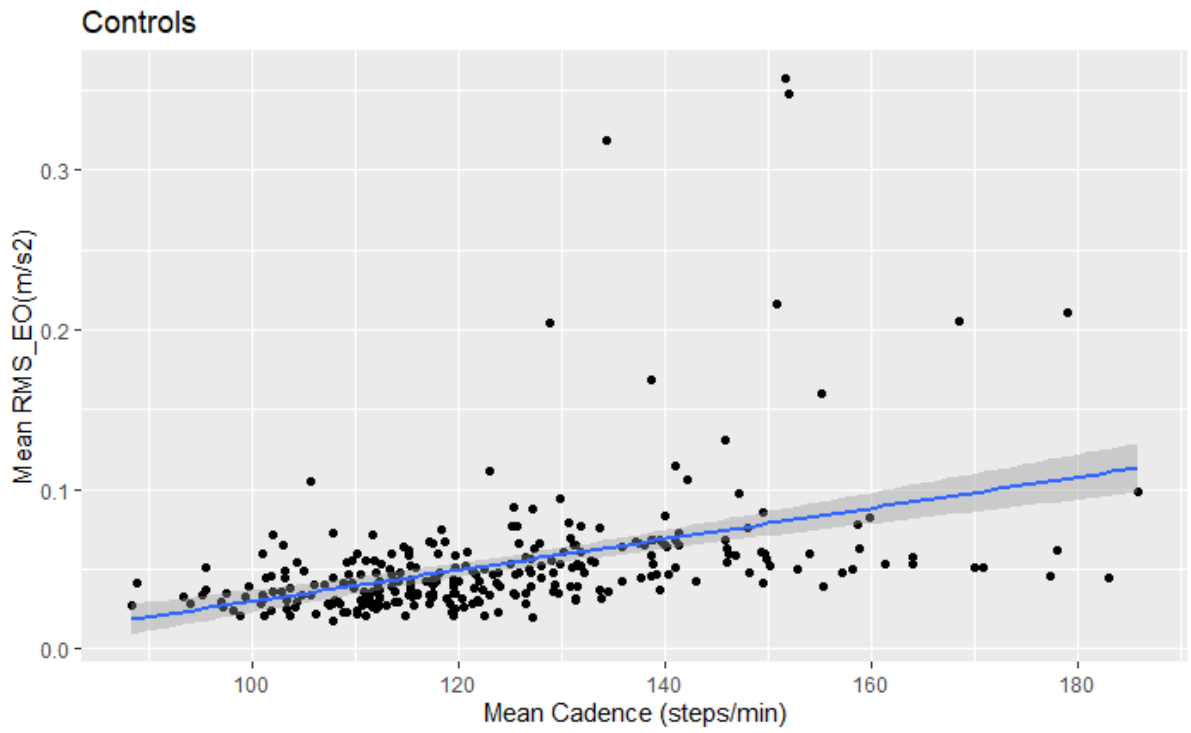


Figure 5.14: Correlation between mean RMS EO (y-axis) and mean cadence (x-axis) in control group (black dots). The blue line is the correlation line.

5.4.1.2. Stride length

Stride length and RMS EC (r = - 0.55):

In regard to stride length, the Pearson test showed that there was a negative correlation between stride length and RMS EC in control group (r = - 0.55, p <0.001; Figure 5.15). Individuals with shorter stride length will have a larger sway area when standing with eyes closed.

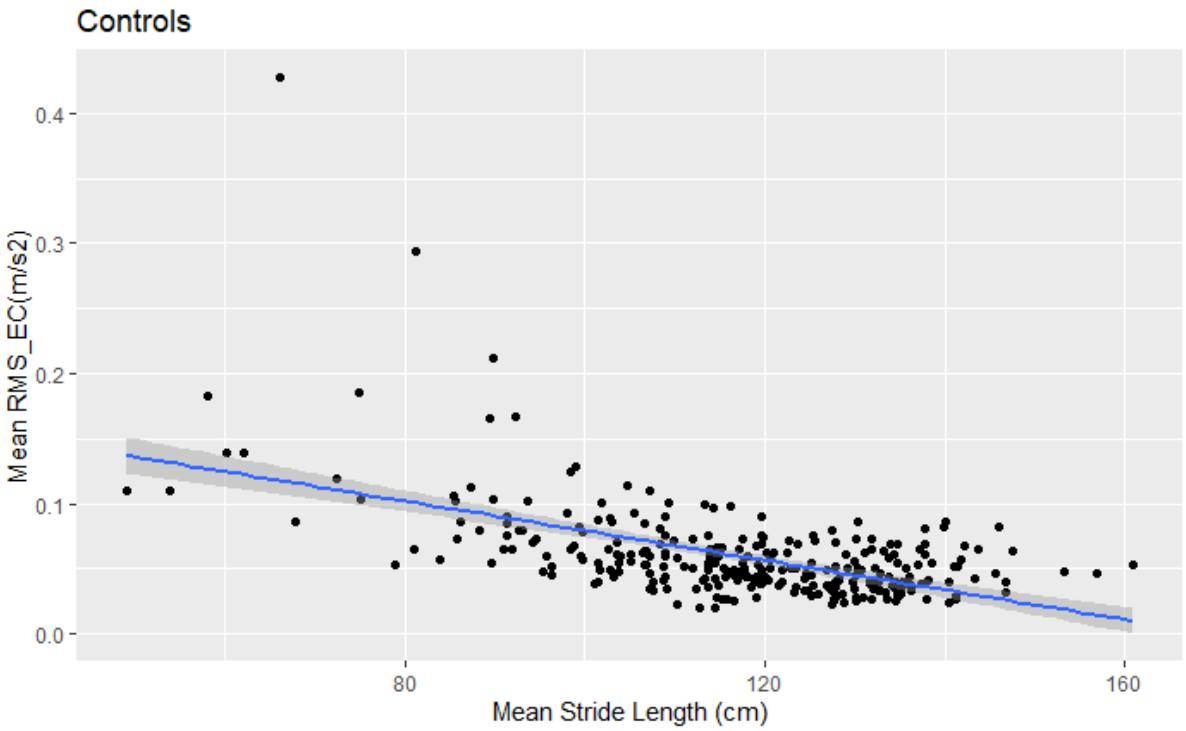


Figure 5.15: Correlation between mean RMS EC (y-axis) and mean stride length (x-axis) in control group (black dots). The blue line is the correlation line.

5.4.2. Patient groups results:

5.4.2.1 NP-C patients:

A. Cadence:

Cadence and RMS EO:

Statistical analysis revealed that NP-C had a large negative effect in this correlation. Their original *r* was -0.58 and the bootstrap *r* was -0.59. While the control group, had a moderate to large effect correlation between these parameters. The original *r* was 0.40 and the bootstrap *r* was 0.53 for control group. The CI for the control group were between -0.0002 and 0.0044, and the patients mean was outside these intervals (Appendix 5 Figure 5.E1). Therefore, there was a significant different between NP-C patients and control group in this correlation. Figure 5.16 showed the bootstrap slopes for control group (0.0007) and NP-C patients (-0.0022) in this correlation.

There was one extreme patient value showed in figure 5.16. After eliminating this patient extreme value, there was no significant difference between NP-C patients and control group. Figure 5.17 presented the bootstrap slopes for control group (0.0007) and NP-C patients (0.0010) in this correlation.

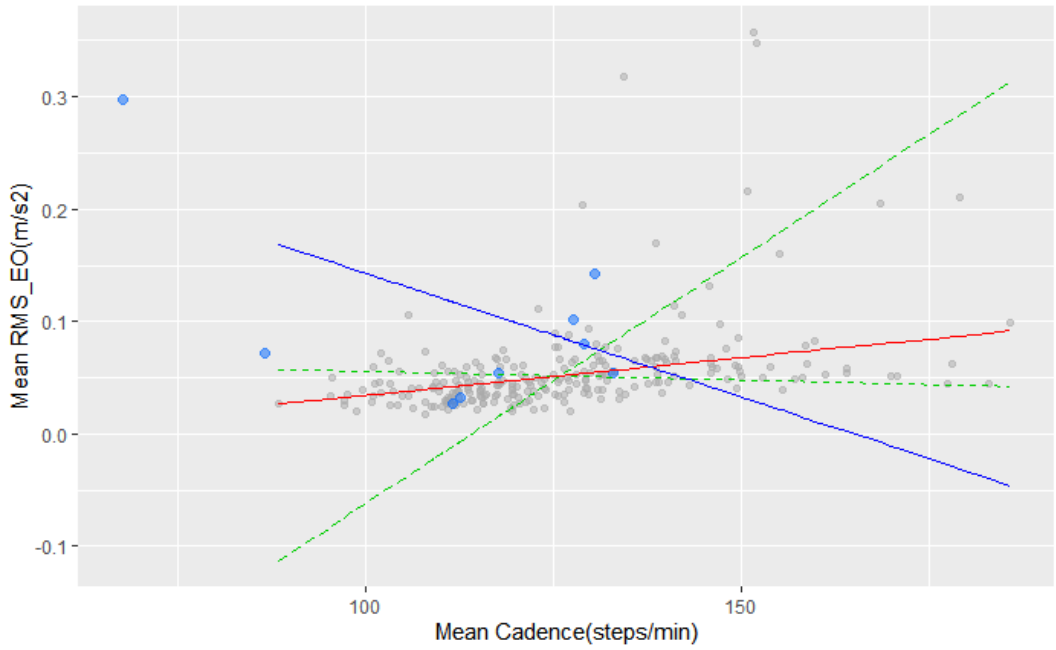


Figure 5.16: Regression slopes for the relationship between mean RMS EO (y-axis) and mean cadence (x-axis) in NP-C patients (blue dots) and controls (grey dots). Dashed green lines are the confidence interval for the slope in controls. The red line is based on the median slope and intercept from the control bootstrap. The blue line is the patients‟ regression line.

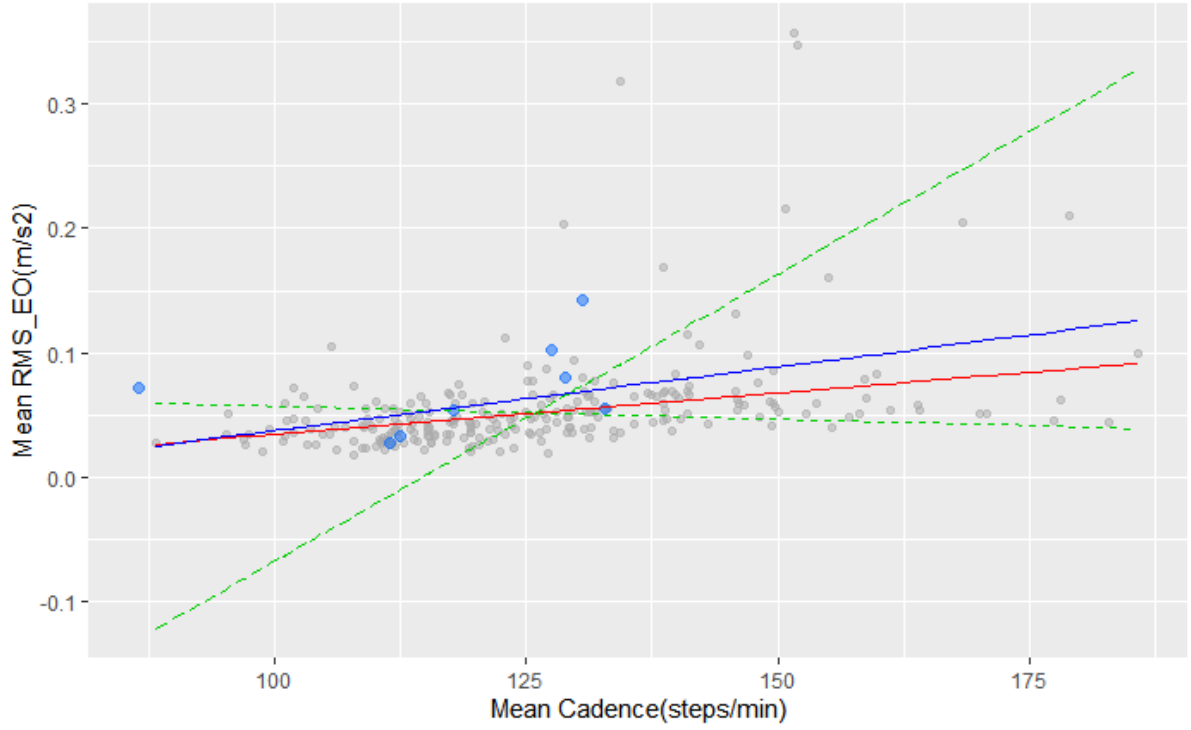


Figure 5.17: Regression slopes for the relationship between mean RMS EO (y-axis) and mean cadence (x-axis) in NP-C patients (blue dots) and controls (grey dots) after removing extreme patient values. Dashed green lines are the confidence interval for the slope in controls. The red line is based on the median slope and intercept from the control bootstrap. The blue line is the patients‟ regression line.

B. Stride length:

Stride length and RMS EC:

In this correlation, NP-C patients had a small negative effect in this correlation (original r = -0.17 and bootstrap r = r = -0.18). While, control group had a large positive effect in this correlation (original r = -0.53 and bootstrap r = -0.60). The control group CI was ranged between -0.0041 to 0.0004, and the control and patient means were within these intervals (Appendix 5 Figure 5.E2). Therefore, there was no significant different between NP-C patients and control group in this correlation. Figure 5.18 showed the bootstrap slopes for both control group (-0.0008) and NP-C patients (-0.0003) in this correlation.

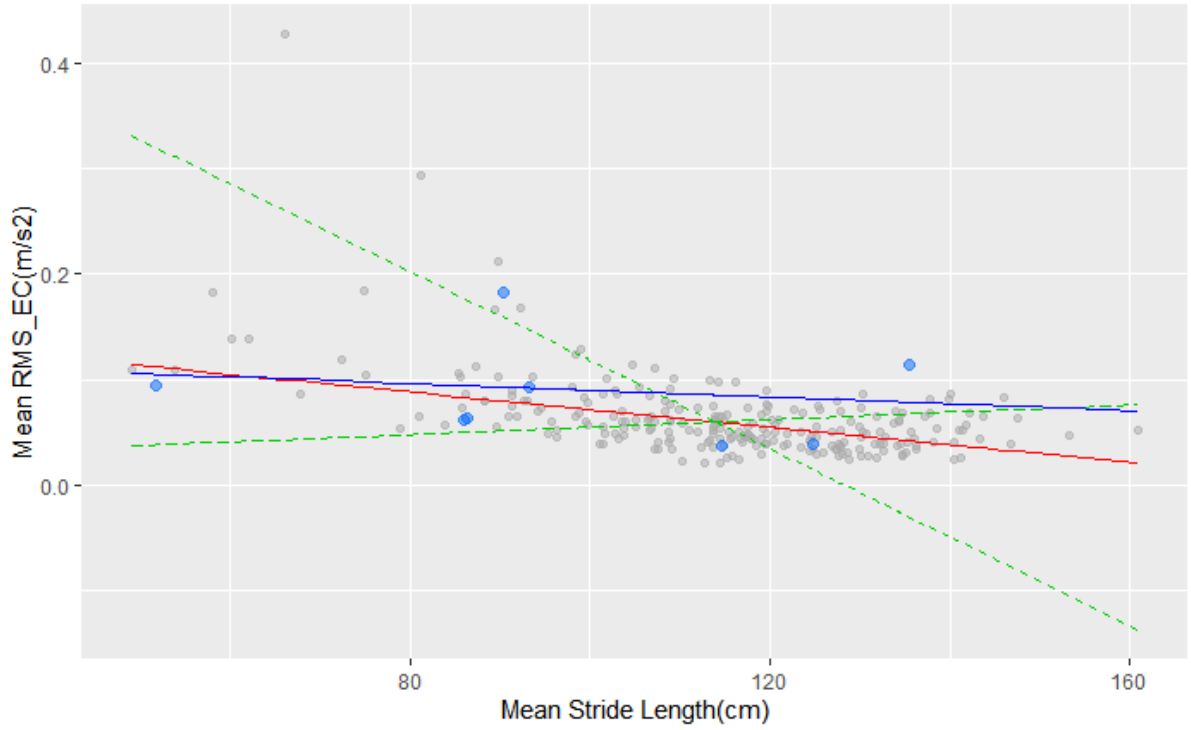


Figure 5.18: Regression slopes for the relationship between mean RMS EC (y-axis) and mean stride length (x-axis) in NP-C patients (blue dots) and controls (grey dots). Dashed green lines are the confidence interval for the slope in controls. The red line is based on the median slope and intercept from the control bootstrap. The blue line is the patients‟ regression line.

In conclusion, NP-C patients correlations findings revealed that there were no significant different between them and control group in gait, balance, and gait and balance correlations. Although some gait individuals‟ parameters showed differences between NP-C and control groups, the relationship between parameters was not distorted. Individual balance parameters did not differ between the NP-C and control group. There were also no significant differences in the relationships between parameters. Finally, the gait and balance parameter correlations showed that the relationships between gait and balance measures was not distorted by NP-C. This indicates that NP-C patients used the same adjustment and compensating strategies as healthy individuals to maintain their postural balance.

5.4.2.2. Fabry patients:

A. Cadence:

Cadence and RMS EO:

Fabry patients had a small positive effect in this correlation (the original *r* was 0.13 and the bootstrap *r* was 0.14). While for the control group, they had a moderate positive effect in this correlation (the original *r* was 0.40 and the bootstrap *r* was 0.48). The control group CI were ranged between 0.0001 and 0.0031, and the control and the patient means were within these intervals (Appendix 5 Figure 5.F1). Therefore, there was no significant different between Fabry patients and control group in this correlation. Figure 5.19 showed the bootstrap slopes between control group (0.0008) and Fabry patients (0.0002) in this correlation.

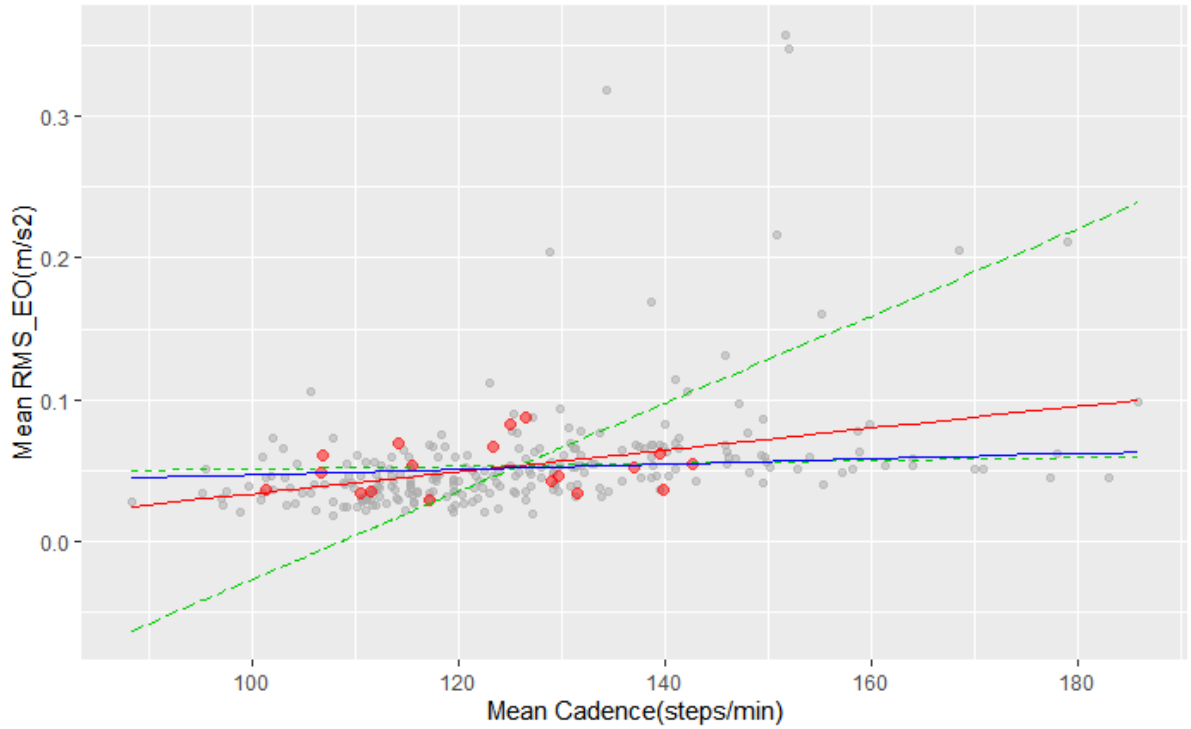


Figure 5.19: Regression slopes for the relationship between mean RMS EO (y-axis) and mean cadence (x-axis) in Fabry patients (red dots) and controls (grey dots). Dashed green lines are the confidence interval for the slope in controls. The red line is based on the median slope and intercept from the control bootstrap. The blue line is the patient regression line.

B. Stride length:

Stride length and RMS EC:

In this correlation, Fabry patients had a small positive effect between these two parameters. Their original *r* was 0.10 and the bootstrap *r* was 0.10. While, the control group had a large negative effect in this correlation (the original *r* was -0.53 and the bootstrap *r* was -0.59). The CI for the control group ranged from -0.0033 to -0.0001, and the patients mean was outside these intervals (Appendix 5 Figure 5.F2). So, there was a significant different between Fabry patients and control group in this correlation. Figure 5.20 showed the bootstrap slopes between both control group (-0.0009) and Fabry patients (0.0001) in this correlation.

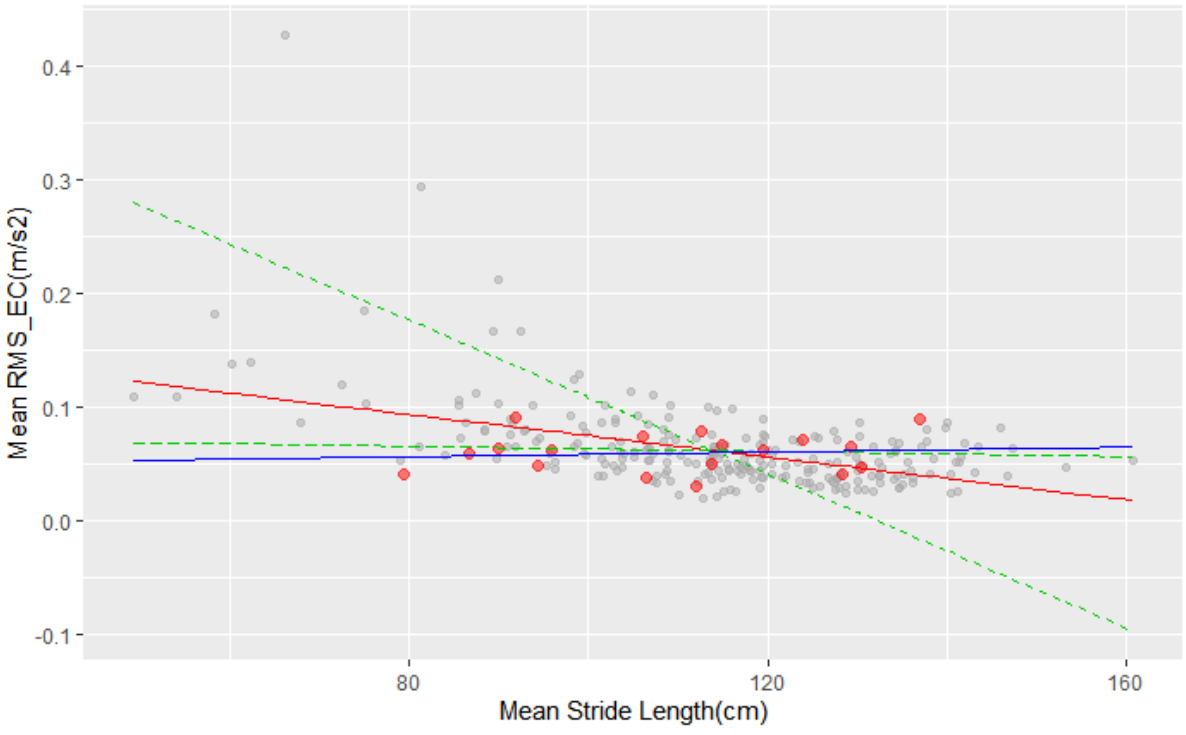


Figure 5.20: Regression slopes for the relationship between mean RMS EC (y-axis) and mean stride length (x-axis) in Fabry patients (red dots) and controls (grey dots). Dashed green lines are the confidence interval for the slope in controls. The red line is based on the median slope and intercept from the control bootstrap. The blue line is the patient regression line.

In conclusion, Fabry patients showed small difference in correlation findings compared to control group findings. In gait correlations, some Fabry gait individuals‟ parameters were different than control group. However, this did not affect the final results, where there were no significant differences in gait correlations between both groups. The balance correlation finding revealed that all Fabry balance individual parameters were similar to control group. As a result of this, there were no significant differences in balance correlations between both groups. In regard to correlation between gait and balance parameters in Fabry patients, some of these correlations were significantly different than control group (e.g. cadence & RMS EC, stride length & RMS EC and stride length & RMS EO). This could be explained due to RMS parameter was less and better in Fabry patient compared to control group, though there was no significant difference between both groups in this parameter. However, this could be explained that cadence and stride length are probably just acting as proxies for changes over time. Therefore, Fabry patients sometimes have more affected balance when they are older and could act differently compared to control group in order to maintain postural stability.

5.5. Correlation discussion:

The third main aim of this thesis was to determine any correlation between gait and balance parameters in healthy individual (control group), and are these correlations similar to patient groups or not. To date, there is limited evidence in the literature about correlations. In this section, three correlations will be discussed: correlations among gait measures, correlations among balance measures, and correlations between gait and balance measures. The limited numbers in patient groups means interpretation of these preliminary results should be approached with caution. However, large differences could be evident. A larger patient sample would be needed to follow up on the preliminary results reported here.

5.5.1. Gait Correlation Discussion:

5.5.1.1. Control group:

The correlation data of the healthy individual had revealed that there was a strong negative relationship between gait parameters. In regard to cadence, data had showed that there was a negative relationship between cadence and stride length. This finding indicate that healthy participants with high cadence tend to have shorter stride length. On the other hand, there were a strong positive correlation between single support % and cadence indicating that participants with high cadence tend to walk with more single support %.

These present findings with healthy individuals were aligned with other evidence from the literature. Lythgo et al. (2009) reported that both cadence and single support % normally reduces with height increase in healthy individuals. On the other hand, Thevenon et al. (2015) found that the stride length always increased with the height. Moreover, they reported that stance % increased gradually after the height of 130 cm. In the present study, the increase of the cadence was associated with decrease of the stride length. In healthy controls a certain

level of correlation may be mediated by development, without stronger connections between parameters. In particular cases there may be more direct connections. Carty and Bennett (2009) reported that healthy individuals at higher walking speed acquired alternative strategies to accumulate different motor plans (e.g. forced gait pattern) (Carty & Bennett, 2009).

5.5.1.2. Patient groups:

The correlation between parameters in patient groups were conducted only on two groups (NP-C and Fabry). Other patient groups were not examined due to their small sample size. Patients and controls were compared to see if there was any evidence of disruption to the relationship between parameters that might not be evident in individual parameter values. In order to obtain more reliable comparison between patients and controls, a sample of the same size as the patient group was drawn repeatedly from the population of healthy individuals and then the comparison between correlation coefficients and regression slopes was based on these control bootstrap samples in comparison to bootstrap samples from the whole patient group.

5.5.1.2.1. NP-C patients:

Table 5.2 shows the summary of all the gait, balance, and gait and balance correlations between NP-C and control group.

Table 5.2: Summary of correlations between parameter values in NP-C patients and controls.

Parameters		Difference in parm 1	Difference in parm 2	Difference in correlation	Difference in correlation w/o extreme values
Gait only					
Cadence	Stride length	√	=	√	=
Single support %	Cadence	√	√	√	=
Balance only					
Jerk EC	RMS EC	=	=	=	
Gait and balance					
Cadence	RMS EO	√	=	√	=
Stride length	RMS EC	=	=	=	

√ Significant different between NP-C patients and controls; = No significant different between NP-C patients and controls; (blank) no extreme values.

The gait data from NP-C patients revealed that there was a negative correlation between cadence and stride length which was similar to the control group findings. There was a positive correlation between single support % and cadence with NP-C patients that matched results from controls.

Taken together, these similar correlations in NP-C patients and controls were very likely given that NP-C patients did not differ from controls on any of the individual measures. For example, NP-C patients and healthy individuals had the same stride length development and Table 5.1 showed that there was no significant difference in stride length in both groups. This also was emphasized by Sansare et al. (2018), who reported that there was no significant difference in step length data between NP-C patients and the control group. This could be one of the reasons for the similarity in the present correlation.

The present findings showed that there was a negative correlation between cadence and stride length in NP-C patient. This presumably is due to biomechanical elements that constrain locomotion. There is a good evidence in the literature emphasis this point, but on other patient group (PD), who share with NP-C the similar cerebellum pathology (Mirdamadi, 2016; Walterfang, Abel, et al., 2013). Morris et al. (1998) demonstrated that PD patient had decrease stride length with increase of cadence during walking. They relay this reason for

some of biomechanical elements (e.g. walking speed, leg late stance, and step size) that restrict more increase in stride length.

In general, these correlation results for NP-C could be due to a small number of unusual patients (1 or 2). When these patients were removed there was no evidence of distorted relationships between parameters.

5.5.1.2.2. Fabry patients:

Table 5.3 showed the summary of all the gait, balance, and gait and balance correlations between Fabry patients and control group.

Table 5.3: Summary of all correlations between Fabry patients and control group.

Parameters		Difference in parm 1	Difference in parm 2	Difference in correlation	Difference in correlation w/o extreme values
Gait only					
Cadence	Stride length	√	=	=	
Single support %	Cadence	√	√	=	
Balance only					
Jerk EC	RMS EC	=	=	=	
Gait and balance					
Cadence	RMS EO	√	=	=	
Stride length	RMS EC	=	=	√	

√ Significant different between Fabry patients and controls; = No significant different between Fabry patients and controls; (blank) no extreme values.

Fabry patients gait parameters data showed that there were negative correlations between cadence and stride length, while the correlation between single support % and cadence was positive. All of these were comparable to control group findings which is shown in Table 5.3, that there is no difference in gait correlation between both groups.

In general, Fabry patients were able to increase stride length by parallel amounts for any given decrease in cadence. It is well established that substantia nigra ,which is part of the

basal ganglia, is affected in Fabry disease and it is responsible for motor movement and balance control (Sonne J et al., 2020). This is achieved when basal ganglia provide internal motor cues to string sub-movements organised in a sequence when the overall movement strategy has been determined (M. Morris et al., 1998).

5.5.2. Balance Correlation Discussion:

5.5.2.1. Control group:

The correlation between balance parameters in control groups revealed that there were four strong positive correlations between all the balance parameters. This indicates that increasing in any balance parameter in healthy individuals will lead to increase in the other balance parameter within any eye condition. For example increasing in jerk EC will be combined with increasing in RMS EC.

These findings generally showing that there is a strong influence of the visual system on postural control with healthy individuals. This is in agreement with previous findings of Silfies et al. (2003) and Nolan et al. (2005), whom reported that there was a significant contribution of eye conditions (EO and EC) on balance parameters with healthy individuals and this relates to both sensing position and adjusting to balance changes. Indeed, this is clarified by the effect of visual sensory reweighting on muscular adjustment in order to maintain the postural balance (Assländer & Peterka, 2014).

5.5.2.2. Patient groups:

5.5.2.2.1. NP-C patients:

NP-C patients balance parameters had revealed that there were a strong positive correlation in jerk EC and RMS EC. This finding in NP-C patients was similar to the finding in the control group, which means there was no significant distortion of the relationship between sway and jerk in NP-C patients.

Generally, NP-C patients swayed significantly more than controls in both eye conditions due to disease severity and postural instability (Sansare et al., 2018) (discussed earlier in Chapter 4). Therefore, they need to adjust the smoothness of their sway by having more jerk values. This is what it found in Chen et al. (2018) study, who examined a similar disease group to NP-C. In their study they found that PD patients had higher jerk compared to control group in both eye conditions. However, in the correlation of balance parameters between NP-C patients and control group there were no significant differences. This can be explained due to the small sample size of NP-C patients (n = 9). Moreover, the difference between sway EO and EC was larger in NP-C patients compared to control group. However, despite the larger EC/EO difference in NP-C patients, there was no evidence that the relationship between the extent of sway and the smoothness of adjustment and corrections was disrupted.

5.5.2.2.2. Fabry patients:

The main findings in the balance parameters correlations with Fabry patients that there were a strong positive correlations in jerk EC and RMS EC. This finding was not significantly different from the control group. In general, the findings of balance parameters with Fabry patients (Chapter 4) were almost similar to the control group. This finding reflects on the correlation between the balance parameters in Fabry patients when it compared to control

group. This conclusion indicates that Fabry patients could compensate in a normal way in these balance correlations. Similar to NP-C, Fabry patients have no disruption to the relationship between the extent of sway and the smoothness of corrections.

5.5.3. Gait and balance correlation discussion*:*

The findings of gait and balance correlations were examined between only two gait parameter against all balance parameters (RMS EC, RMS EO, jerk EC, and jerk EO) (see section 5.4, p: 217). However, only two balance parameters showed some difference when they were compared with controls. Therefore, in this section, both of cadence and RMS EO and stride length and RMS EC were tested.

5.5.3.1. Control group:

The finding of the control group revealed that there were positive correlations (moderate effect) between the cadence and RMS EO. This indicated that individual with high cadence will have a high sway area and jerk in both eye conditions. The other finding was there were negative correlations (strong effect) between the stride length and RMS EC. Suggesting individuals with shorter stride length will have a high sway area and jerk in both eye conditions. These findings was suggested by Hausdorff (2005) who reported that an increased in gait parameters variability"s effect on the movement of COP leading to increased postural instability and risk of falling. Generally, step length, stride length, and BOS modify the challenge to equilibrium through gait, and this could reflect balance ability (Alderson et al., 2019).

5.5.3.2. Patient group*s:*

5.5.3.2.1. NP-C patients:

NP-C patients data showed that there was a positive correlation (moderate effect) between cadence and RMS EO. This finding was not significantly different from the control group after the extreme values were eliminated. Moreover, their data revealed that there were a negative correlation (strong) between stride length and RMS EC, which was similar to control group findings. These findings of NP-C patients correlation came supporting the observation of Stolze et al. (2002) who found that patients with cerebellar degeneration had decrease cadence leading to decrease some balance parameters, which in turn increased postural stability during walking. Both of the present findings and Stolze‟s findings suggesting that gait parameters variability had contribution on balance parameters that could be associated with postural stability. In conclusion, there were a small number of NP-C patients with extreme values. When these patients were excluded, the relationships between gait and balance parameters were not abnormal. While, there was also a small number of patients were substantially different from controls. Therefore, a good number of NP-C patients can contribute in more certain conclusion.

5.5.3.2.2. Fabry patients:

The correlation findings of Fabry patients revealed that there were a positive correlation between cadence RMS EO. This finding was not significantly different from the control group, except one correlation which was between cadence and RMS EC for Fabry patient. This correlation was significantly different from control group. On the other hand, finding of the stride length and RMS EC revealed a positive correlation (small effect) in Fabry patients, which was significantly different to control group.

The correlation data of the Fabry patients showed some variability, when it compared to control group. This can be potentially explained due to greater variability of the gait data with Fabry patient (see Chapter 3, p: 94-95), which had a greater impact on the correlation findings. Moreover, there were a couple of results where balance parameters didn‟t improve in the normal way as gait parameters changed. This may indicate some disruption to balance development with age (since the gait parameters showed strong developmental effects). This pattern is strongest in RMS EC, but also evident in RMS EO, which is just inside rather than outside the control range, but still a pretty unusual value. While, the jerk values are closer to the control values, so they look more normal.

On the other hand, in the present study, some of gait and balance correlations with Fabry patients showed a significant relationship between them that contribute on postural stability. Unfortunately, there are no studies investigated these correlations in Fabry patients, however, there are some studies investigated similar correlations in other patient groups. For example; a study done by Cameron and Lord (2010) on MS patients, which shared with Fabry patient the involvement of substantia nigra, reported that walking abnormalities (e.g. reduced cadence and stride length) was correlated with balance impairment resulting in increase of postural instability and risk of falling.

CHAPTER 6: GENERAL CONCLUSIONS

6.1. General conclusions:

IMDs are rare diseases caused by dysfunction of metabolic enzymes resulting an accumulation of toxic metabolites, which, in turn, affect the normal development of the CNS (Wraith, 2012). Degeneration of the CNS can play a crucial role in the developing abnormal physiology of neurological and/or musculoskeletal systems with these patients (Martin et al., 2008). Abnormalities can be observed in the abnormal gait pattern and/or postural imbalance of some of the IMD patients we studied, in particular NP-C, Fabry, Hurler, Morquio, Maroteaux-Lamy, and Pompe. For example, NP-C and Hurler patients had abnormal gait and balance, while Fabry patients had abnormal gait but normal balance.

Each of these neurodegenerative diseases developed a specific abnormality in their gait and balance parameters. In NP-C patients single support % and cadence were the most affected gait parameters and the EC/EO jerk difference was the most affected balance parameter. Stance %, single support %, and cadence were the most affected gait parameters in Fabry patients. In Hurler patients, single support % and stride width were the most affected gait parameters and both RMS and jerk were affected in his group.

Previous studies have tried to identify affected parameters in these patients by using gait and balance measurement tools, and have provided preliminary data in this area (Sansare et al., 2018; Wood et al., 2009). The current thesis provided more accurate and sensitive measurements of gait and balance changes by using sensors: a Zeno mat and accelerometers. It measured changes in the gait parameters in neurodegenerative disease patients and compared them with healthy controls. It also measured balance changes to detect differences between patients and healthy individuals, and to measure how patients responded to changes with sensory reweighting. Finally, this thesis aimed to quantify any relationship between gait

and balance parameters, and to assess whether relationships between parameters were altered by disease.

To measure posture and balance in patients it was necessary to establish baseline data and a comprehensive understanding of the developmental changes in gait and balance patterns in healthy controls. Control data can help clinicians to track disease progression in order to improve therapeutic interventions and manage further complications for neurodegenerative disease patients. In this section the findings of each neurodegenerative disease in gait, balance and correlation will be summarised separately.

6.1.1. NP-C patient‟s conclusion:

The gait findings for NP-C patients showed that they had an abnormal gait pattern. Some parameters, including shorter stride lengths, higher stance percentage and wider stride width were only different when extreme patients were included compared to the control group. Other parameters were different even when severe patients were eliminated, including fewer steps per minute (cadence) and significantly reduced single support percentage compared to the control group. Single support percentage and cadence were more sensitive to early changes (i.e. in the less affected individuals) and values lower than the control mean were widespread in the population.

For balance, RMS is related to sway area, or the sensing of movement that approaches an unstable position, while jerk reflects the smoothness of corrections to bring the body back to a stable central position. RMS was not abnormal in NP-C patients and there was a normal difference between eyes-open and eyes-closed conditions, reflecting normal weighting of visual and other signals (proprioception and vestibular signals). The jerk EC/EO difference was larger than in the control group, without EO or EC being clearly different from controls

on their own. This was because the EO value was numerically *smoother* than controls and close to the control boundary for low jerk, while the EC value was close to the control mean. This pattern may indicate a shift to greater reliance on visual signal, but only for corrections and not for monitoring position. Overall, the main and important finding in balance results for NP-C patient is that the EC/EO difference was larger than control group for jerk, but not for RMS.

Finally, correlations were in the control range for NP-C patients when the extreme patients‟ values were excluded. The relationships among gait parameters themselves, among balance parameters themselves and between gait and balance parameters had not been disrupted. The NP-C sample was small and there were only 1 or 2 more extreme patients, so conclusions about intact relationships should be cautious.

NP-C is a rare metabolic disorder that is caused by a defect of LDL and sphingolipids in fibroblast lysosomes (Floyd et al., 2007), and characterized by neurological and visceral manifestations (Alobaidy, 2015). An early and prominent feature of NP-C neuropathology is cerebellar degeneration (Floyd et al., 2007). Changes in cerebellar volume are associated with measures of ataxia and ocular-motor function (Walterfang et al., 2013). Moreover, the cerebellum can affect the feedback mechanism that is required to maintain and adjust static and dynamic posture (Yanagihara, 2014). In addition to cerebellar degeneration, a reduction in the volume of the hippocampus, thalamus and grey matter and variations in the volume of white matter in most regions played a considerable role in motor control which could influence NP-C patients‟ gait and balance (Walterfang et al., 2010; Walterfang et al., 2013).

In the current thesis, the findings of gait parameters revealed that both single support % and cadence were significantly different in NP-C patients compare to healthy individuals. This indicates that these parameters are the most effected gait parameters in NP-C patients. This

partially supports the Sansare et al. (2018) findings, who demonstrated that NP-C patients had a reduction in single support time compared to healthy individuals. However, in cadence, Sansare et al reported that there was no significant difference between NP-C patients and healthy individuals, which is not consistent with the findings here or with Paciorkowski et al. (2008). Both the current results and Paciorkowski et al. (2008) found that NP-C patients had significantly slower cadences than healthy individuals. The potential explanation in Sansare et al. findings is that they have larger variance in the control cadence data than both the current thesis and the Paciorkowski study.

In respect to the current thesis balance findings, the most important finding is that NP-C patients had a significantly increased EC/EO difference in jerk compared to the control group. Sansare et al (2018), found that postural *sway* was significantly increased during EC condition compared to EO conditions. The current results found a difference in jerk and Sansare found a difference in RMS. What is in common is that both results found that balance was affected in NP-C patients. Since Sansare didn‟t measure jerk it is possible that jerk is affected more than RMS. Together, these results do indicate a re-weighting toward vision. The visual signal is more important in NP-C patients, showing that the other signals are impaired (proprioception or the vestibular signal). However, in the current thesis the difference appears in the smoothness of the adjustment (jerk), where in Sansare the difference was in sensing the safe area for sway.

The relationship between the gait and balance parameters findings was interesting. This is because the findings revealed that there was no significant difference in gait, balance, and gait and balance correlations between NP-C patients and healthy individuals. Even when some NP-C patient parameters were not normal, the *relationship* between parameters was not disrupted in any dramatic way. However, there is really too little data to be definite about these correlations (due to the small number of NP-C participants).

6.1.2. Fabry patient‟s conclusion:

Fabry patients had an abnormal gait pattern, with an increased stance %, decreased single support % and reduced cadence.

The Fabry balance measures were not different from the control group. Neither RMS nor jerk values were different from control group and the difference between EO and EC conditions was also not abnormal for either RMS or jerk. Balance in Fabry patients, as a group, appeared to be unaffected.

In regard to correlations, Fabry patients showed variations in the results. Both gait correlations, on their own, and balance correlations, on their own, revealed no significant differences between Fabry patients and healthy individuals. However, some of the gait and balance correlation (e.g. cadence & RMS EC and stride length & RMS EC) were significantly different from healthy individuals. Balance parameters were not affected in Fabry patients, so this suggest that gait changes are not connected to or caused by balance changes. Gait gets worse, relative to controls, even if balance stays within the control range, or, more precisely, gait measures didn‟t show the normal improvement with age while static balance did.

Fabry disease is an X-linked lysosomal storage disorder that is caused by deficit of AGA enzyme. Fabry patients are known to developed nervous system dysfunction. Several neuropathological studies done by using MRI and/or electrophysiology reported that there are brain regions that are affected in Fabry patients, for example, the substantia nigra (de Veber et al., 1992; Kaye et al., 1988; Löhle et al., 2015). Substantia nigra is a part of the basal ganglia located in the midbrain. It plays a vital role in locomotion and balance control (Barter et al., 2014; Sonne J et al., 2020). In Fabry patients, the substantia nigra is affected, resulting

in an abnormal gait pattern. This is what was found in the current thesis, and also by Löhle et al. (2015), who reported that Fabry patients had slower gait and transfer speed compared to an aged-matched control group. Although the Löhle et al. (2015) finding provided a general idea about the Fabry patient gait pattern, the current thesis characterized the exact affected gait parameters.

If the current thesis findings are compared with findings from PD patients, who share with Fabry patients the same affected area (substantia nigra, e.g. (Sonne J et al., 2020)), the results are similar. Several studies conducted on PD patients demonstrated that PD patients had decreased gait speed step and stride length (Bond & Morris, 2000; Mak, 2013; M. E. Morris, Iansek, Matyas, & Summers, 1996; O'Shea, Morris, & Iansek, 2002).

On the other hand, the balance findings were surprising. Fabry patients were not different compared to the control group. Löhle et al. (2015) reported that Fabry patients had postural instability compared to the control group during a TUG test. Their findings are not consistent with the present findings. This could be related to the different methodologies used in both studies to measure balance (TUG vs. accelerometer) and/or patient age. In general, TUG measures dynamic balance (balance under movement), while here accelerometers were used to measure static balance.

Some of the correlations between gait and balance in Fabry patients were significantly different from the control group. Patterns evident there might help to explain the discrepancy with the Löhle et al. (2015) result. For example, in the stride length and RMS EC plot (Figure 5.29), the control group RMS decreases as stride length increases, whereas for Fabry patients, RMS stays the same while stride length increases. If we note that stride length consistently lengthens with age, the changes in correlation could be explained if Fabry patients show decline with age in some of the parameters (in this case, RMS). This explanation could

support the findings from Löhle et al. (2015) who tested adult patients, if, with age, Fabry patients develop more balance abnormalities.

6.1.3. Hurler (MPS I) patient‟s conclusion:

Hurler patients showed different signs of abnormal gait parameters compared to healthy individuals. These abnormal gait parameters include shorter stride length, reduced cadence and increase stance %. However, after removing extreme patient values, these parameters were not different than the control group. Instead, single support % and stride width were significantly different compared to healthy individuals even after extreme values were removed. Overall, the most affected gait parameter was single support % and, to a lesser extent, stride width.

Compared to controls, Hurler patients had higher RMS and jerk values in both eye conditions. In general, there are too few Hurler‟s patients to be very confident about group-level conclusions. Some participants had high RMS values in both EO and EC conditions, but despite the high values, the EO/EC difference was not abnormal in RMS. It was higher than normal in jerk, but influenced by extreme values. There was some ambiguity, but no clear evidence that the visual signal had been weighted more strongly to make up from problems with proprioceptive or vestibular signals. In conclusion, both the balance parameters RMS and jerk were affected in Hurler patients.

Hurler is one of the rare autosomal recessive diseases from the Mucopolysaccharidosis family (Aldenhoven et al., 2008). It is a chronic progressive disease that can affect multiple systems. Effects on the musculoskeletal system leads to numerous orthopaedic complications such as

restrictions in joint ROM, especially in the spine, hips and knee, that can affect patients‟ gait pattern and balance (Bjoraker et al., 2006).

The current thesis found various gait parameters were abnormal in Hurler patients, but the most significant effect was a reduction in single support %.

There is shortage in the literature of studies that examine single support % or stride width in Hurler patients. On the other hand, a good number of studies have examined these parameters in CP patients, who share with Hurler patients similar abnormalities in the musculoskeletal system (see page: 187) (H. K. Graham & Selber, 2003). One of these studies, conducted by Kim and Son (2014), found that CP patients had a significant decrease in the single support time compared to the control group. Moreover, Johnson et al. (1997) reported that single support significantly decreased with time and growth with CP patients. These findings in CP patients and the current thesis findings in Hurler patients suggest that decreased joint ROM and wasting of the lower limb muscles plays a crucial role in reducing the single support % or time. Reduced ROM will influence the swing movement part of the GC, resulting in decreased single support time to avoid losing balance (Wood et al., 2009). Also, due to the restriction of hip abduction, ROM and valgus knee, which are found in both groups (Hurler and CP), feet will be placed wider apart than usual (increased stride width), which will affect gait and balance in these groups (Leviae et al. 2012).

The present study is the first study to provide sensitive measurement of balance control with Hurler patients. The important balance finding was that both RMS and jerk were affected. However, it was challenging to determine whether the EO/EC difference was abnormal (nominally „no‟ for RMS and „yes‟ for jerk, but based on a very small sample). This finding may be in agreement with J. Rose et al. (2002) who found that CP patients had a slight increase in ARD in EC compared to EO conditions, but not significant. These findings

indicate that CP patients, and perhaps, by extension, also Hurler patients, had normal dependence on visual feedback, or in other words, no impaired sensory reweighting. Instability in Hurler could be due to an impaired weight shifting ability and the sway area increase could be related to the weakness of the hip abductors (Wood et al., 2009). These musculoskeletal factors may lead, in turn, to decrease balance control and postural instability. In general, these results are quite uncertain because of the small number of patients and the large variance within patients (some patients are within the normal range and some are not).

6.1.4. Morquio (MPS IV) patient‟s conclusion:

The following sections are based on very small numbers of individuals, which means that the results are only preliminary indications of what can happen, but not measures of what typically *does* happen in the full population.

Morquio (MPS IV) is a rare autosomal recessive disease, caused by a metabolic disorder, which leads to many symptoms (section: 1.2.2.2, p:14). The most important symptoms that affect patients‟ activities of daily living are severe gross motor delays with decreased muscle tone and strength (Hendriksz et al., 2014). The results from Morquio patients in this study were statistically inconclusive. However, the results could help begin to establish baseline data for this patient group. In gait findings, Morquio patients showed some gait abnormalities compared to control. Morquio patients were above the control mean in stance %, while in single support % and cadence they were below the control range. Stride width results were varied. One patient had a wider stride width than controls, while the other patient had a narrower stride width and two patients were within the control range. Moreover, the gait findings revealed that Morquio patients and controls had similar stride length. Overall, single support %, cadence, and stride width were the most affected gait parameters.

Full balance measures were obtained from only one patient, as the rest of the patients didn‟t successfully complete the test. The findings revealed that this patient had higher RMS and jerk value in both eye conditions compared to the control group. Comparing the two eye conditions, RMS EC and jerk EC were higher compared to the EO condition, and the difference appeared abnormally large, although this was not formally assessed. This suggests that this patient may depend more heavily on vision for balance than controls. Overall, from these findings it can be reported that both of RMS and jerk were affected in Morquio patients, especially in the EC condition.

The present gait parameter results (in particular, cadence) support the findings of Dhawale et al. (2013). They reported that Morquio patients had significantly decreased cadence compared to the control group. Potentially, this was due to abnormal ROM and muscle strength.

Although balance results were taken from only one participant, these preliminary data parallel other studies conducted on different diseases that share similarities to Morquio syndrome. One of these diseases is MS, which shares with Morquio syndrome an enlargement of the perivascular spaces. This, in turn, results in a motor weakness (Ge et al., 2005; Saeki et al., 2005; Zamani, 2008). Our balance findings from Morquio syndrome are backed up by McLoughlin et al. (2015), who found that MS patients had increased sway in an EC condition compared to an EO condition. These findings suggest the importance of the sensory reweighting mechanism for balance control. This means that Morquio patients may depend on visual inputs in their balance control to compensate for some of the effects of muscle weakness which is due to a relative failure of proprioceptive input. Proprioceptive

sensitivity is linked to and relies on muscle receptors. Subjects with muscle weakness have less mass and fewer sensory units and, as a consequence, joint sensory input is diminished (Butler et al., 2008).

6.1.5. Maroteaux-Lamy (MPS VI) patient‟s conclusion:

The gait pattern of Maroteaux-Lamy patients was different from controls. Abnormal gait parameters included higher stance % and lower single support % compared to the control group. The other gait parameters (e.g. stride length, cadence, and stride width) were similar and within the control group range.

In regard to balance findings, Maroteaux-Lamy RMS and jerk values were similar to the control group in both eye conditions. Balance was not affected in the Maroteaux-Lamy patients studied here.

Maroteaux-Lamy produces skeletal deformities and joint abnormalities leading to gait abnormalities (Harmatz & Shediac, 2017). Maroteaux-Lamy patients are also known to have abnormal development of the CNS, which includes white matter, perivascular spaces and cerebral atrophy (Azevedo et al., 2013; Vedolin et al., 2007). These neural abnormities lead to developing musculoskeletal problems, especially muscle weakness with Maroteaux-Lamy patients which limit their physical performance.

In the present study, single support % was one of the most affected gait parameters and single support % is highly depend on lower limb joint ROM. Any lower limb joint stiffness and bone deformities can affect single support %. This is supported by studies conducted on CP patients (Johnson et al., 1997; Kim & Son, 2014) who are known to have a cerebral atrophy. These studies reported that CP patients have lower single support % during walking. This

was interpreted as due to the musculoskeletal problems (e.g. decreased joint ROM and muscle imbalance) that CP patients develop.

In Maroteaux-Lamy patients RMS and jerk were similar in both eye conditions, indicating normal dependence and sensory weighting in maintaining their postural stability. However, this finding should be considered with caution. The balance data were obtained from only two patients, and their data were influenced by treatment differences. One of the patients was diagnosed and received treatment early and showed better balance results (within the control range), while the other patient was diagnosed and received treatment later and showed more abnormal balance data (slightly above the control range; Figure 4.31). The average of these patients would be normal or borderline normal. These data suggest that early diagnosis and intervention *might* result in better outcomes, but more data would be required to follow up on this very preliminary result.

6.1.6. Pompe patient‟s conclusion:

The gait parameters of the early ERT-treated Pompe patient were similar to the control group and didn‟t show any abnormalities. However, the balance findings of this group were different. Both RMS and jerk values in both eye conditions were higher than the control group. Further examination revealed that RMS and jerk values were increased in the EC condition compared to the EO condition, indicating a higher dependence on the visual signal. Overall, this finding indicates that both RMS and jerk (especially in EC condition) were affected in the Pompe patient.

Pompe is another autosomal recessive metabolic disorder that mainly affects the proximal lower limb muscles, resulting in muscle weakness and hypotonia. This is caused by accumulation of lysosomal glycogen in many tissues such as skeletal, heart and smooth muscle (Case et al., 2015; Kishnani et al., 2006). In addition to the smooth muscles, several studies have reported accumulation of the lysosomal glycogen in the cerebellum and cerebral cortex (Hobson-Webb et al., 2012; Mancall et al., 1965; Martini et al., 2001; Thurberg et al., 2006). This suggests there could be a contribution of the CNS to the motor deficit seen in Pompe patients (Hobson-Webb et al., 2012; Prater et al., 2012).

Although most of the evidence in the literature reports that Pompe patients develop musculoskeletal problems, especially lower limb muscle weakness, the present findings in gait showed the opposite. The current findings revealed that this Pompe patient had similar gait parameters to healthy controls, despite mild muscle weakness. It is worth mentioning that this Pompe patient was diagnosed and treated early, which may have influenced his better gait parameters results. Fukuhara et al. (2018) concluded, in their study, that timing of the diagnosis and treatment can influence Pompe patients‟ clinical features.

Contrary to gait findings, the balance findings showed some abnormalities. There was an increase in RMS and jerk during the EC condition. This indicates a comparative failure of proprioceptive postural control linked with muscle weakness (Butler et al., 2008). These findings suggest the patient depended more strongly on visual feedback for maintaining their balance. This finding was obtained only from one patient, so it should be interpreted with caution. Having mild muscle weakness and impaired sensory reweighting during EC condition, resulted in using a compensatory strategy of movement to avoid postural instabilities (Kishnani et al., 2006), and this is what was observed with the Pompe patient.

Abnormal RMS occurring with abnormal jerk may be linked. Having high sway may lead to high jerk in order to adjust body position to avoid falling.

The following table (Table 6.1.) summarizes all gait, balance, and correlation parameters results for the patient groups after the extreme values have been eliminated.

Table 6.1: Summary for all the gait, balance, and correlation parameters results for all the patient groups.

Parameters	Parameters	NP-C	Fabry	Hurler	Maroteaux-Lamy	Morquio	Pompe
Gait Parameters							
	Stride length	=	=	=	=	=	=
	Stance %	=	√	=	√	=	=
	Single support %	√	√	√	√	√	=
	Cadence	√	√	=	=	√	=
	Stride width	=	=	√	=	√	=
Balance Parameters							
	RMS EC/EO difference	=	=	=	?	?	?
	RMS EC	=	=	√	=	√	√
	RMS EO	=	=	√	=	√	√
	Jerk EC/EO difference	√	=	√	?	?	?
	Jerk EC	=	=	√	=	√	√
	Jerk EO	=	=	√	=	√	√
Correlation parameters							
	cadence and stride length	=	=				
	single support % and cadence	=	=				
	Jerk CE and RMS EC	=	=				
	Cadence and RMS EO	=	=				
	Stride length and RMS EC	=	√-				

√ Significant different between patient group and controls; = No significant different between patients‟ groups and controls; ? uncertain; (blank) N/A; √- significant different and weaker correlation in patients than controls.

6.2. Clinical implications:

Most of the tested IMDs patients in this thesis are known to have musculoskeletal deformities that range from mild to severe, and these abnormalities affect patients‟ physical activities, especially the activities that include gait and balance control (Martin et al., 2008). Treatment of IMDs mainly depends on treating symptoms. ERT and UCBT are the most common treatments (Dusing & Thorpe, 2007). Several sudies conducted on different IMD patients, have revealed promising results improving gait patterns and balance control.

In addition to the medical managment for the IMDs, physical therapy is considerd a critical element of a comprehensive treatment for these patients. The general aim for physical therapy interventions with these patients is to improve patient physical activity including gait and balance, and decrease dependency in their activities of daily living. This could be achieved by training body systems to compensate for neurological problems using motor control training rehabilitation, which could improve patients‟ gait and balance control. Therefore, knowing the most affected gait and balance parameters can be useful during the physical therapy assessment session to focus on these parameters. For example, the findings of this thesis suggested that cadence, single support %, and EC/EO jerk difference were abnormal and were the most affected gait and balance parameters in NP-C patients. Therefore, the treatment plan should be focused on improving and treating these abnormalities. For instance, exercise training had been shown to be an effective method for improving motor disorders (e.g. gait, balance and physical function; (Collado-Garrido, Parás-Bravo, Calvo-Martín, & Santibáñez-Margüello, 2019; Fowler et al., 2007; Verschuren et al., 2007) and could be used with this patient group. Exercise training could include joint ROM, strength and flexibility exercises for the lower limbs, and balance training, taking into consideration each patient‟s physical limitations.

Moreover, physical therapy management can have a vital role in improving gait patterns for Hurler, Morquio, and Maroteaux-Lamy, especially in improving cadence, single support %, and stride width, which were the most affected parameters in these groups. For example, Sashika et al., (1996) reported that 6 weeks of hip ROM exercises and hip abducation isometric exercises for patient with hip arthroplasty abnormalities improves cadence significantly. This could be used with Hurler, Morquio, Maroteaux-Lamy, and Pompe patients. Moreover, Unlu et al. (2007), who used the same exercise rehabilatiation as Sashika et al. (1996), Found that cadence was improved with total hip arthoplasty patients in home-based and supervised sessions. Sohmiya et al. (2013) found that stretching exercises for the lower limbs of PD patients significantly increased hip and knee flexibility. This was reflected in a mild increase in cadence and single support time. Morover, in regards to single support %, most of the patients in the current thesis have reduced single support percentage compared to healthy controls. This can be improved by using different clinical therapeutic methods. For example, in clinical practice physical therapists can add obstacles in front of patients during gait training to help patients to lift their lower limbs more than usual. This task can help the patient to have higher single than double support % and help to improve postural stability.

Most of the IMD patients in this thesis had balance disorders such as Hurler, Morquio, and Maroteaux-Lamy, which resulted in a fear of falling. Balance disorders and fear of falling play a huge role in limiting physical activities in these patients. The major causes for the balance disorders were decreases in lower limb and spine muscle strength and ROM and up-weighting of the visual signal when the visual signal is intact but other signals are affected.

Exercise training has produced good outcomes in improving balance control. Balance training exercise usually works on challenging a person to control their body‟s centre of gravity during different movements with or without small BOS.

Several studies have evaluated the effect of the balance training exercises on postural stability in PD patients. Hirsch et al. (2003) demonstrated that progressive resistance exercises for affected muscles produced better postural stability and a reduced risk of falling for PD patients. In addition, Mhatre et al. (2013) investigated the effect of the balance training exercises on balance and gait in PD patients. They found that balance training using the Nintendo Wii Fit video game and balance board system for 8 weeks improved the dynamic gait index and postural sway. These findings supported earlier finding by Esculier et al. (2012), who reported that using the Nintendo Wii Fit and balance board for balance training exercises resulting an increase in static and dynamic balance control with PD patients. Overall, exercise-game training as a method of balance training is more attractive for young patients. These exercises could be used with NP-C, Hurler, Morquio, and Pompe patients. An advantage is that game stimulate both the motor and cognitive functions. This, in turn, might produce improvements for these patients, which assist them in their everyday activities.

6.3. Limitations:

Due to the rarity of the metabolic disorders investigated in this thesis, some of the patient groups have small numbers and sometimes even some of those patients were outliers. As a result, there was a need to define which groups were suitable for group comparison analysis after excluding these extreme data points. Anytime a group of patients had less than 50% of the patients remaining after excluding outliers, group comparisons were not carried out. Excluding outliers gives a conservative estimate of group parameters compared to controls. Outliers could reflect a normal range of disease effects (i.e. outliers are the most severely affected patients) or they might be determined by co-morbid factors that don‟t always co-occur with the disease. Because outliers can affect very strongly the parameter estimates for a patient group, we have calculated differences with and without outliers included. Where patients and controls are different even after outliers have been removed the conclusion that there is a difference between groups is conservative. Where patients and controls are not different when outliers are excluded, but then including outliers creates a difference, concluding that there is truly no difference should be subject to some caution.

6.4. Future study:

The current findings were obtained from very rare IMD patients age starting from age 4 years old. Future studies starting earlier, from the age when walking begins, could provide a valuable record of very early gait and balance development in these patients. The current thesis used a cross-sectional research design. The cross-sectional approach was used because it takes less time to conduct and involves less obligation from participating patients from rare disease groups who already have relatively full clinical schedules. As we have seen, many outcomes can be characterised in this way. However, future studies on these IMDs patients

should consider a longitudinal approach to evaluate the gait and balance developmental *trajectories*. In general, these degenerative patients were expected to decline over time and this doesn‟t necessarily show up in cross-sectional study, especially when patients are relatively intact. Trajectories could produce a sensitive measure to detect change over time because the slope of developmental change might become abnormal before any individual observation is outside the control range. The current findings from this cross-sectional study and future longitudinal studies could provide a comprehensive understanding of the developmental changes in gait and balance for these rare IMD patients.

Moreover, the resources and the data from this thesis will be available to other studies (subject to approval from the NHS ethics) for further investigations and research. For example, the anonymised database from the Zeno mat can provide a rich source of information for future analysis, e.g. foot progression angle is one example which can show if the participant walks with in-toeing or out-toeing during gait. Another example, it might be interesting to carry out a regression analysis of the effects of joint/muscle weakness or developmental delay on gait measures by including these variables as a predictors.

Knowing the most affected gait and balance parameters could help in designing a gait or sway monitoring mobile phone app which would concentrate on these parameters to monitor patients during daily life activity. This could help the therapist and the patients to track their gait quality and postural balance control and prevent adverse outcomes.

6.5. Final conclusion:

In this thesis, detailed characteristics of the development changes to gait and balance for 6 IMD groups (NP-C, Fabry, Hurler, Morquio, Maroteaux-Lamy and Pompe) were studied to established new baseline data. Sensitive and reliable new measurement tools (Zeno Mat and accelerometers) were used to assess a number of gait and balance parameters. This helped to determine each disease‟s progression and the most affected parameters in each group. Table 6.2 summarises where differences were observed in the general areas of gait, balance, and correlation results.

Table 6.2: Summary table for all the patient groups gait, balance, and correlation results.

Patient groups	Gait	Balance	Correlation
NP-C	√	√	√
Fabry	√	=	√
Hurler	√	√	?
Maroteaux-Lamy	√	=	?
Morquio	√	√	?
Pompe	=	√	?

√ Significant different between patient group and controls; = No significant different between patients‟ groups and controls; ? uncertain or N/A.

Several affected parameters in the general domain of gait (cadence, single support %, and stride width) or balance (RMS and jerk) were identified for each disease group and compared to healthy individuals. These affected parameters can provide valuable information for researchers and clinicians to track disease progression and to evaluate the effectiveness of therapeutic interventions for each disease.

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APPENDICES

Appendix 1:

A) Participant information sheet.

B) Consent form.

Appendix 2:

A) Zeno mat PK MASS software.

B) Accelerometer Mobility lab software.

C) Gait R code example.

D) Balance R code example.

Appendix 3:

A) NP-C patient gait figures.

B) Fabry patient gait figures.

C) Hurler patient gait figures.

Appendix 4:

A) NP-C patient balance figures.

B) Fabry patient balance figures.

C) Hurler patient balance figures.

Appendix 5:

A) NP-C patient gait correlation figures.

B) Fabry patient gait correlation figures.

C) NP-C patient balance correlation figures.

D) Fabry patient balance correlations figures.

E) NP-C patient gait and balance correlation figures.

F) Fabry patient gait and balance correlation figures.

Appendix 1

A. *Participant information sheet:*



School of Psychology

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Cognitive assessment of paediatric neurodegenerative disease

Your child is being invited to take part in a research study. Before you decide if you want your child to take part it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Please ask us if you have questions or if you would like more information. You may take time to decide whether or not you wish to take part.

What is the purpose of the study?

We are researching how inherited metabolic disorders affect abilities in several areas: memory, language development, attention, executive function and motor control. We need to give children who participate a selection of tasks (see below). We want to know if some abilities are affected more severely or earlier than others. We also want to know if individuals are all similar or show very different patterns. The study is for research purposes. We want to understand how these diseases affect the brain. We also want to develop ways to measure a child"s progress so that when new treatments are available, we will be able to tell if they are working. We will be able to give you information about how your child is doing on our tasks, but the tasks are not designed to be therapeutic, and we do not expect them to provide beneficial health effects.

Where and when will the study take place?

We may ask to see children on several occasions. We would like to follow progress every six months for a number of years. You will be able to decide how much to participate and you can stop at any time. The study will take place at a dedicated clinical research facility at Birmingham Children's Hospital or at the University of Birmingham. The sessions can be scheduled at the time when you come for regular visits to the Children's Hospital, or at a separate time, depending what is most convenient for you. Parents can normally be present during the sessions.

Why has your child been chosen?

Any child with a metabolic disorder who we think would be able to try our selection of tasks could be asked if they want to take part.

Does my child have to take part?

Your child does not have to do the study. It is up to you to choose whether or not you want your child to take part. If you allow your child to take part you will be asked to sign a form giving your consent. If you do decide to take part, you are still free to withdraw your child at any time and without giving any reason. You may request that your child's data are removed from the study and destroyed at any time. If you decide not to take part or if you decide to withdraw your child from the study at any time, this will not affect any treatment your child receives from the Birmingham Children‟s Hospital.

What will happen to my child if he/she participates in the study?

If you decide to let your child take part, we will arrange a convenient time for you (this could be at the same time you come for clinical visits if that is convenient). Your child will be asked to do one or more tasks, in sessions that we can arrange to suit your child's abilities (sessions would normally last between 15 and 90 minutes).

The tasks we will do will be chosen from the following list:

Attention tasks. *Simple reaction time* measures time to respond when a ladybird character appears on a computer screen. *Respond/don't respond* measures time to respond to the ladybird and not respond to a nasty bug. *Task switching* changes the target to the nasty bug. *Searching* measures time to find the target when it appears with other distracting items. *Rapid visual information* measures ability to notice particular 3-digit combinations embedded in a stream of digits presented rapidly in the centre of the screen. The *Stroop Task* asks participants to name the colour a word is written in while ignoring the word (e.g. for RED written in green ink, say "green"). These are all measures of visual processing and attention.

Motor control tasks. The *pegboard task* measures how quickly children can fill a board by putting a peg in each hole. *Postural stability* asks children to stand with eyes open or while wearing a blindfold while sensors measure how much they sway. *Gait assessment* asks children to walk down a sensor mat which records how they walk (speed, step size, stability). *Range of motion* measures the angles joints are able to move through. *Muscle testing* measures how easily muscles can resist slight pressure applied by the examiner. *Baseline motor tasks* asks children to do some simple movements (touch your nose, touch the examiner‟s finger). *Eye-movement tasks* use a high speed camera to measure how children‟s eyes move when they look at targets appearing or moving on a screen.

Memory tasks. Children will be asked to *remember which words were in a longer list, repeat back a short list of words or digits, remember the order of boxes that flash on a screen, learn the nonsense names* for a set of cartoon characters, *remember nonsense words* and *remember visual patterns* after a delay. Children will be asked to remember items hidden behind boxes on a computer screen (like the game "memory") and learn to associate a nonsense word and a picture of a real object.

Language development. Children will be asked to name pictures, point to the picture that matches a spoken word, re-tell a well-known fairy tale (Cinderella), remember words from a list immediately and after a distracting list, spell real words and nonsense words, read real words and nonsense words and manipulate the sounds in words (e.g. repeat the word *table* without the "t").

Executive functions (planning, problem solving). Children will be asked to solve a puzzle where they must move different size disks from one peg to another based on a set of rules, trace a trail on paper that joins numbers or that joins alternating letters and numbers and match cards based on colour, number or shape. In this last task, the rule for matching changes once the child has understood which rule is operating and we measure how quickly children switch the rule they are using.

You may be asked to provide a small blood sample (a blood spot) prior to activities from the list above to measure the level of critical metabolic chemicals.

Will my child's participation in this study be kept confidential?

Any information collected during our research will be kept strictly confidential. None of the assessments will have names on them and the record of participant‟s names will be kept securely and separately from any assessments, which are identified by number. When we report the results of this study we will only report results from groups or we will report numbers, so individual participants cannot be identified.

What will happen to the results of the research study?

The anonymized data collected during the project will be analyzed by members of the research team and/or by students and research fellows under their supervision. During some of our tasks we may need to make audio or video recordings in order to measure the time it took to do the task or score how it was completed. These recordings could be used during scientific presentations of the results. If you do not want recordings of your child to be used during scientific presentations, please indicate this in the box that asks about recordings on the consent form. All scientific data from the project, which includes audio and video recordings, will be retained for a minimum of three years following the end of the project. We keep the information because the diseases we are studying involve changes over time that could be important to consider in future research. We may ask participants from this study to participate in follow-up studies in the future. However, agreeing to this project does not mean you need to participate in any future studies. In fact, if you would prefer that we do not contact you regarding research that we do in the future, please indicate this in the box for this purpose on the consent form.

You will be able to request a summary of the results from your child after they have been scored. If you are concerned about any results we will be happy to provide feedback once we have scored the data and can summarize it for you (we would not normally be able to show you results on the same day as the test). You can make an appointment with us to discuss the progress of the project at any time. We will prepare a non-scientific summary of the study that you may also request when the study is complete.

Who is organizing and funding the research?

This study has been funded by the University of Birmingham, the Economic and Social Research Council (ESRC), The Society for Mucopolysaccharide Diseases (MPS Society) and Actelion Pharmaceuticals.

Who has reviewed the study?

This study has been reviewed by the South Birmingham Research Ethics Committee.

Who can I contact if things go wrong or I am unhappy about what happens in the study?

If you wish to complain or have any concerns about any aspect of the way you have been approached or have been treated during the course of this study you may contact us with your concerns. You may also use the normal National Health Service complaint mechanisms. Details are available on the website below:

http://www.nhs.uk/England/AboutTheNhs/ComplainCompliment.cmsx

Alternatively, you can contact the Patient Advice and Liaison Service (PALS) at your local hospital where you receive treatment and they will able to assist you with any complaint.

The PALS office at Birmingham Children‟s Hospital is situated next to the Main Reception with the Interpreting Team and Equality & Diversity/PALS Officer. They are available Monday – Friday 9am – 5pm

PALS Tel: or email:

Further information

If you want any further information about this study you can contact:

- Dr Andrew Olson
- Email
- Fax –
- Telephone
- Address - School of Psychology, University of Birmingham, Edgbaston, Birmingham, B15 2TT.

Thank you for considering taking part in this study!

B. *Consent form:*

School of Psychology

The University of Birmingham

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Study Number:

Participant Number:

CONSENT FORM

Project title: **Cognitive assessment of paediatric neurodegenerative disease**

Name of Researcher: Dana Al-Saqer

Please initial each box

1. I confirm that I have read and understood the information sheet dated 24 September 2016 (version 5) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my child's participation is voluntary and that I am free to withdraw them at any time. ☐

3. I understand that data collected during the study may be looked at by individuals from regulatory authorities or from the NHS trust where it is relevant to my taking part in this research. I give my permission for these individuals to have access to my data. ☐

4. I agree to allow my child take part in the above study. ☐

5. I agree to allow my child to be videotaped for this project ☐

6. I agree that my child's video can be used in scientific presentations of the data from this project. ☐

7. I agree that I may be contacted regarding future research that follows up on this project (initial one box). yes ☐ no ☐

_____

Name of child

_____ _____ _____

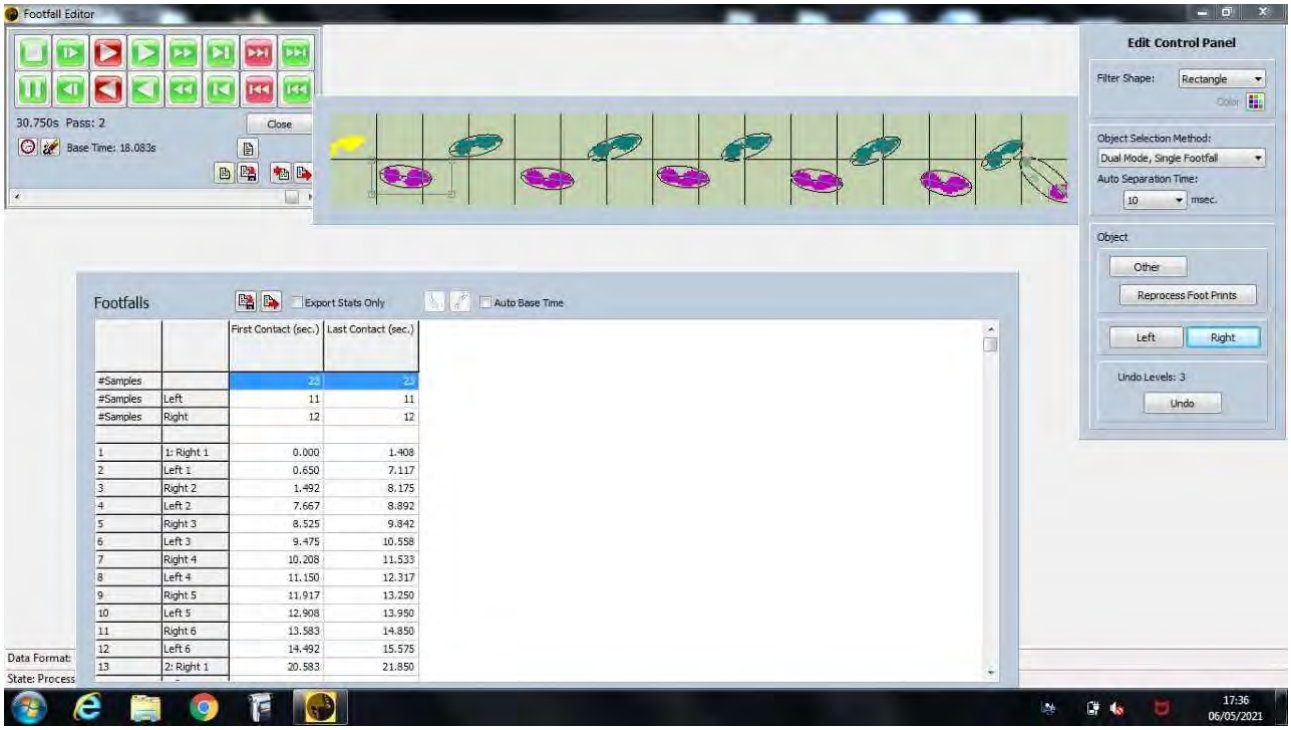
Name of carer Date Signature

_____ _____ _____

Name of person taking consent Date Signature

Appendix 2

A. *Zeno mat PKMASS software:*



B. *Accelerometer Mobility lab software:*



C. *Gait R code example:*

Analysis of cadence - example for appendix

Remember to do cntl-shift-F10 before running the script to clear the environment

version 7 - adds parallel processing. needs new predinternalfunctions and bootstraproutines

```
library(ggplot2)
library(tidyverse)

## ── Attaching packages ─────────────────────────────────────── tid
yverse 1.3.0 ──

## ✓ tibble  3.0.6     ✓ dplyr   1.0.4
## ✓ tidyr   1.1.2     ✓ stringr 1.4.0
## ✓ readr   1.4.0     ✓ forcats 0.5.1
## ✓ purrr   0.3.4

## ── Conflicts ────────────────────────────────────────── tidyverse
_conflicts() ──
## x dplyr::filter() masks stats::filter()
## x dplyr::lag()    masks stats::lag()

library(lme4)

## Loading required package: Matrix

##
## Attaching package: 'Matrix'

## The following objects are masked from 'package:tidyr':
##
##     expand, pack, unpack

library(nls2)

## Loading required package: proto

library(minpack.lm)
#library(kableExtra)
library(parallel)

#source("C:/Users/dana_/OneDrive/Desktop/Rstudio/Gait/UtilityFunctio
ns.R")
#source("C:/Users/dana_/OneDrive/Desktop/Rstudio/Gait/PredIntervalFu
nctions.R")
#source("C:/Users/dana_/OneDrive/Desktop/Rstudio/Gait/AsymptoteFunct
ions.R")
#source("C:/Users/dana_/OneDrive/Desktop/Rstudio/Gait/BootstrapRouti
nes.R")
source("/Users/olsonac-admin/Documents/current/R/UtilityFunctions.R"
```

```
)
source("/Users/olsonac-admin/Documents/current/R/PredIntervalFunctio
ns.R")
source("/Users/olsonac-admin/Documents/current/R/AsymptoteFunctions.
R")
source("/Users/olsonac-admin/Documents/current/R/BootstrapRoutines.R
")

#source("/rds/projects/2015/olsonac-01/DanaBootstrap/UtilityFunction
s.R")
#source("/rds/projects/2015/olsonac-01/DanaBootstrap/PredIntervalFun
ctions.R")
#source("/rds/projects/2015/olsonac-01/DanaBootstrap/AsymptoteFuncti
ons.R")
#source("/rds/projects/2015/olsonac-01/DanaBootstrap/BootstrapRoutin
es.R")

 NumCores<-detectCores()

CrossPatientUpperSResidLimit<- 5
CrossPatientLowerSResidLimit<- -15

setwd(CurDir)
GData<-read.csv("AllRawGaitData.csv")
GData<-GData[GData$Height<180,] # eliminate heights > 180
head(GData)

##        PID Age Group Height LegLen WtInKg Trial StepLen StrideLen
GaitCycleTime
## 1  RS-Y1S1   6     c    117      0     19     1  44.732    89.490
0.928
## 2  RS-Y1S1   6     c    117      0     19     2  45.083    90.206
1.016
## 3  RS-Y1S1   6     c    117      0     19     3  47.164    94.610
0.923
## 4 RS-Y1S10   6     c    108      0     20     1  42.761    86.236
0.999
## 5 RS-Y1S10   6     c    108      0     20     2  49.057    97.241
0.740
## 6 RS-Y1S10   6     c    108      0     20     3  46.172    93.656
0.831
##   StancePercent SwingPercent SingleSupportPercent DoubleSupportPe
rcent Velocity
## 1        57.077       42.923               42.999                1
4.212   96.457
## 2        57.525       42.475               41.944                1
5.335   88.808
## 3        60.172       39.828               43.057                2
1.812   98.121
## 4        61.525       38.475               39.612                2
```

```
2.187   86.356
## 5        59.417       40.583               40.114                1
8.967  131.481
## 6        61.026       38.974               39.256                2
1.757  112.719
##   Cadence Stride.Width
## 1 129.032        6.493
## 2 117.551        7.990
## 3 130.553        5.007
## 4 120.401       10.073
## 5 161.798        6.233
## 6 144.152        7.475

names(GData)

##  [1] "PID"                 "Age"                 "Group"
##  [4] "Height"              "LegLen"              "WtInKg"
##  [7] "Trial"               "StepLen"             "StrideLen"
## [10] "GaitCycleTime"       "StancePercent"       "SwingPercent"
## [13] "SingleSupportPercent" "DoubleSupportPercent" "Velocity"
## [16] "Cadence"             "Stride.Width"
```

Set variable you want to analyze here

```
# set the dependent variable (DV) for the analysis
GData$DV<-GData$Cadence
DependentVariableName<-"Cadence"

dir.create(paste0(CurDir,"/",gsub(" ","",DependentVariableName)))

# do height bins and separate patient and control data
GData$HtBin<-cut(GData$Height,breaks=c(90,100,110,120,130,140,150,16
0,170,180),right=FALSE,include.lowest=TRUE)
GData$HtBin<-CutMidpoints(GData$HtBin,1)
GData$AgeBin<-cut(GData$Age,breaks=c(0,5,8,11,15,17,30),right=TRUE)
GData$ObsID<-seq(1,length(GData[,1]))

CData<-GData %>% filter(Group == "c")
PData<-GData %>% filter(Group != "c")

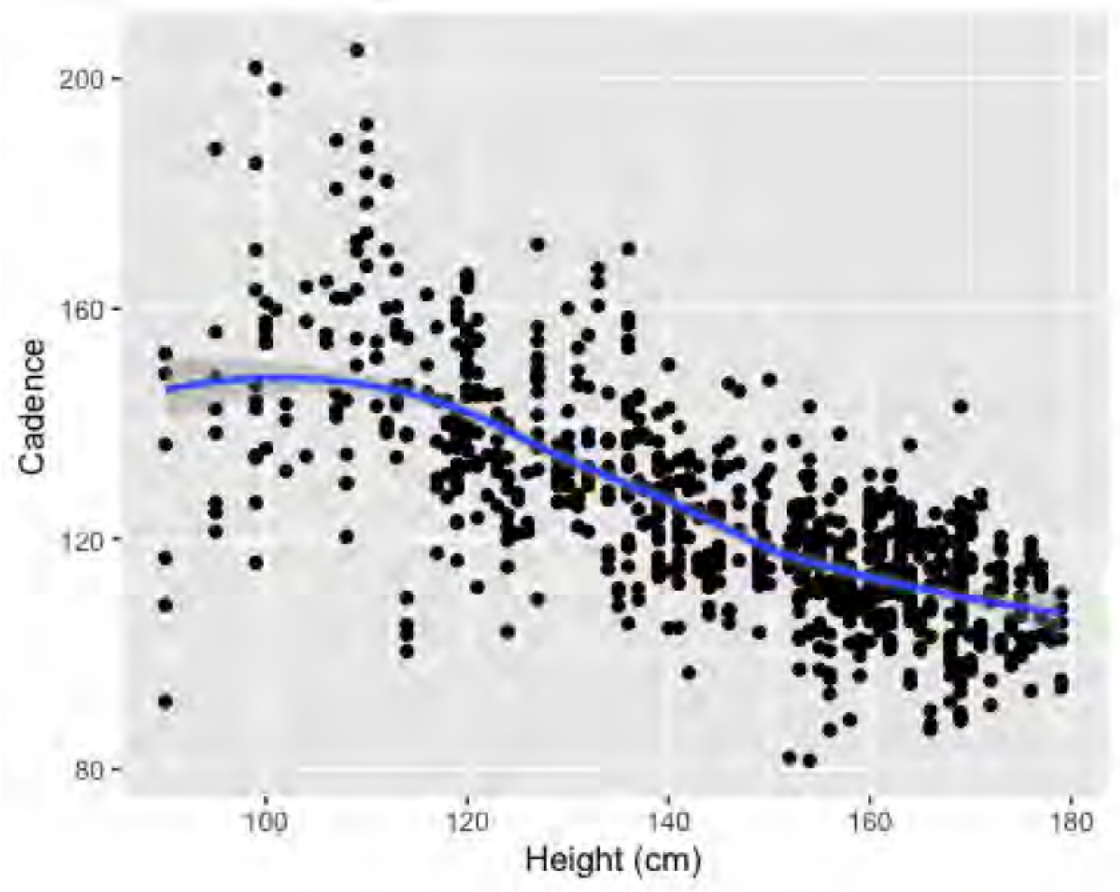
# mark outliers that are 3 standard deviations (SD) away from the me
an where SD is calculated separately for each height bin
CDataOut<-MarkOutliers(CData,"DV","HtBin",3)
# print information about how many data points there are that are no
```

```
t outliers and how many outliers there are
CDataNO<-CDataOut[CDataOut$DVOutlier == 0,]
print(paste("All control data N: ",length(CDataOut[,1])," w/o outlie
rs N: ",length(CDataNO[,1])," Number out outliers: ",length(CDataOut
[,1])-length(CDataNO[,1])))
```

```
## [1] "All control data N:  885  w/o outliers N:  877  Number out o
utliers:  8"
```

```
# plot data without outliers
CPlotNO<-ggplot(CDataNO,aes(x=Height,y=DV))+geom_point()
CPlotNO<-CPlotNO + geom_smooth()
CPlotNO<-CPlotNO + labs(x="Height (cm)", y=DependentVariableName)
print(CPlotNO)
```

```
## `geom_smooth()` using method = 'loess' and formula 'y ~ x'
```




```
# get means and sd for each ppt
# look for outlier ppts

# calculate participant means
PptMeans<-CDataNO %>% dplyr::group_by(PID,HtBin) %>% dplyr::summaris
e(PptMean=mean(DV,na.rm=TRUE))
```

```
## `summarise()` has grouped output by 'PID'. You can override using
the `.groups` argument.
```

```
# look for participants who are 3 SD away from mean of all participa
nts -- these would be unusual ppts
PptMeanOutliers<-MarkOutliers(PptMeans,"PptMean","HtBin",3)

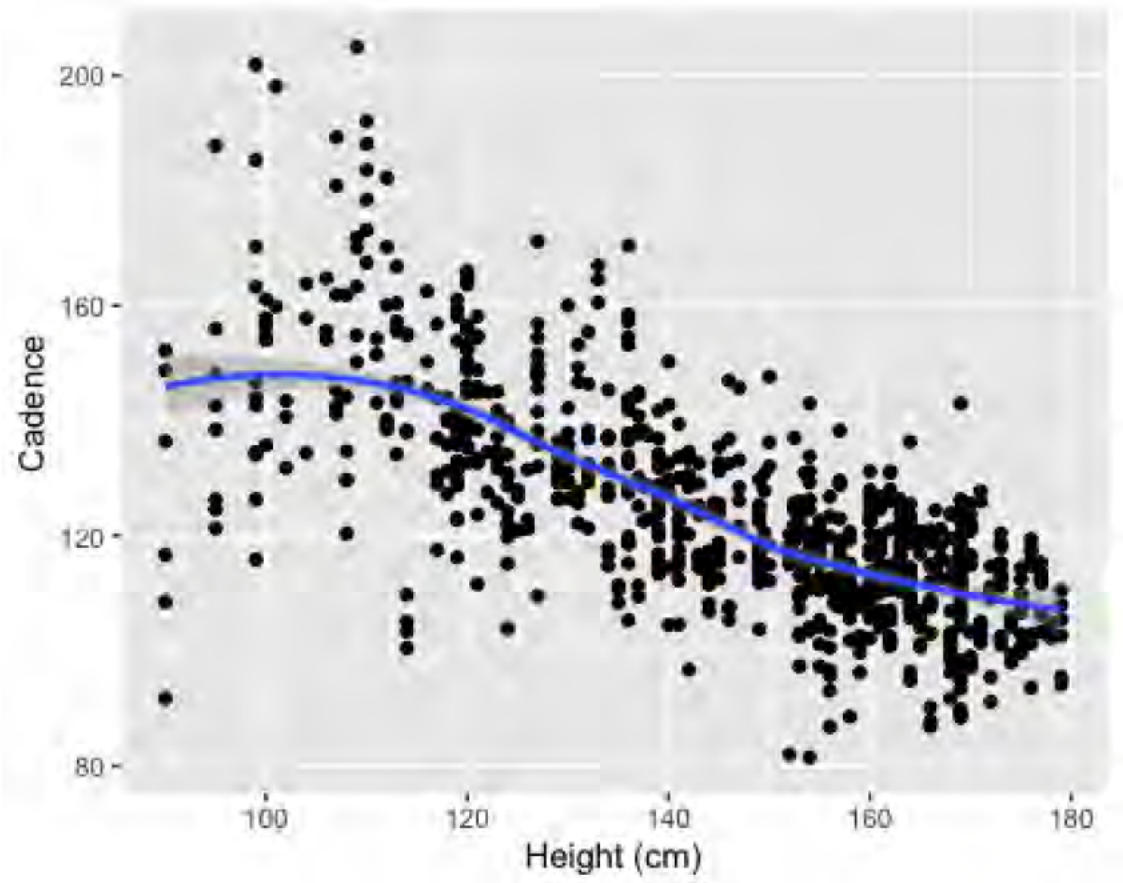
# print out any outliers to see how many there are -- if this says "
0 rows" there are no outlier participants
OutlierPpts<-PptMeanOutliers %>% filter(PptMeanOutlier == 1)
if(nrow(OutlierPpts[,1])>0){
  tibble:::print.tbl(OutlierPpts)
}else{
  print("No whole participants are outliers...")
}

## [1] "No whole participants are outliers..."

# take outlier ppts out of control sample
PptOutlierPID<-as.character(PptMeanOutliers$PID[PptMeanOutliers$PptM
eanOutlier == 1])
CDataNO<-CDataNO[!(CDataNO$PID %in% PptOutlierPID),]

# plot control data without any trial outliers and without any outli
er participants
CPlotNO<-ggplot(CDataNO,aes(x=Height,y=DV))+geom_point()
CPlotNO<-CPlotNO + geom_smooth()
# CPlot<-CPlot+ylim(0,0.004)
CPlotNO<-CPlotNO + labs(x="Height (cm)", y=DependentVariableName)
print(CPlotNO)

## `geom_smooth()` using method = 'loess' and formula 'y ~ x'
```




```
# options(bitmapType='cairo') # use on BlueBEAR
png(paste0(CurDir,"/",gsub(" ","",DependentVariableName),"/",
                  DependentVariableName,"_controls_RawDataNoOutliers
.png"),
           width=20,height=15,units="cm",res=800)
CPlotNO

## `geom_smooth()` using method = 'loess' and formula 'y ~ x'

dev.off()

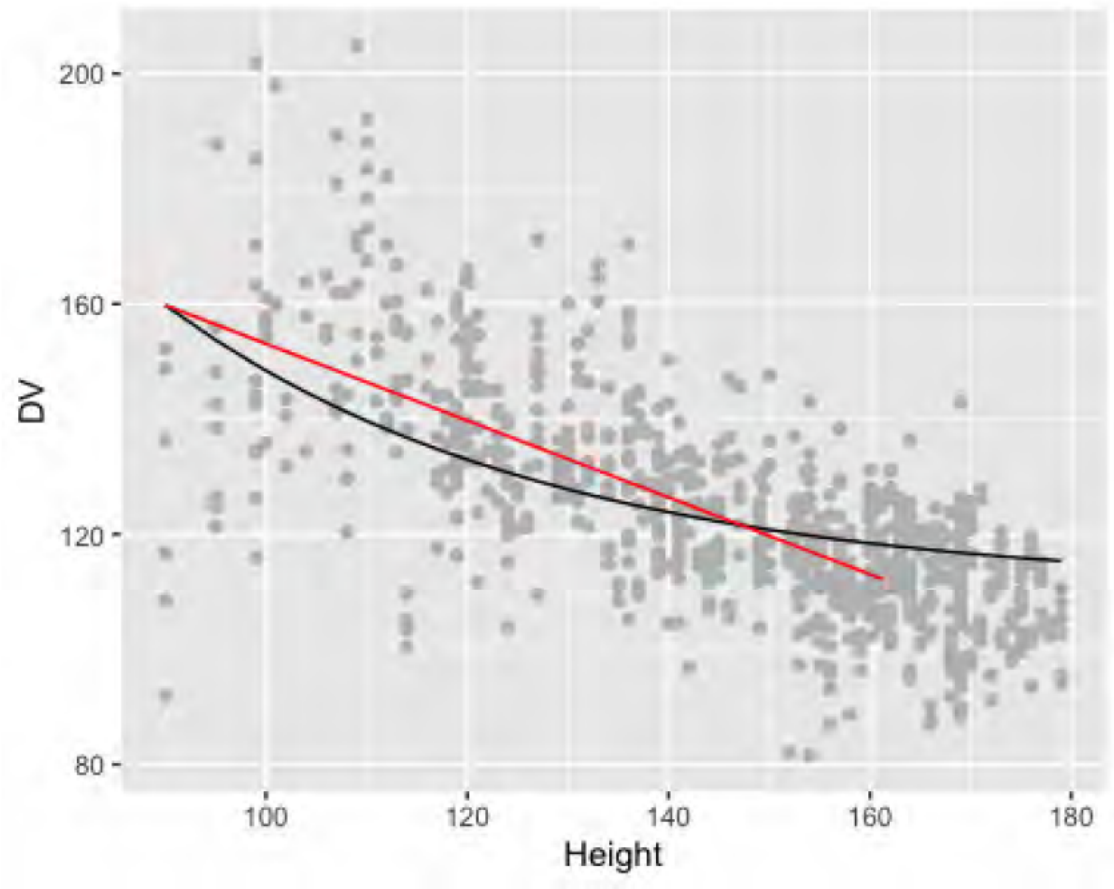
## quartz_off_screen
##                 2

LrcStart<-0.45 # this would be a pretty flat function
LrcEnd<-5 # this would be a sharp corner
LrcStep<-0.1 # go between 0.5 and 5 in steps of 0.5

########################################
# AsmpPortion may need to be changed to get a good fit
########################################
AsympPortion <- 0.8 # portion of the curve that is curved

YName<-"DV"
XName<-"Height"
```

```
AStartList<-PlotStartingAsympFunction(CDataNO,XName,YName,LrcStart,L
rcEnd,LrcStep,AsympPortion)
print(AStartList$Plot)
```



Red line is the guess for the first part of the curve. This sets the y-intercept for the asymptote. If the red line is not fitting the first portion very well, adjust the AsymPortion to fit either more of the data (make AsymPortion larger; usually this is a flatter line) or less of the data (make AsymPortion smaller; usually this is a steeper line). You are aiming for the red line to stop at about the asymptote (the flat portion)

```
## NULL

print(AsympModel)

## NULL
```

Does not converge to an asymptote (because the curve never really flattens out)

```
QuadraticModel<-lm(DV ~ Height + I(Height^2),data=CDataNO)
LinearModel<-lm(DV ~ Height,data=CDataNO)
ConstantModel<-lm(DV ~ 1,data=CDataNO)
# no reason why these shouldn't converge

AICResult<-GetAICResult(AsympModel,QuadraticModel,LinearModel,Consta
ntModel)

##
##
## Warning:  Asymptotic model could not be fit (error condition gene
rated)
##  Asymptotic model: NA
## Quadratic Model: 6955.37602952487
##  Linear Model: 6953.44179660913
##  ConstantModel: 7606.74840246847

print(AICResult)

##                        AIC Order   deltaAIC
## Asymptotic Model        NA     3         NA
## Quadratic Model  6955.376     2   1.934233
## Linear Model     6953.442     4   0.000000
## ConstantModel    7606.748     1 653.306606
```

linear model is best

```
# plot models to choose the best model based on AIC and theoretical
plausibility

ModelPlot<-PlotModels(CDataNO,"Height","DV",DependentVariableName, A
sympModel, QuadraticModel, LinearModel, ConstantModel)

# options(bitmapType='cairo') # use on BlueBEAR
png(paste0(CurDir,"/",gsub(" ","",DependentVariableName),"/",
                  DependentVariableName,"_controls_ModelsForMean.png
"),
           width=20,height=15,units="cm",res=800)
ModelPlot

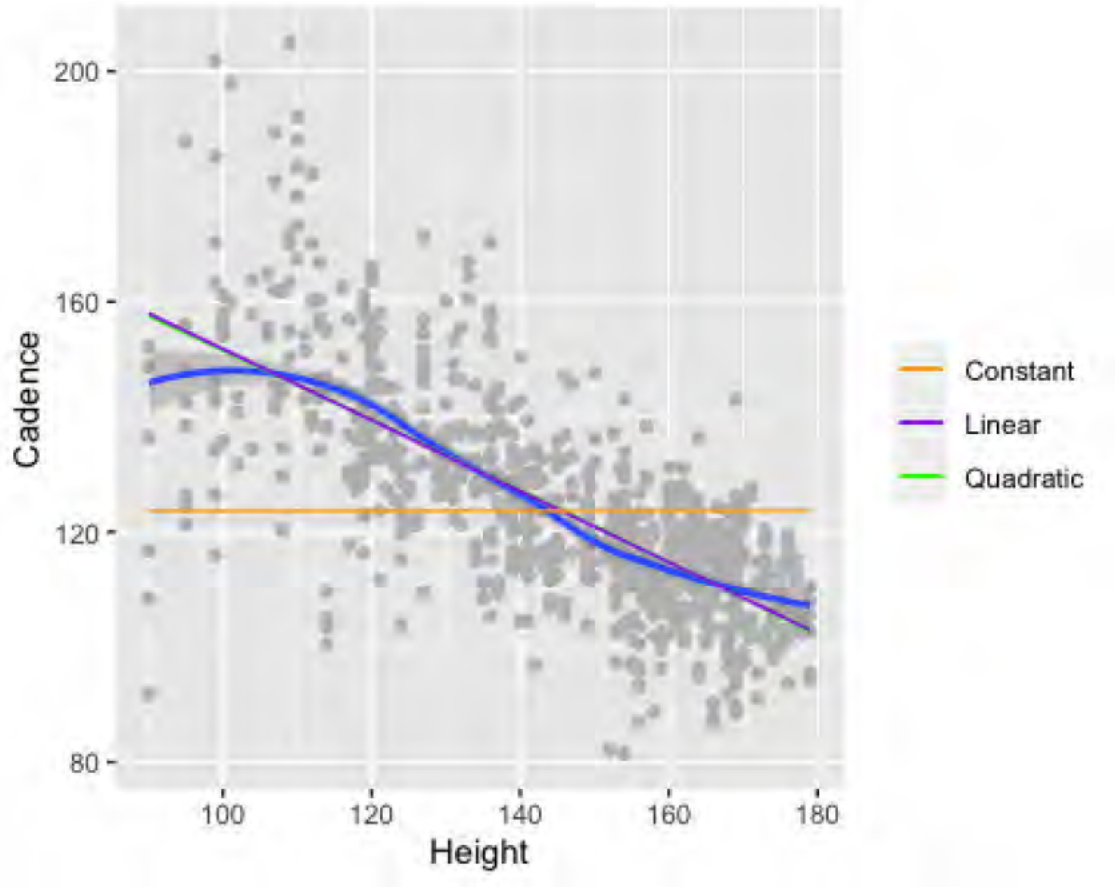
## `geom_smooth()` using method = 'loess' and formula 'y ~ x'

dev.off()
```

```
## quartz_off_screen
##                   2

print(ModelPlot)

## `geom_smooth()` using method = 'loess' and formula 'y ~ x'
```



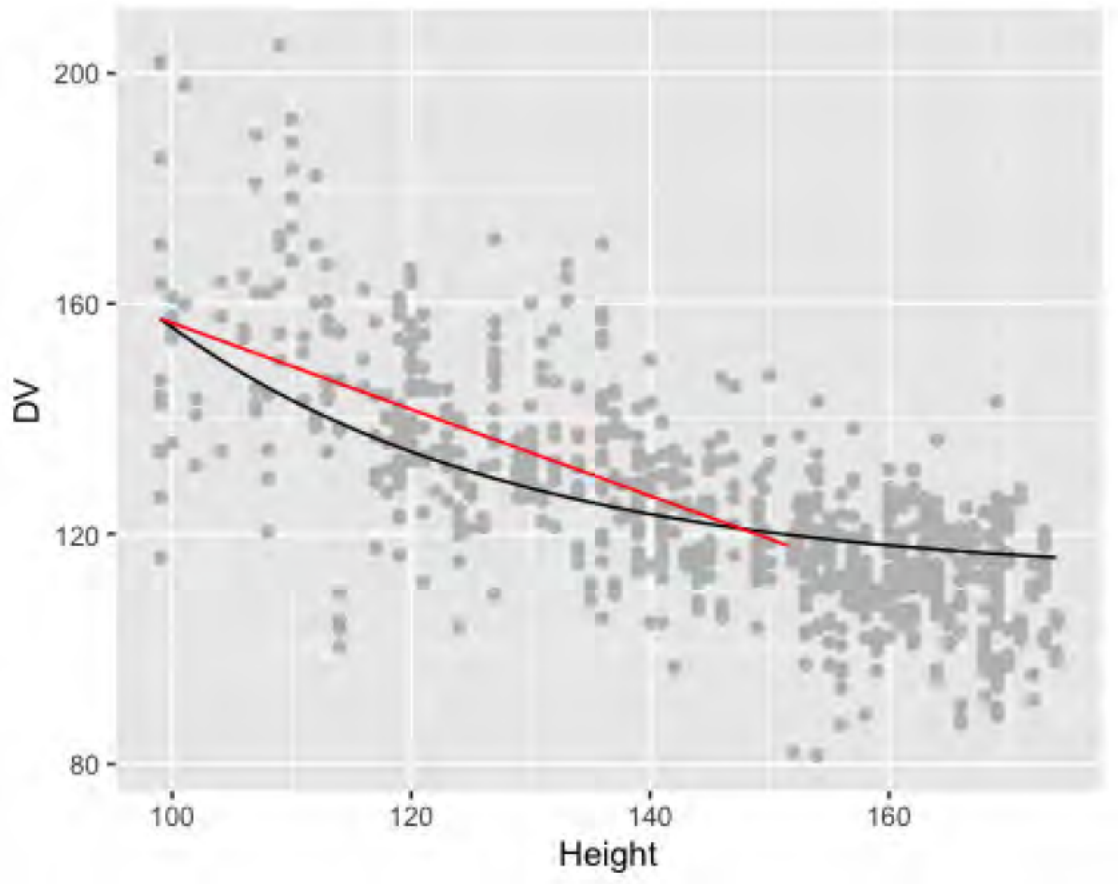

```
# Fit models without the extreme, small N points -- make sure best m
odel is consistent in both analyses

CDataNONE<-CDataNO[(CDataNO$Height > 95) & (CDataNO$Height < 175),]
# CDataNONE<-CDataNO[CDataNO$Height < 175,]

# adjust values here (95 / 175) if the range isn't right

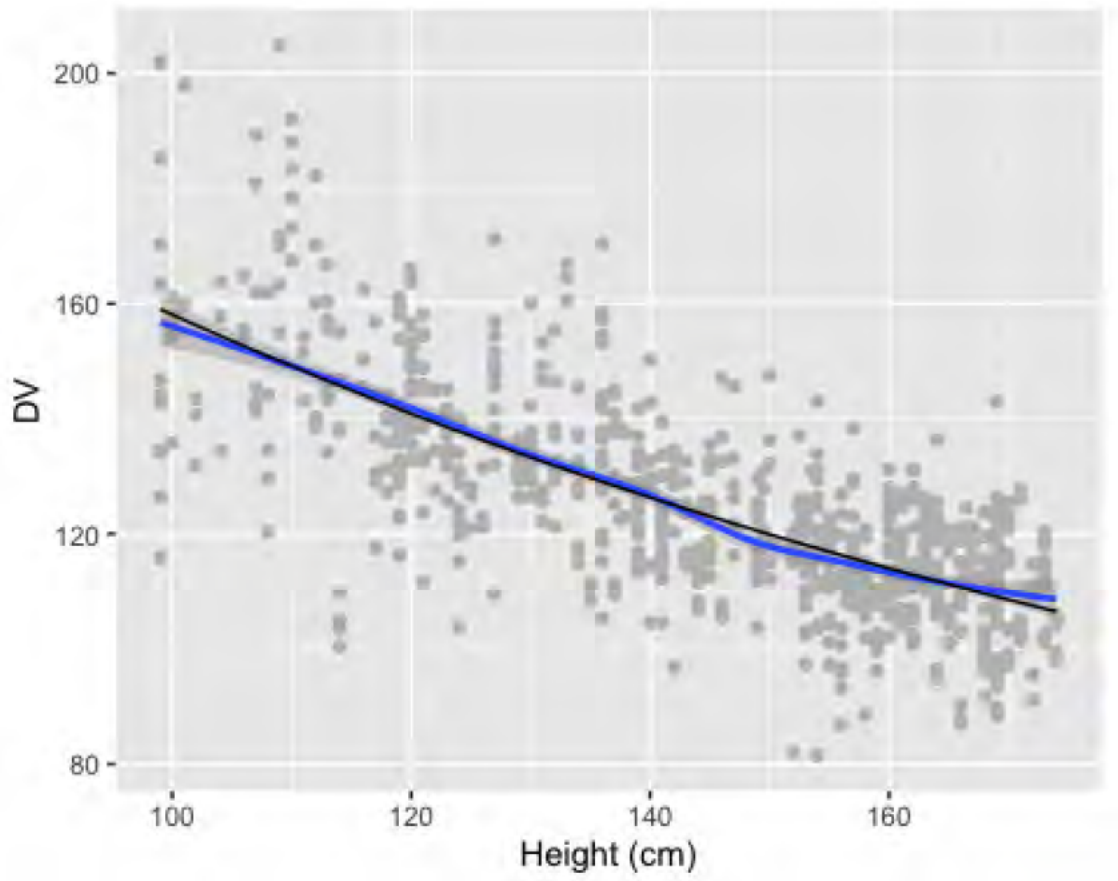
AsympPortion <- 0.7 # portion of the curve that is curved

NEAStartList<-PlotStartingAsympFunction(CDataNONE,XName,YName,LrcSta
rt,LrcEnd,LrcStep,AsympPortion)
print(NEAStartList$Plot)
```




```
NEAModelList<-FitAsymptoteModel(CDataNONE,"Height","DV",NEAStartList
$StartValues)
NEAsympModel<-NEAModelList$Model
print(NEAModelList$Plot)

## `geom_smooth()` using method = 'loess' and formula 'y ~ x'
```




```
NEQuadraticModel<-lm(DV ~ Height + I(Height^2),data=CDataNONE)
NELinearModel<-lm(DV ~ Height,data=CDataNONE)
NEConstantModel<-lm(DV ~ 1,data=CDataNONE)
# no reason why these shouldn't converge

NEAICResult<-GetAICResult(NEAsympModel,NEQuadraticModel,NELinearMode
l,NEConstantModel)

##  Asymptotic model: 6462.57618223795
## Quadratic Model: 6461.81656344226
##  Linear Model: 6467.70157601943
##  ConstantModel: 7122.35354556776

print(NEAICResult)

##                       AIC Order    deltaAIC
## Asymptotic Model 6462.576     2   0.7596188
## Quadratic Model  6461.817     1   0.0000000
## Linear Model     6467.702     3   5.8850126
## ConstantModel    7122.354     4 660.5369821
```

quadratic is best.

```
summary(NEQuadraticModel)
```

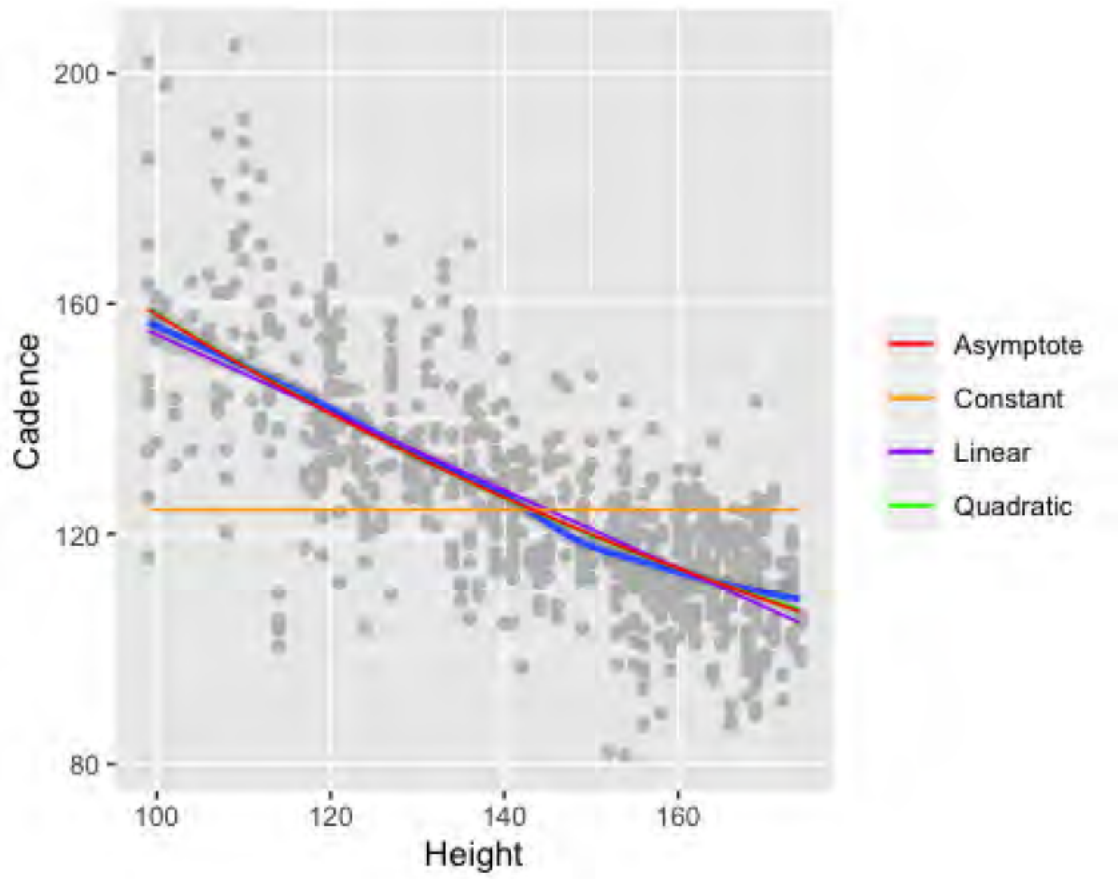
```
##
## Call:
## lm(formula = DV ~ Height + I(Height^2), data = CDataNONE)
##
## Residuals:
##     Min      1Q  Median      3Q     Max
## -45.355  -7.173  -0.429   7.457  54.776
##
## Coefficients:
##               Estimate Std. Error t value Pr(>|t|)
## (Intercept) 282.808953  21.785587  12.981  < 2e-16 ***
## Height       -1.562985   0.316326  -4.941 9.42e-07 ***
## I(Height^2)   0.003173   0.001129   2.810  0.00508 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 12.29 on 819 degrees of freedom
## Multiple R-squared:  0.5544, Adjusted R-squared:  0.5534
## F-statistic: 509.6 on 2 and 819 DF,  p-value: < 2.2e-16
```

Note that exponent is very small in quadratic model, so not very different from linear, which was the best "all data" choice. Use linear.

```
# plot models to choose the best model based on AIC and theoretical
plausibility

NEModelPlot<-PlotModels(CDataNONE,"Height","DV",DependentVariableNam
e, NEAsympModel, NEQuadraticModel, NELinearModel, NEConstantModel)
print(NEModelPlot)

## `geom_smooth()` using method = 'loess' and formula 'y ~ x'
```




```
# options(bitmapType='cairo') # use on BlueBEAR
png(paste0(CurDir,"/",gsub(" ","",DependentVariableName),"/",
                  DependentVariableName,"_controls_ModelsForMeanNoEx
tremeValues.png"),
           width=20,height=15,units="cm",res=800)
NEModelPlot

## `geom_smooth()` using method = 'loess' and formula 'y ~ x'

dev.off()

## quartz_off_screen
##                 2
```

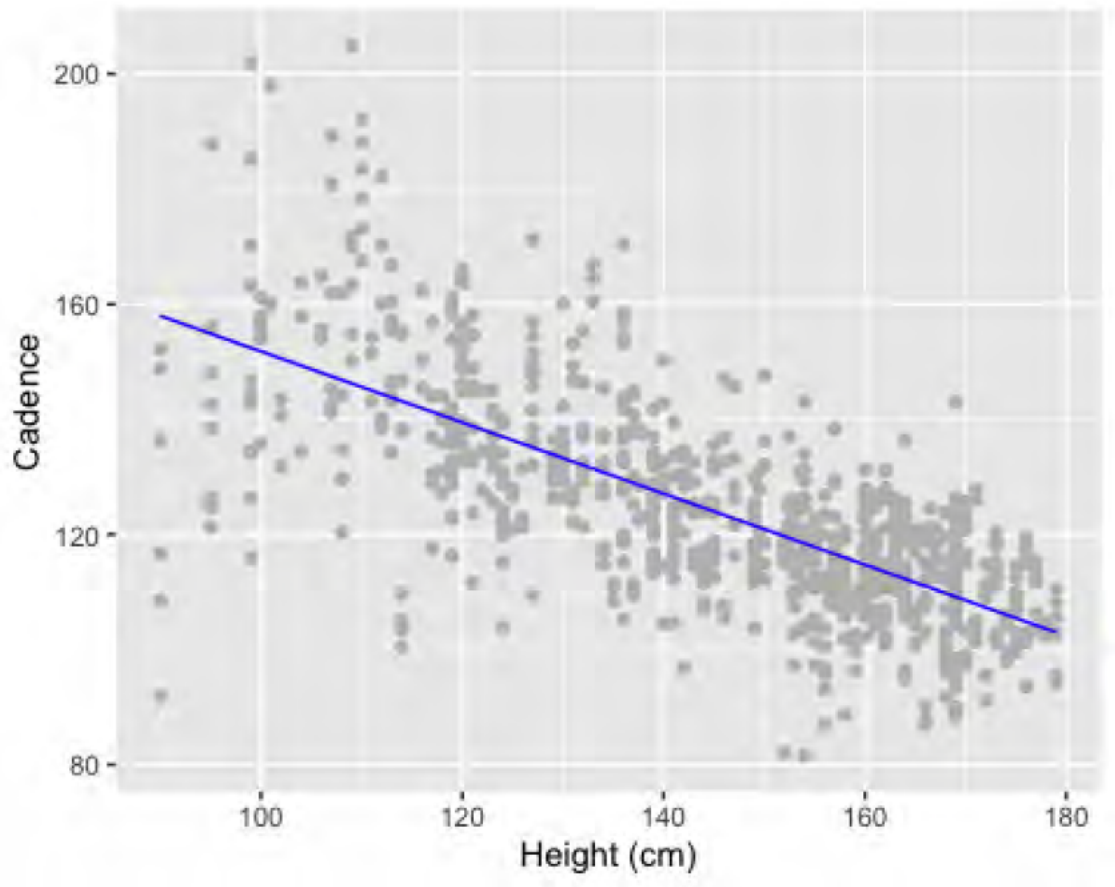
use linear

Must set best model here based on the previous section

```
############################################################
#
# Must set best model here based on the previous section
#
############################################################

BestModel<-LinearModel
# plot model
CDataNO$PredDV<-fitted(BestModel)

CPlotNO<-ggplot(CDataNO,aes(x=Height,y=DV))+geom_point(color="grey")
CPlotNO<-CPlotNO + geom_line(aes(x=Height,y=PredDV),color="blue")
CPlotNO<-CPlotNO + labs(x="Height (cm)", y=DependentVariableName)
print(CPlotNO)
```




```
# options(bitmapType='cairo') # use on BlueBEAR
png(paste0(CurDir,"/",gsub(" ","",DependentVariableName),"/",
                  DependentVariableName,"_controls_BestModelForMean.
png"),
           width=20,height=15,units="cm",res=800)
```

```
CPlotNO
dev.off()

## quartz_off_screen
##                 2

# calculate residuals for control data
CDataNO$Residual<-CDataNO$DV-CDataNO$PredDV

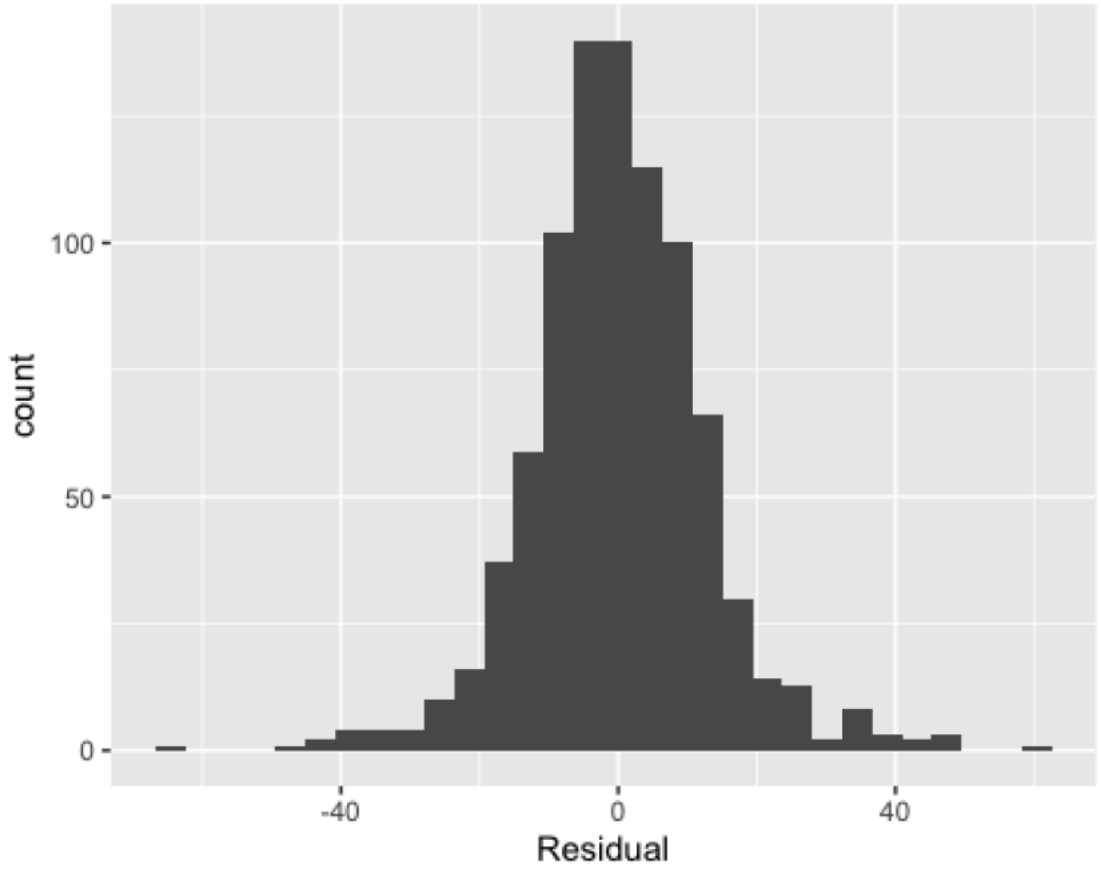
# calculate residuals for all data (including patients)
AllDatNO<-rbind(CDataNO[,1:length(PData[1,])],PData)
AllDatNO$PredDV<-predict(BestModel,newdata=AllDatNO)
AllDatNO$Residual<-AllDatNO$DV-AllDatNO$PredDV

# plot residuals
CPlotRes<-ggplot(CDataNO,aes(x=Height,y=Residual))+geom_point()
CPlotRes<-CPlotRes + geom_smooth()
# CPlot<-CPlot+ylim(0,0.004)
CPlotRes<-CPlotRes + labs(x="Height (cm)", y=DependentVariableName)
print(CPlotRes)

## `geom_smooth()` using method = 'loess' and formula 'y ~ x'
```

```
RDistPlot<-ggplot(CDataNO,aes(x=Residual))+geom_histogram()
RDistPlot<-RDistPlot
print(RDistPlot)

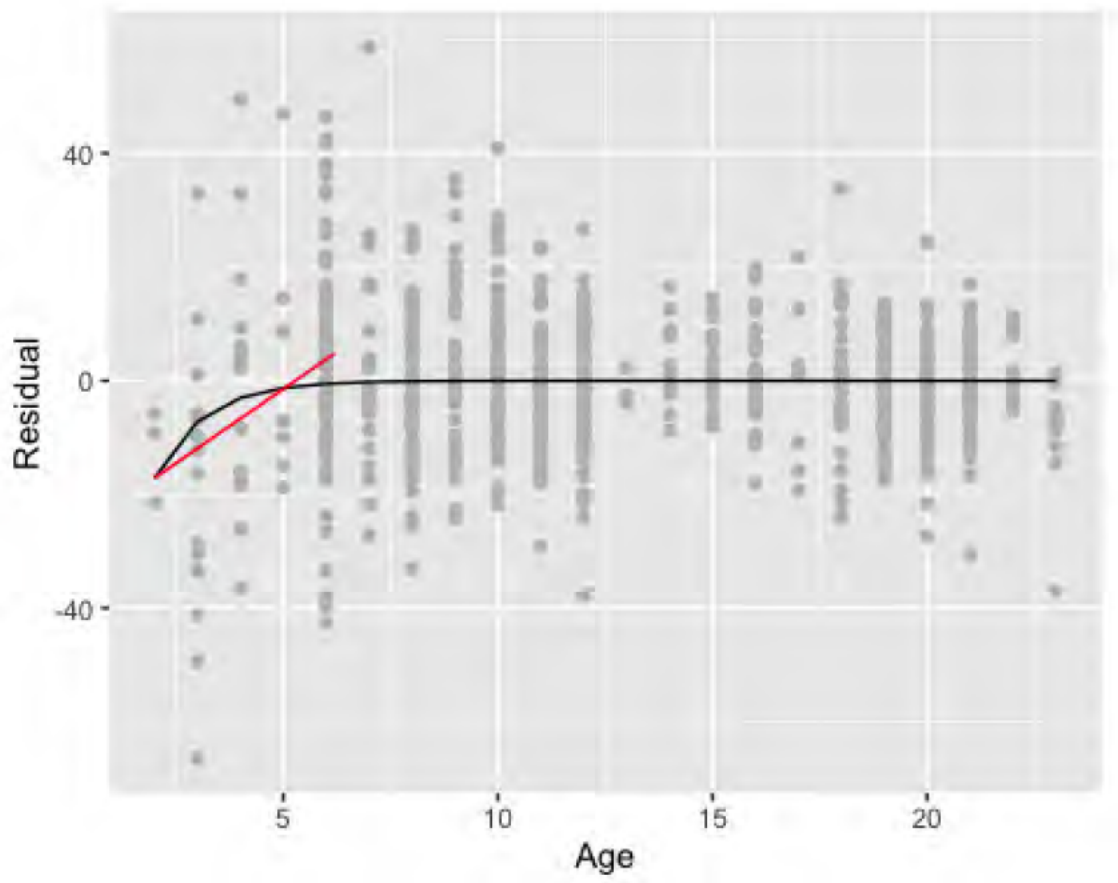
## `stat_bin()` using `bins = 30`. Pick better value with `binwidth`
.
```



We are looking for a roughly normal distributionn here.

```
LrcStart<-0.1 # this would be a pretty flat function
LrcEnd<-5 # this would be a sharp corner
LrcStep<-0.1 # go between 0.5 and 5 in steps of 0.5
AsympPortion <- 0.2 # portion of the curve that is curved
YName<-"Residual"
XName<-"Age"

RAStartList<-PlotStartingAsympFunction(CDataNO,XName,YName,LrcStart,
LrcEnd,LrcStep,AsympPortion)
print(RAStartList$Plot)
```




```
# asymnptotic function starting values for residuals fit
```

Check that this is a theoretically plausible shape if Age is shown to be a factor below

```
# check if there is any effect of age once height has been removed
RAModelList<-FitAsymptoteModel(CDataNO,"Age","Residual",RAStartList$
StartValues)
RAsympModel<-RAModelList$Model
print(RAModelList$Plot)

## `geom_smooth()` using method = 'loess' and formula 'y ~ x'
```

```
RQuadraticModel<-lm(Residual ~ Age + I(Age^2),data=CDataNO)
RLinearModel<-lm(Residual~ Age,data=CDataNO)
RConstantModel<-lm(Residual ~ 1,data=CDataNO)
# no reason why these shouldn't converge

RAICResult<-GetAICResult(RAsympModel,RQuadraticModel,RLinearModel,RC
onstantModel)

##  Asymptotic model: 6935.67082630841
## Quadratic Model: 6948.36581570985
##  Linear Model: 6952.48021463937
##  ConstantModel: 6951.44179660913
```

```
print(RAICResult)
```

```
##                        AIC Order deltaAIC
## Asymptotic Model 6935.671     1  0.00000
## Quadratic Model  6948.366     2 12.69499
## Linear Model     6952.480     4 16.80939
## ConstantModel    6951.442     3 15.77097
```

asymptotic model is best, but this is only capturing a few points at the youngest ages, where the data are rather sparse. Let's see what happens with middle ages.

```
cat("Constant model intercept is: ",RConstantModel$coefficients[1])
```

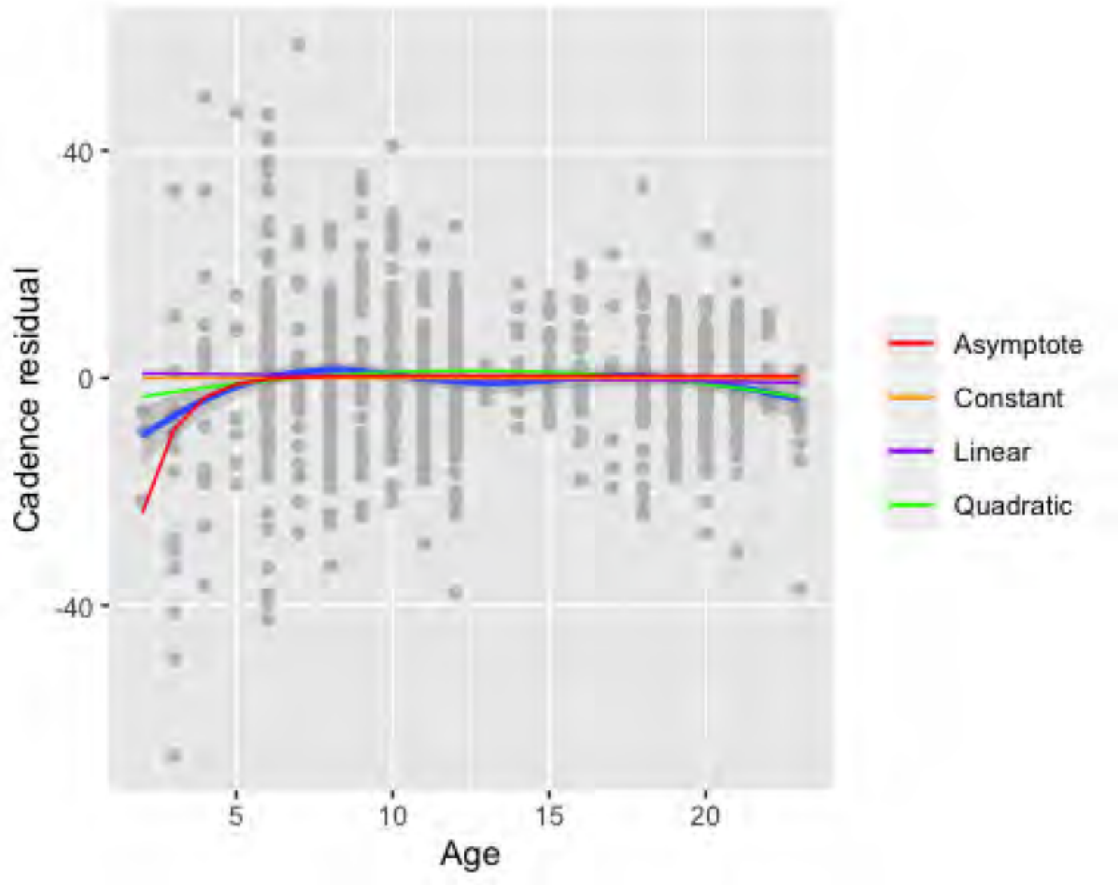
```
## Constant model intercept is:  -1.199666e-16
```

If constant model is best, the constant intercept value should be near zero

```
# plot models to choose the best model based on AIC and theoretical plausibility

RModelPlot<-PlotModels(CDataNO,"Age","Residual",paste(DependentVariableName," residual",sep=""), RAsympModel, RQuadraticModel, RLinearModel, RConstantModel)
print(RModelPlot)
```

```
## `geom_smooth()` using method = 'loess' and formula 'y ~ x'
```



```
# options(bitmapType='cairo') # use on BlueBEAR
png(paste0(CurDir,"/",gsub(" ","",DependentVariableName),"/",
                  DependentVariableName,"_controls_ResidualsModelsFo
rAge.png"),
           width=20,height=15,units="cm",res=800)
RModelPlot

## `geom_smooth()` using method = 'loess' and formula 'y ~ x'

dev.off()

## quartz_off_screen
##                 2
```

asymptote is best, but curve might be artificial. If not, it means that the youngest participants have a slower cadence than their height would predict.

```
# Fit models without the extreme, small N points -- make sure best m
odel is consistent in both analyses

LrcStart<-0.1 # this would be a pretty flat function
LrcEnd<-5 # this would be a sharp corner
LrcStep<-0.1 # go between 0.5 and 5 in steps of 0.5
AsympPortion <- 0.2 # portion of the curve that is curved
YName<-"Residual"
XName<-"Age"

CDataNONE<-CDataNO[(CDataNO$Height > 95) & (CDataNO$Height < 175),]

# adjust values here (95 / 175) if the range isn't right

NERAStartList<-PlotStartingAsympFunction(CDataNONE,XName,YName,LrcSt
art,LrcEnd,LrcStep,AsympPortion)
print(NERAStartList$Plot)
```

```
# check if there is any effect of age once height has been removed
NERAModelList<-FitAsymptoteModel(CDataNONE,"Age","Residual",NERAStar
tList$StartValues)

## Asymptote model generated an error

NERAsympModel<-NERAModelList$Model
print(NERAModelList$Plot)

## NULL
```

Very little sign of an asymptote in the data without extreme values - asymptote model fails to be fit successfully.

```
NERQuadraticModel<-lm(Residual ~ Age + I(Age^2),data=CDataNONE)
NERLinearModel<-lm(Residual~ Age,data=CDataNONE)
NERConstantModel<-lm(Residual ~ 1,data=CDataNONE)
# no reason why these shouldn't converge

NERAICResult<-GetAICResult(NERAsympModel,NERQuadraticModel,NERLinear
Model,NERConstantModel)

##
##
## Warning:  Asymptotic model could not be fit (error condition gene
rated)
##  Asymptotic model: NA
## Quadratic Model: 6467.79249006186
##  Linear Model: 6465.80772336593
##  ConstantModel: 6473.2246681344

print(NERAICResult)

##                        AIC Order deltaAIC
## Asymptotic Model        NA     3       NA
## Quadratic Model  6467.792     2 1.984767
## Linear Model     6465.808     4 0.000000
## ConstantModel    6473.225     1 7.416945
```

linear is best, quadratic is also good. Use linear based on data without extremes

```
# Linear vs constant
anova(NERLinearModel,NERConstantModel)

## Analysis of Variance Table
##
## Model 1: Residual ~ Age
## Model 2: Residual ~ 1
##   Res.Df    RSS Df Sum of Sq     F   Pr(>F)
## 1    820 124556
## 2    821 125991 -1   -1435.1 9.448 0.002184 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Linear effect of age

```
# plot models to choose the best model based on AIC and theoretical
plausibility

NERModelPlot<-PlotModels(CDataNONE,"Age","Residual",paste(DependentV
ariableName," residual",sep=""), NERAsympModel, NERQuadraticModel, N
ERLinearModel, NERConstantModel)
print(NERModelPlot)
```

```
## `geom_smooth()` using method = 'loess' and formula 'y ~ x'
```

```
print(NERLinearModel)

##
## Call:
## lm(formula = Residual ~ Age, data = CDataNONE)
##
## Coefficients:
## (Intercept)          Age
##      3.3545      -0.2441

PredCadenceAt3<-NERLinearModel$coefficients[1] +  NERLinearModel$coe
fficients[2]*3
PredCadenceAt23<-NERLinearModel$coefficients[1] +  NERLinearModel$co
efficients[2]*23
AgeDiffAcrossRange<-PredCadenceAt23 - PredCadenceAt3
print(paste("Different in cadence predicted for 20 year span: ",AgeD
iffAcrossRange))

## [1] "Different in cadence predicted for 20 year span:  -4.8815600
9556192"

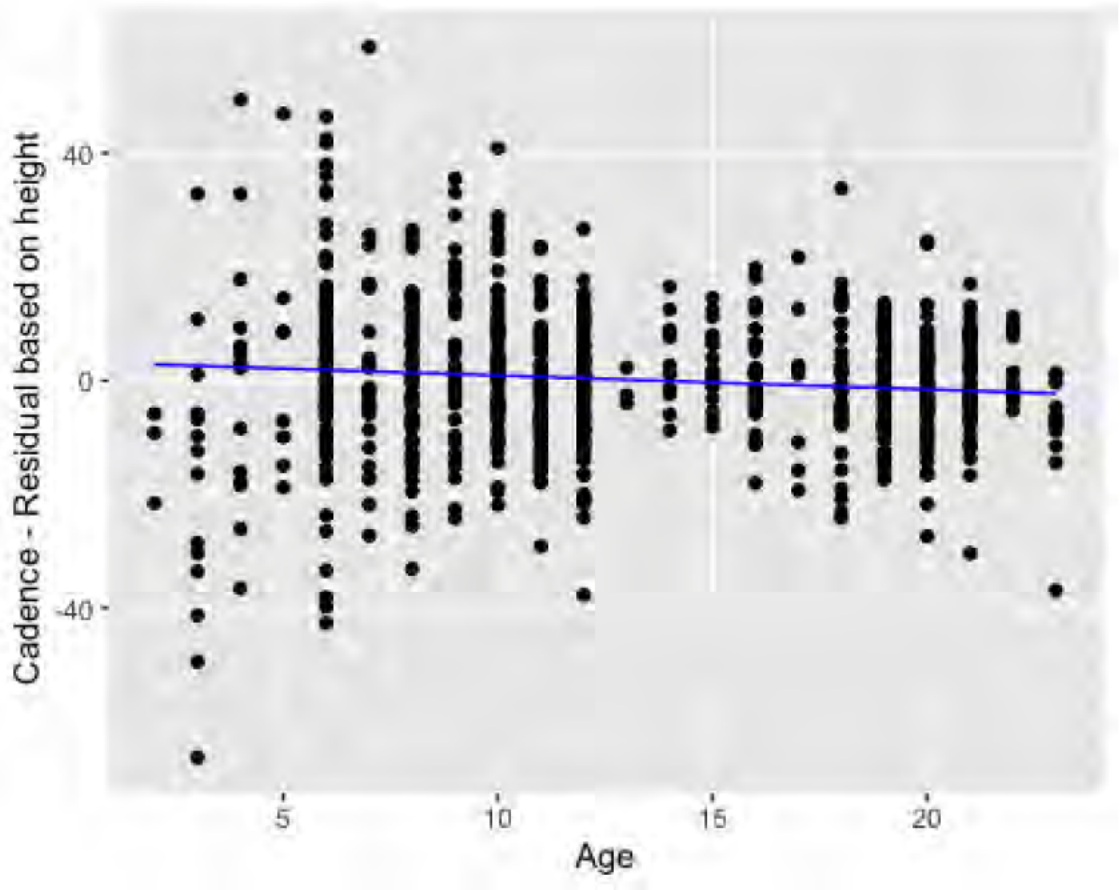
EachYearDecrease<-AgeDiffAcrossRange/20
print(sprintf("Each year cadence decreases by: %.4f steps per minute
",EachYearDecrease))

## [1] "Each year cadence decreases by: -0.2441 steps per minute"

#############################################################
#
#  use only if Constant model is not best above - if ConstantModel i
s best, skip to down below
#  (see comments)
#
#############################################################

BestModel<-NERLinearModel
# plot model
CDataNO$PredDV<-predict(BestModel,newdata=CDataNO) # this is age res
iduals on top of height residuals

CPlotNO<-ggplot(CDataNO,aes(x=Age,y=Residual))+geom_point()
CPlotNO<-CPlotNO + geom_line(aes(x=CDataNO$Age,y=CDataNO$PredDV),col
or="blue")
CPlotNO<-CPlotNO + labs(x="Age", y=paste0(DependentVariableName," -
Residual based on height "))
print(CPlotNO)
```




```
# options(bitmapType='cairo') # use on BlueBEAR
png(paste0(CurDir,"/",gsub(" ","",DependentVariableName),"/",
                  DependentVariableName,"_ResidualsWithModelOfAgeEff
ect.png"),
           width=20,height=15,units="cm",res=800)
CPlotNO
dev.off()

## quartz_off_screen
##                 2
```

Blue line shows the effect of age

```
# calculate residuals for control data
CDataNO$Residual<-CDataNO$Residual-CDataNO$PredDV

# calculate residuals for all data (including patients)
AllDatNO$PredDV<-predict(BestModel,newdata=AllDatNO)
AllDatNO$Residual<-AllDatNO$Residual-AllDatNO$PredDV
write.csv(AllDatNO,"Gait_AllDataCadence_WithResiduals.csv")

# plot  new residuals
CPlotRes<-ggplot(CDataNO,aes(x=Height,y=Residual))+geom_point()
CPlotRes<-CPlotRes + geom_smooth()
CPlotRes<-CPlotRes + labs(x="Height (cm)", y=DependentVariableName)
print(CPlotRes)
```

```
## `geom_smooth()` using method = 'loess' and formula 'y ~ x'
```

```
# options(bitmapType='cairo') # use on BlueBEAR
png(paste0(CurDir,"/",gsub(" ","",DependentVariableName),"/",
                  DependentVariableName,"_ResidualsPlotHeightAndAge.
png"),
           width=20,height=15,units="cm",res=800)
CPlotRes

## `geom_smooth()` using method = 'loess' and formula 'y ~ x'

dev.off()

## quartz_off_screen
##                   2

RDistPlot<-ggplot(CDataNO,aes(x=Residual))+geom_histogram()
RDistPlot<-RDistPlot
print(RDistPlot)

## `stat_bin()` using `bins = 30`. Pick better value with `binwidth`
.
```

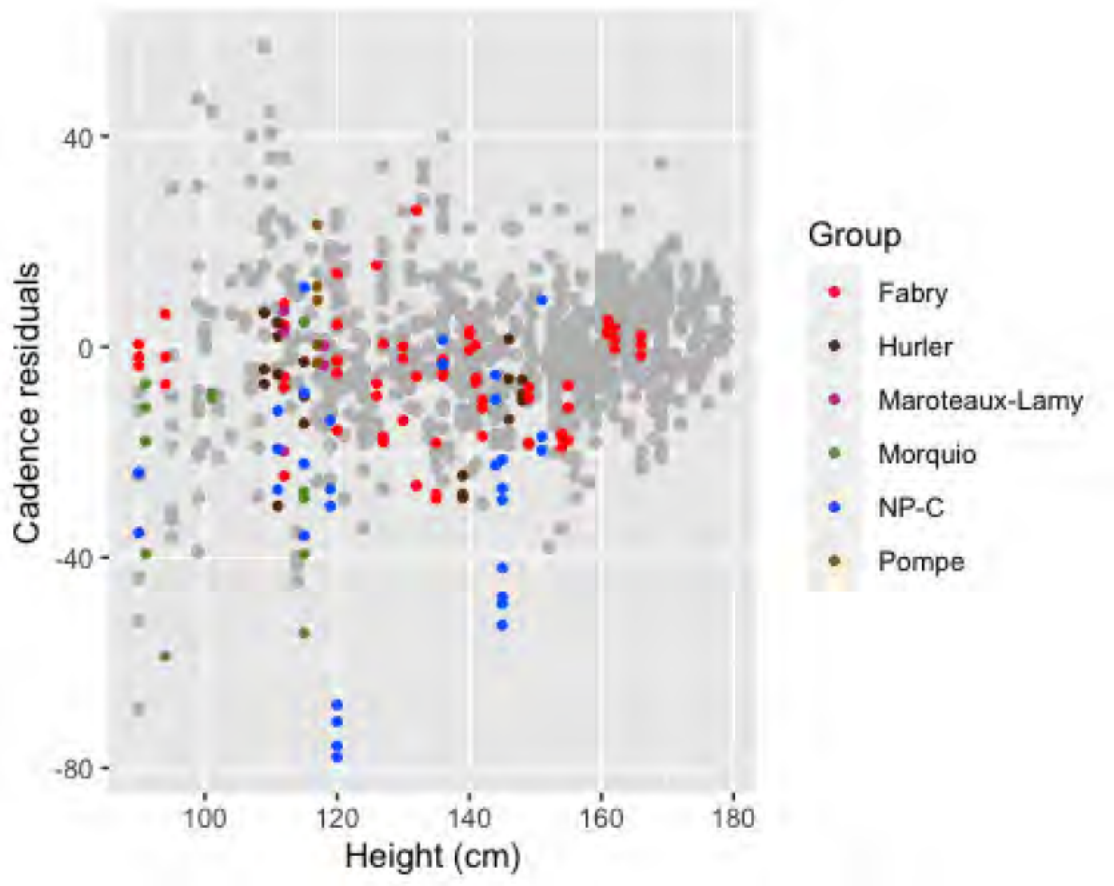
The effect of age after height is pretty small, but it has been removed in any case.

Skip to here if age has no effect

```
myColors <- c("#CCCCCC","#FF0000", "#663300", "#CC3399","#669933","#
0066FF","#996600")
names(myColors) <- levels(AllDatNO$Group)
colScale <- scale_colour_manual(name = "Group",
                                values = myColors,
                                labels=c("control", "Fabry", "Hurler
", "Maroteaux-Lamy", "Morquio", "NP-C", "Pompe"),
                                breaks=c("c","pf","ph","pl","pm","pn
","pp")
)

fillScale <- scale_fill_manual(name = "Group",
                               values = myColors,
                               labels=c("control", "Fabry", "Hurler"
, "Maroteaux-Lamy", "Morquio", "NP-C", "Pompe"),
                               breaks=c("c","pf","ph","pl","pm","pn"
,"pp")
)
```

```
# plot all groups
PatDat<-AllDatNO[AllDatNO$Group != "c",]
PPlot<-ggplot(CDataNO,aes(x=Height,y=Residual)) + geom_point(color="
grey")
PPlot<-PPlot + geom_point(data=PatDat,aes(x=Height,y=Residual,color=
Group),size=1)
PPlot<-PPlot + labs(x="Height (cm)", y=paste0(DependentVariableName,
" residuals"))
PPlot <- PPlot + colScale
print(PPlot)
```




```
# options(bitmapType='cairo') # use on BlueBEAR
png(paste0(CurDir,"/",gsub(" ","",DependentVariableName),"/",
                  DependentVariableName,"_ResidualsAllPatientGroups.
png"),
           width=20,height=15,units="cm",res=800)
PPlot
dev.off()

## quartz_off_screen
##                 2

ControlSD<-sd(AllDatNO$Residual[(AllDatNO$Group == "c")] )
print(sprintf("Control SD for standardising residuals %.3f",ControlS
D))
```

```
## [1] "Control SD for standardising residuals 12.739"

AllDatNO$SResid<-AllDatNO$Residual/ControlSD
CDataNO$SResid<-CDataNO$Residual/ControlSD

# set limits for plots that then will be used across plots for a com
mon format
YLowerPlotLimit<- min(AllDatNO$Residual)
YUpperPlotLimit<- max(AllDatNO$Residual)
SYLowerPlotLimit<- min(AllDatNO$SResid)
SYUpperPlotLimit<- max(AllDatNO$SResid)
# values lower than this will be excluded when we calculate p-values
below in the
# section for excluded p-values

# get the number of patients in each group to see which have enough
to do group comparisons
GroupN<-AllDatNO %>% dplyr::group_by(Group) %>% dplyr::summarise(N=l
ength(unique(PID)))
print(GroupN)

## # A tibble: 7 x 2
##   Group     N
## * <chr> <int>
## 1 c       294
## 2 pf       20
## 3 ph        6
## 4 pl        2
## 5 pm        4
## 6 pn        9
## 7 pp        1
```

pf, pn and maybe ph can be analyzed by group

```
# multiplier for control SD that sets cutoff for extreme
ExtremeValuesSDMult<-3

# get control means to set extreme values limit
CData<-AllDatNO[(AllDatNO$Group == "c"),]
CMeans<-CData %>% dplyr::group_by(PID) %>% dplyr::summarise(SResMean
=mean(SResid))
CMeanSD<-sd(CMeans$SResMean)
ExtremeValuesLimit<-ExtremeValuesSDMult * CMeanSD
print(sprintf("Mean of residuals = %.3f, SD = %.3f Extreme values li
mit = %.3f", mean(CMeans$SResMean),CMeanSD,ExtremeValuesLimit))

## [1] "Mean of residuals = -0.004, SD = 0.892 Extreme values limit
= 2.677"

# ********************* Fabry's ***********************
PGroup<-"pf"
GroupName<-"Fabry"
```

```
GroupData<-AllDatNO[(AllDatNO$Group == "c") | (AllDatNO$Group == PGr
oup),]

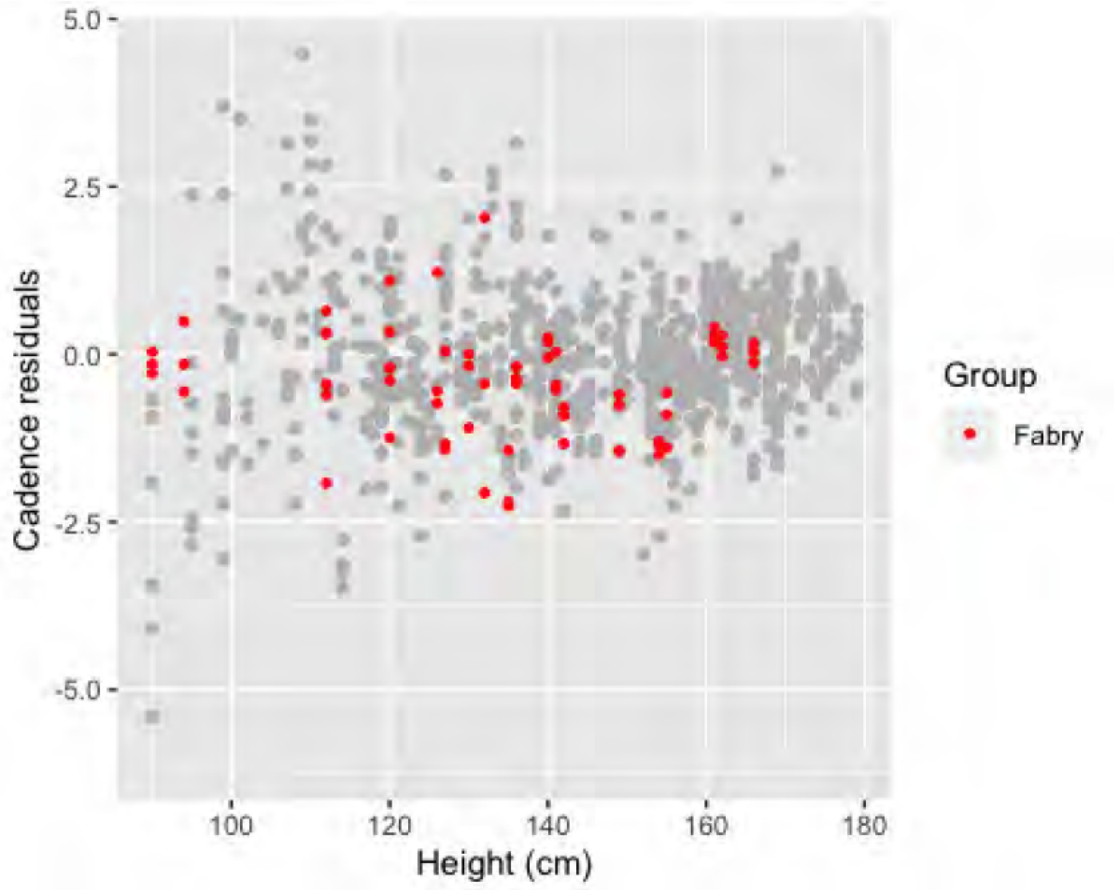
#  test group effect with mixed models, but we will bootstrap this b
elow
M1<-lmer(DV ~ Group + (1|PID),data=GroupData,REML=FALSE)
M2<-lmer(DV ~ 1 + (1|PID),data=GroupData,REML=FALSE)
anova(M1,M2)

## Data: GroupData
## Models:
## M2: DV ~ 1 + (1 | PID)
## M1: DV ~ Group + (1 | PID)
##    npar    AIC    BIC  logLik deviance  Chisq Df Pr(>Chisq)
## M2    3 7262.6 7277.1 -3628.3   7256.6
## M1    4 7264.2 7283.6 -3628.1   7256.2 0.4269  1     0.5135

GroupSummary<-GroupData %>% dplyr::group_by(Group) %>% dplyr::summar
ise(MeanResid=mean(Residual))
print(GroupSummary)

## # A tibble: 2 x 2
##   Group MeanResid
## * <chr>     <dbl>
## 1 c        -0.163
## 2 pf       -5.36

# plot one patient group
PPlot<-ggplot(CDataNO,aes(x=Height,y=SResid)) + geom_point(color="gr
ey")
PPlot<-PPlot + geom_point(data=GroupData[GroupData$Group == PGroup,]
,aes(x=Height,y=SResid,color=Group),size=1)
PPlot<-PPlot + labs(x="Height (cm)", y=paste0(DependentVariableName,
" residuals"))
PPlot<-PPlot + ylim(SYLowerPlotLimit,SYUpperPlotLimit)
PPlot<-PPlot + colScale
print(PPlot)
```

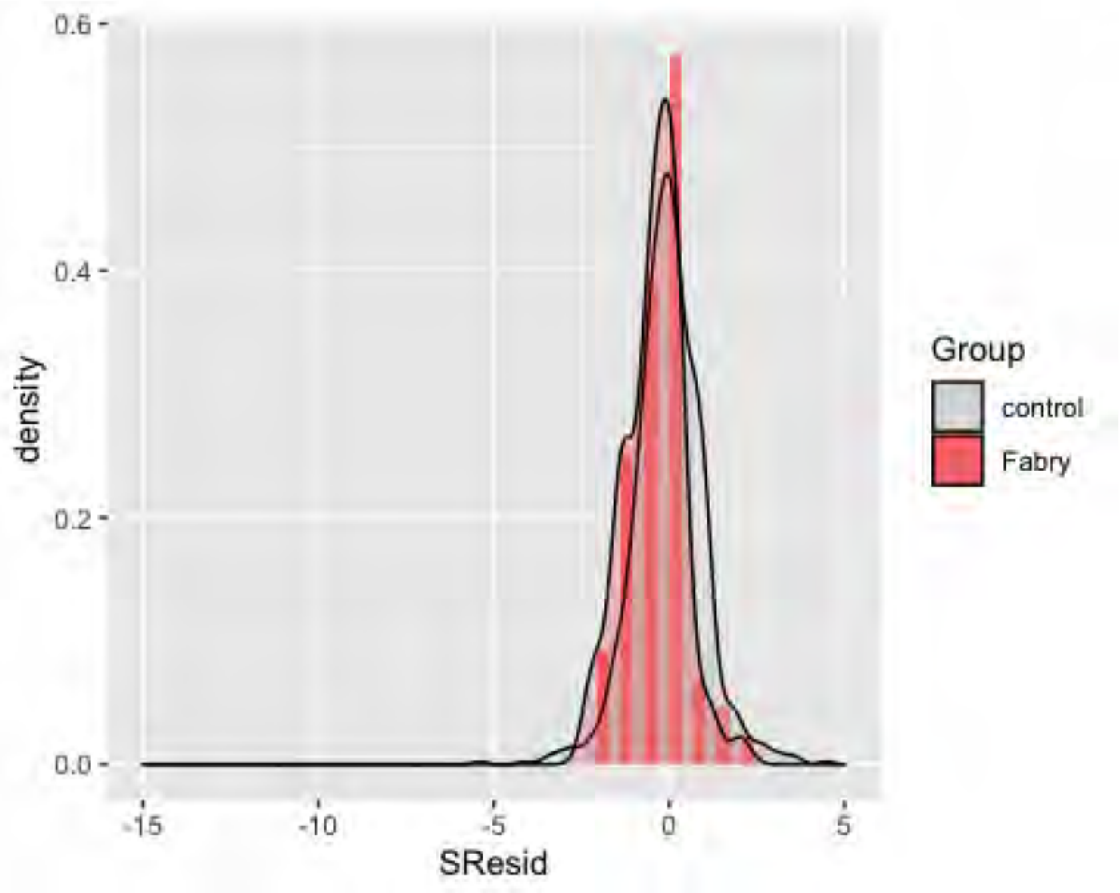



```
# options(bitmapType='cairo') # use on BlueBEAR
png(paste0(CurDir,"/",gsub(" ","",DependentVariableName),"/",
                  DependentVariableName,"_",GroupName,"_RawData.png"
),
           width=20,height=15,units="cm",res=800)
PPlot
dev.off()

## quartz_off_screen
##                 2

# plot one patient group histogram against controls
HPlot<-ggplot(GroupData,aes(x=SResid,y=..density..,group=Group,fill=
Group)) + geom_histogram(position="dodge",alpha=0.5) + geom_density(
alpha=0.2)
HPlot<-HPlot + fillScale + colScale + xlim(CrossPatientLowerSResidLi
mit,CrossPatientUpperSResidLimit)
print(HPlot)

## `stat_bin()` using `bins = 30`. Pick better value with `binwidth`
.
```




```
# options(bitmapType='cairo') # use on BlueBEAR
png(paste0(CurDir,"/",gsub(" ","",DependentVariableName),"/",
                  DependentVariableName,"_",GroupName,"AndControl_Di
stributions.png"),
           width=20,height=15,units="cm",res=800)
HPlot

## `stat_bin()` using `bins = 30`. Pick better value with `binwidth`
.

dev.off()

## quartz_off_screen
##                 2

# get patient means for bootstrapping
PatData<-GroupData[GroupData$Group == PGroup,]
PMeans<-PatData %>% dplyr::group_by(PID) %>% dplyr::summarise(SResMe
an=mean(SResid))
OrigData<-PMeans$SResMean
print(PMeans)

## # A tibble: 20 x 2
##    PID         SResMean
##  * <chr>          <dbl>
##  1 Fabry_50001  -1.38
```

```
##  2 Fabry_50002   0.122
##  3 Fabry_50003  -1.01
##  4 Fabry_50004  -0.320
##  5 Fabry_50005  -0.283
##  6 Fabry_50006  -0.0202
##  7 Fabry_50007  -0.330
##  8 Fabry_50008  -0.114
##  9 Fabry_50009   0.125
## 10 Fabry_50010  -0.906
## 11 Fabry_50011  -0.424
## 12 Fabry_50012   0.0239
## 13 Fabry_50013  -0.0727
## 14 Fabry_50014  -0.158
## 15 Fabry_50015   0.280
## 16 Fabry_50016  -0.958
## 17 Fabry_50017  -0.133
## 18 Fabry_50018  -0.937
## 19 Fabry_50019  -1.96
## 20 Fabry_50020  -0.0889
```

```
PDataN<-length(PMeans$PID)
print(sprintf("Number of patients = %d",PDataN))
```

```
## [1] "Number of patients = 20"
```

```
# bootstrap the CI for patient mean
# source("/Users/olsonac-admin/Documents/current/R/BootstrapRoutines
.R")
DbCI<-DoubleBootstrapCIForMean(OrigData,2000,500,0.05)
print(sprintf("bootstrap confidence interval for %s = %.4f to %.4f",
GroupName,DbCI$CI[1],DbCI$CI[2])) # this is the bootstrap confidence
interval
```

```
## [1] "bootstrap confidence interval for Fabry = -0.7768 to -0.2116
"
```

```
# if this contains zero controls and patients are not reliably diffe
rent
# if this does not include zero controls and patients are significan
tly different
```

```
# get patient means for bootstrapping
ContData<-GroupData[GroupData$Group == "c",]
CMeans<-ContData %>% dplyr::group_by(PID) %>% dplyr::summarise(SResM
ean=mean(SResid))
OrigDataC<-CMeans$SResMean
# print(CMeans)
```

Bootstrap control

```
ContBootstrap<-DoubleBootstrapCIForMeanSetN(OrigDataC,PDataN,2000,500,Alpha=0.05)
# OldContBootstrap<-DoubleBootstrapCIForMean(OrigDataC,2000,500,Alpha=0.05)
# saveRDS(ContECEOBootstrapDiff,"RMSControlECEOBootstrapDiff.RData")
print(sprintf("Bootstrap control mean for sample size = %d: %.4f to %.4f",PDataN,ContBootstrap$CI[1],ContBootstrap$CI[2]))
```

```
## [1] "Bootstrap control mean for sample size = 20: -0.4366 to 0.4325"
```

```
# print(OldContBootstrap$CI)
```

```
# patient bootstrap and data means
PBootstrapMeans<-data.frame(Group=PGroup,BootMeans=DbCI$BootMeans)
PMeanOfBootMeans<-mean(PBootstrapMeans$BootMeans)
print(paste0("Patient bootstrap mean: ",PMeanOfBootMeans, " mean from data: ",mean(OrigData)))
```

```
## [1] "Patient bootstrap mean: -0.419903890642821 mean from data: -0.427388915972603"
```

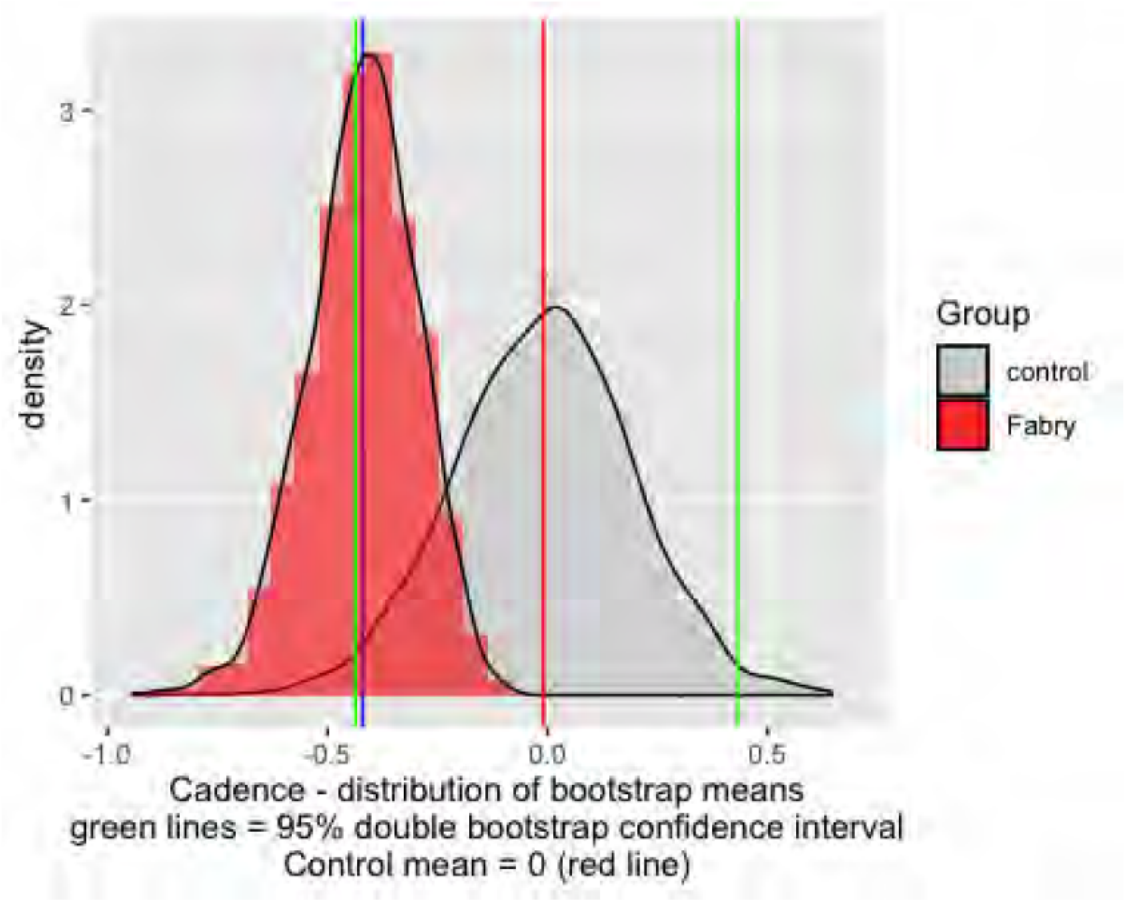
```
# plot bootstrap means and CI given by the double bootstrap
CBootstrapMeans<-data.frame(Group="c",BootMeans=ContBootstrap$BootMeans)
CMeanOfBootMeans<-mean(ContBootstrap$BootMeans)
print(paste0("Control bootstrap mean: ",CMeanOfBootMeans," control data mean: ",mean(OrigDataC)))
```

```
## [1] "Control bootstrap mean: -0.00904695996357235 control data mean: -0.00420977649006812"
```

```
CBMeanPlot<-ggplot(CBootstrapMeans,aes(x=BootMeans,y=..density..,fill=Group)) + geom_histogram(alpha=0.5) + geom_density(alpha=0.2) +  geom_vline(xintercept=PMeanOfBootMeans,color="blue")
CBMeanPlot<-CBMeanPlot + geom_histogram(data=PBootstrapMeans,aes(x=BootMeans,y=..density..,fill=Group),alpha=0.5) + geom_density(data=PBootstrapMeans,aes(x=BootMeans,y=..density..,fill=Group),alpha=0.2)
CBMeanPlot <- CBMeanPlot + geom_vline(xintercept=CMeanOfBootMeans,color="red")
CBMeanPlot <- CBMeanPlot + geom_vline(xintercept=ContBootstrap$CI[1],color="green")
CBMeanPlot <- CBMeanPlot + geom_vline(xintercept=ContBootstrap$CI[2],color="green")
CBMeanPlot <- CBMeanPlot + fillScale + colScale +
  xlab(paste0(DependentVariableName," - distribution of bootstrap means\ngreen lines = 95% double bootstrap confidence interval\nControl
```

```
mean = 0 (red line)"))
print(CBMeanPlot)

## `stat_bin()` using `bins = 30`. Pick better value with `binwidth`
.
## `stat_bin()` using `bins = 30`. Pick better value with `binwidth`
.
```




```
# options(bitmapType='cairo')
png(paste0(CurDir,"/", gsub(" ","", DependentVariableName), "/",Depe
ndentVariableName, "_",GroupName, "_ControlPatientBootstrapDistribut
ions.png"), width=20,height=15,units="cm",res=800)
CBMeanPlot

## `stat_bin()` using `bins = 30`. Pick better value with `binwidth`
.
## `stat_bin()` using `bins = 30`. Pick better value with `binwidth`
.

dev.off()

## quartz_off_screen
##                 2

# non-extreme values
OrigDataNE<-OrigData[(OrigData > (-1*ExtremeValuesLimit)) &
```

```
                        (OrigData < ExtremeValuesLimit)]
print(OrigDataNE)

##  [1] -1.38006312  0.12155960 -1.01272238 -0.31998184 -0.28331674
-0.02015513
##  [7] -0.32964398 -0.11445434  0.12548009 -0.90560510 -0.42352453
0.02386610
## [13] -0.07272132 -0.15787340  0.27992210 -0.95757772 -0.13262194
-0.93671248
## [19] -1.96274243 -0.08888976

PDataNEN<-length(OrigDataNE)
print(sprintf("Number of patients, excluding extremes = %d",PDataNEN
))

## [1] "Number of patients, excluding extremes = 20"

# bootstrap the CI for patient mean

DbCINE<-DoubleBootstrapCIForMean(OrigDataNE,2000,500,0.05)
print(sprintf("Bootstrap CI for %s with extreme values excluded: %.4
f to %.4f",GroupName,DbCINE$CI[1],DbCINE$CI[2])) # this is the boots
trap confidence interval

## [1] "Bootstrap CI for Fabry with extreme values excluded: -0.7758
to -0.2141"

# if this contains zero controls and patients are not reliably diffe
rent
# if this does not include zero controls and patients are significan
tly different

ContBootstrapNE<-DoubleBootstrapCIForMeanSetN(OrigDataC,PDataNEN,200
0,500,Alpha=0.05)
print(sprintf("Bootstrap CI for controls for sample of %d = %.4f to
%.4f",PDataNEN,ContBootstrapNE$CI[1],ContBootstrapNE$CI[2]))

## [1] "Bootstrap CI for controls for sample of 20 = -0.4031 to 0.45
75"

PBootstrapMeansNE<-data.frame(Group=PGroup,BootMeans=DbCINE$BootMean
s)
PMeanOfBootMeansNE<-mean(PBootstrapMeansNE$BootMeans)
print(paste0("Patient bootstrap mean, without extreme values: ",PMea
nOfBootMeansNE, " mean from data: ",mean(OrigDataNE)))

## [1] "Patient bootstrap mean, without extreme values: -0.429192751
610161 mean from data: -0.427388915972603"

# plot bootstrap means and CI given by the double bootstrap
CBootstrapMeansNE<-data.frame(Group="c",BootMeans=ContBootstrapNE$Bo
otMeans)
```

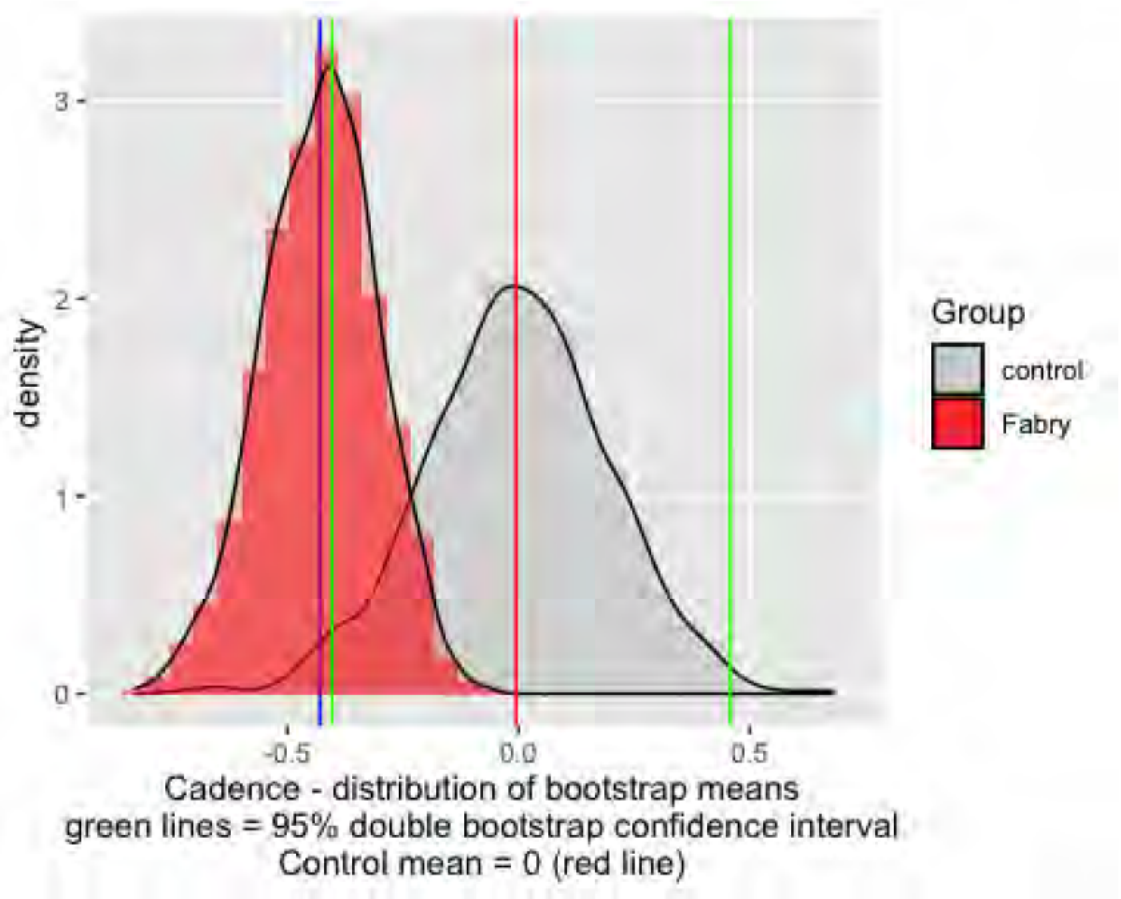
```
CMeanOfBootMeansNE<-mean(ContBootstrapNE$BootMeans)
print(sprintf("Control bootstrap mean with N = %d to match number of
non-extreme patient values: %.4f",PDataNEN,CMeanOfBootMeansNE))
```

```
## [1] "Control bootstrap mean with N = 20 to match number of non-ex
treme patient values: -0.0051"
```

plot patient bootstrap mean and CI for mean

```
CBMeanPlotNE<-ggplot(CBootstrapMeansNE,
                     aes(x=BootMeans,y=..density..,fill=Group)) +
  geom_histogram(alpha=0.5) + geom_density(alpha=0.2) +
  geom_vline(xintercept=PMeanOfBootMeansNE,color="blue")
CBMeanPlotNE<-CBMeanPlotNE +
  geom_histogram(data=PBootstrapMeansNE,
                 aes(x=BootMeans,y=..density..,fill=Group),
                 alpha=0.5) +
  geom_density(data=PBootstrapMeansNE,
               aes(x=BootMeans,y=..density..,fill=Group),
               alpha=0.2)
CBMeanPlotNE <- CBMeanPlotNE + geom_vline(xintercept=CMeanOfBootMean
sNE,color="red")
CBMeanPlotNE <- CBMeanPlotNE + geom_vline(xintercept=ContBootstrapNE
$CI[1],color="green")
CBMeanPlotNE <- CBMeanPlotNE + geom_vline(xintercept=ContBootstrapNE
$CI[2],color="green")
CBMeanPlotNE <- CBMeanPlotNE + fillScale + colScale +
  xlab(paste0(DependentVariableName," - distribution of bootstrap me
ans\ngreen lines = 95% double bootstrap confidence interval\nControl
mean = 0 (red line)"))
print(CBMeanPlotNE)
```

```
## `stat_bin()` using `bins = 30`. Pick better value with `binwidth`
.
## `stat_bin()` using `bins = 30`. Pick better value with `binwidth`
.
```




```
png(paste0(CurDir,"/", gsub(" ","", DependentVariableName), "/",Depe
ndentVariableName,"_",GroupName,"ControlBootstrapDistributions_NoExt
remeValues.png"),width=20,height=15,units="cm",res=800)
CBMeanPlotNE
```

```
## `stat_bin()` using `bins = 30`. Pick better value with `binwidth`
.
## `stat_bin()` using `bins = 30`. Pick better value with `binwidth`
.
```

```
dev.off()
```

```
## quartz_off_screen
##                 2
```

Calculate cutoffs for individual data

```
# get normal range cutoffs for patients based on control ppt means

PptMeans<-CDataNO %>% dplyr::group_by(PID,Height,HtBin) %>% dplyr::s
ummarise(PptMean=mean(Residual))

## `summarise()` has grouped output by 'PID', 'Height'. You can over
ride using the `.groups` argument.

head(PptMeans)

## # A tibble: 6 x 4
## # Groups:   PID, Height [6]
##   PID     Height HtBin PptMean
##   <chr>    <dbl> <dbl>   <dbl>
## 1 EN-H1       99    95 -20.5
## 2 EN-H2      104   105   0.551
## 3 EN-H3       90    95 -54.9
## 4 FS-Y1S1    120   125   5.97
## 5 FS-Y1S2    109   105  20.5
## 6 FS-Y1S3    119   115 -15.9

# get prediction intervals for height bins based on ppt mean residua
ls
PCutoff<-0.95
PIByHeight<-GroupedPredictionInterval(PptMeans,"PptMean","HtBin",PCu
toff)
print(PIByHeight)

## # A tibble: 9 x 7
##   HtBin  MyMean  MySD   MyN MyTCrit UpperCutoff LowerCutoff
##   <dbl>   <dbl> <dbl> <int>   <dbl>       <dbl>       <dbl>
## 1    95 -13.8   25.5      8    2.36        50.3       -77.8
## 2   105   4.90  15.7     12    2.20        40.9       -31.1
## 3   115   0.291 16.6     24    2.07        35.3       -34.7
## 4   125  -0.106 10.8     29    2.05        22.4       -22.6
## 5   135   0.730 11.7     34    2.03        24.8       -23.3
## 6   145  -3.10   8.22    34    2.03        13.9       -20.1
## 7   155  -3.00   9.00    47    2.01        15.3       -21.3
## 8   165   1.79   8.56    75    1.99        19.0       -15.4
## 9   175   3.84   7.86    31    2.04        20.2       -12.5

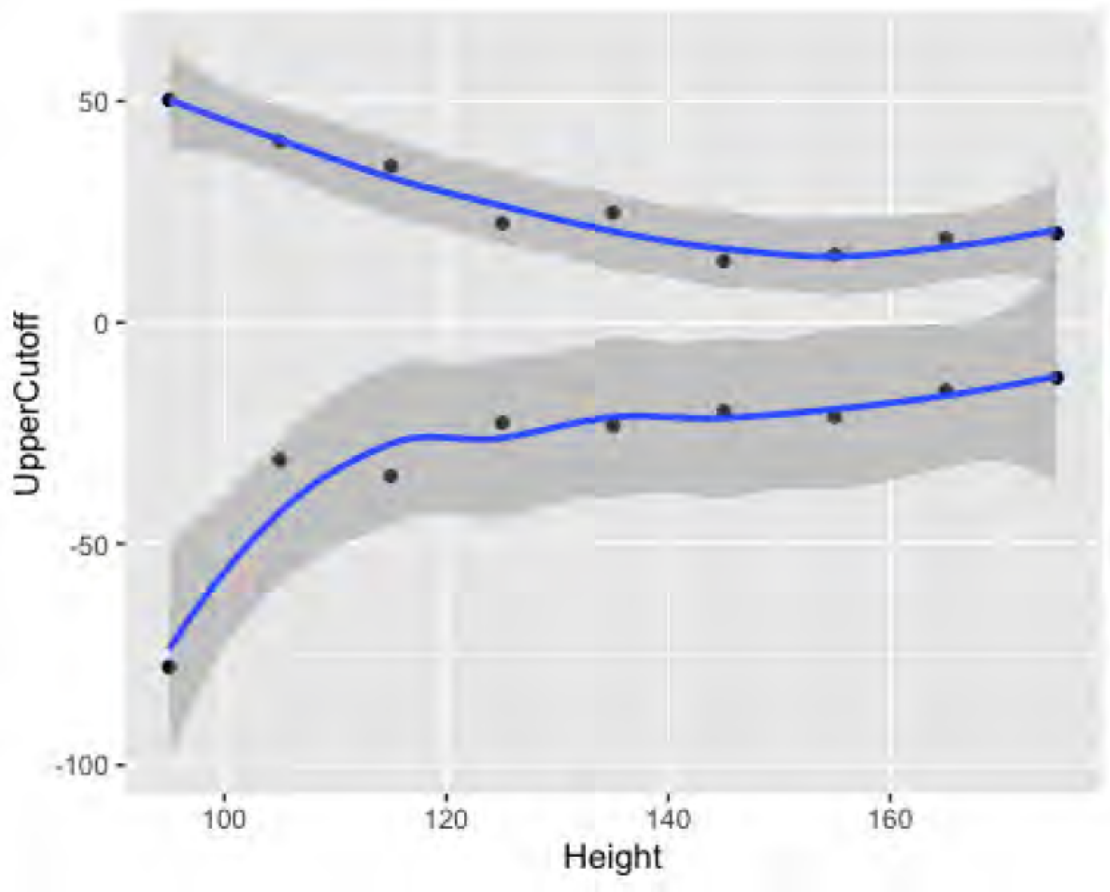
# rename HtBin to Height because when we apply the cutoff to the dat
a we will
# use each ppts Height variable, so the model will need to predict b
ased on a variable called
# Height rather than HtBin
```

```
PIByHeight<-PIByHeight %>% dplyr::rename(Height=HtBin)
head(PIByHeight)
```

```
## # A tibble: 6 x 7
##   Height  MyMean  MySD   MyN MyTCrit UpperCutoff LowerCutoff
##    <dbl>   <dbl> <dbl> <int>   <dbl>       <dbl>       <dbl>
## 1     95 -13.8   25.5      8    2.36        50.3       -77.8
## 2    105   4.90  15.7     12    2.20        40.9       -31.1
## 3    115   0.291 16.6     24    2.07        35.3       -34.7
## 4    125  -0.106 10.8     29    2.05        22.4       -22.6
## 5    135   0.730 11.7     34    2.03        24.8       -23.3
## 6    145  -3.10   8.22    34    2.03        13.9       -20.1
```

```
# plot prediction interval cutoffs
CurData<-PIByHeight
CutoffPlot<-ggplot(CurData,aes(x=Height,y=UpperCutoff))+geom_point()
+geom_smooth()
CutoffPlot<-CutoffPlot + geom_point(aes(x=Height,y=LowerCutoff))+geo
m_smooth(aes(x=Height,y=LowerCutoff))
print(CutoffPlot)
```

```
## `geom_smooth()` using method = 'loess' and formula 'y ~ x'
## `geom_smooth()` using method = 'loess' and formula 'y ~ x'
```




```
png(paste0(CurDir,"/", gsub(" ","", DependentVariableName), "/",Depe
ndentVariableName,"_PredictionIntervalCutoffsRaw.png"),width=20,heig
```

```
ht=15,units="cm",res=800)
CutoffPlot

## `geom_smooth()` using method = 'loess' and formula 'y ~ x'
## `geom_smooth()` using method = 'loess' and formula 'y ~ x'

dev.off()

## quartz_off_screen
##                 2

# model upper cutoff

LrcStart<-0.1 # this would be a pretty flat function
LrcEnd<-5 # this would be a sharp corner
LrcStep<-0.1 # go between 0.5 and 5 in steps of 0.5
AsympPortion <- 0.5 # portion of the curve that is curved
YName<-"UpperCutoff"
XName<-"Height"

UCOAStartList<-PlotStartingAsympFunction(CurData,XName,YName,LrcStar
t,LrcEnd,LrcStep,AsympPortion)
print(UCOAStartList$Plot)
```

```
UCOAModelList<-FitAsymptoteModel(CurData,"Height","UpperCutoff",UCOA
StartList$StartValues)
if(!is.null(UCOAModelList)){
  UCOAsympModel<-UCOAModelList$Model
  print(UCOAModelList$Plot)
} else{
  message("\nAsymptote model was not fit successfully")
  UCOAsympModel<-NULL
}

## `geom_smooth()` using method = 'loess' and formula 'y ~ x'
```

```
UCOQuadraticModel<-lm(UpperCutoff ~ Height + I(Height^2),data=CurDat
a)
UCOLinearModel<-lm(UpperCutoff ~ Height,data=CurData)
UCOConstantModel<-lm(UpperCutoff ~ 1,data=CurData)
# no reason why these shouldn't converge

UCOAICResult<-GetAICResult(UCOAsympModel,UCOQuadraticModel,UCOLinear
Model,UCOConstantModel)

##  Asymptotic model: 55.1874763388653
## Quadratic Model: 49.9889639819464
```

```
##  Linear Model: 63.9986121086207
##  ConstantModel: 73.9533612756277

print(UCOAICResult)

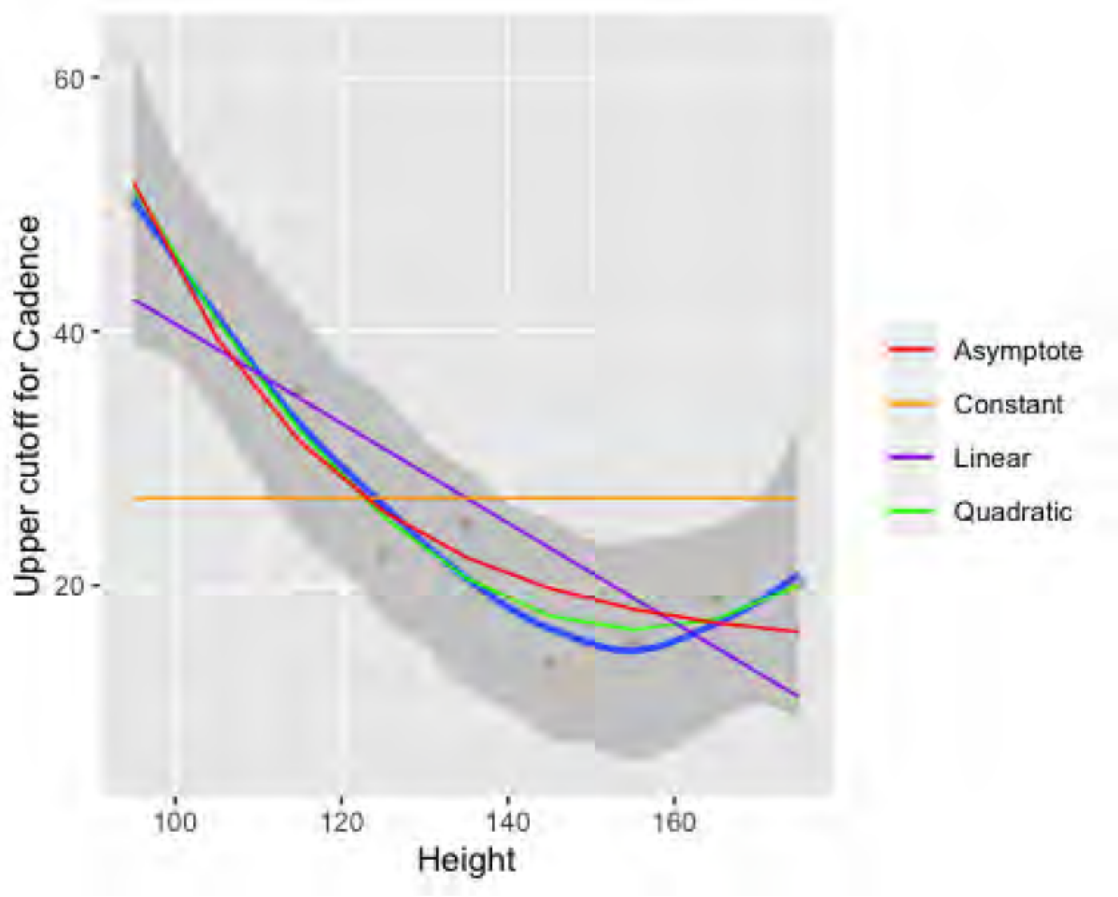
##                        AIC Order  deltaAIC
## Asymptotic Model 55.18748     2  5.198512
## Quadratic Model  49.98896     1  0.000000
## Linear Model     63.99861     3 14.009648
## ConstantModel    73.95336     4 23.964397
```

Quadratic is best, but upward curve at the end may be due to small number of tall ppts

```
# plot models to choose the best model based on AIC and theoretical
plausibility

ModelPlot<-PlotModels(CurData,"Height","UpperCutoff",paste("Upper cu
toff for ",DependentVariableName,sep=""), UCOAsympModel, UCOQuadrati
cModel, UCOLinearModel, UCOConstantModel)
print(ModelPlot)

## `geom_smooth()` using method = 'loess' and formula 'y ~ x'
```




```
png(paste0(CurDir,"/", gsub(" ","", DependentVariableName), "/",Depe
ndentVariableName,"_UpperCutoffModels.png"),width=20,height=15,units
```

```
="cm",res=800)
ModelPlot

## `geom_smooth()` using method = 'loess' and formula 'y ~ x'

dev.off()

## quartz_off_screen
##                 2
```

Try models with data that doesn't include extreme high/low values to make sure that the preferred model doesn't change.

```
# Fit models without the extremes of height, small N points -- make
sure best model is consistent in both analyses

CurDataNE<-CurData[(CurData$Height > 95) & (CurData$Height < 175),]

NEUCOAStartList<-PlotStartingAsympFunction(CurDataNE,XName,YName,Lrc
Start,LrcEnd,LrcStep,AsympPortion)
print(NEUCOAStartList$Plot)
```

```
NEUCOAModelList<-FitAsymptoteModel(CurDataNE,"Height","UpperCutoff",
NEUCOAStartList$StartValues)
if(!is.null(NEUCOAModelList)){
  NEUCOAsympModel<-NEUCOAModelList$Model
  print(NEUCOAModelList$Plot)
}else{
  message("\nAsymptote model was not fit successfully")
  NEUCOAsympModel<-NULL
}

## `geom_smooth()` using method = 'loess' and formula 'y ~ x'
```

```
NEUCOQuadraticModel<-lm(UpperCutoff ~ Height + I(Height^2),data=CurD
ataNE)
NEUCOLinearModel<-lm(UpperCutoff ~ Height,data=CurDataNE)
NEUCOConstantModel<-lm(UpperCutoff ~ 1,data=CurDataNE)
# no reason why these shouldn't converge

NEUCOAICResult<-GetAICResult(NEUCOAsympModel,NEUCOQuadraticModel,NEU
COLinearModel,NEUCOConstantModel)

##  Asymptotic model: 43.8984639033464
## Quadratic Model: 41.9179286226307
##  Linear Model: 47.3894421325568
##  ConstantModel: 55.2395583523748
```

```
print(NEUCOAICResult)
```

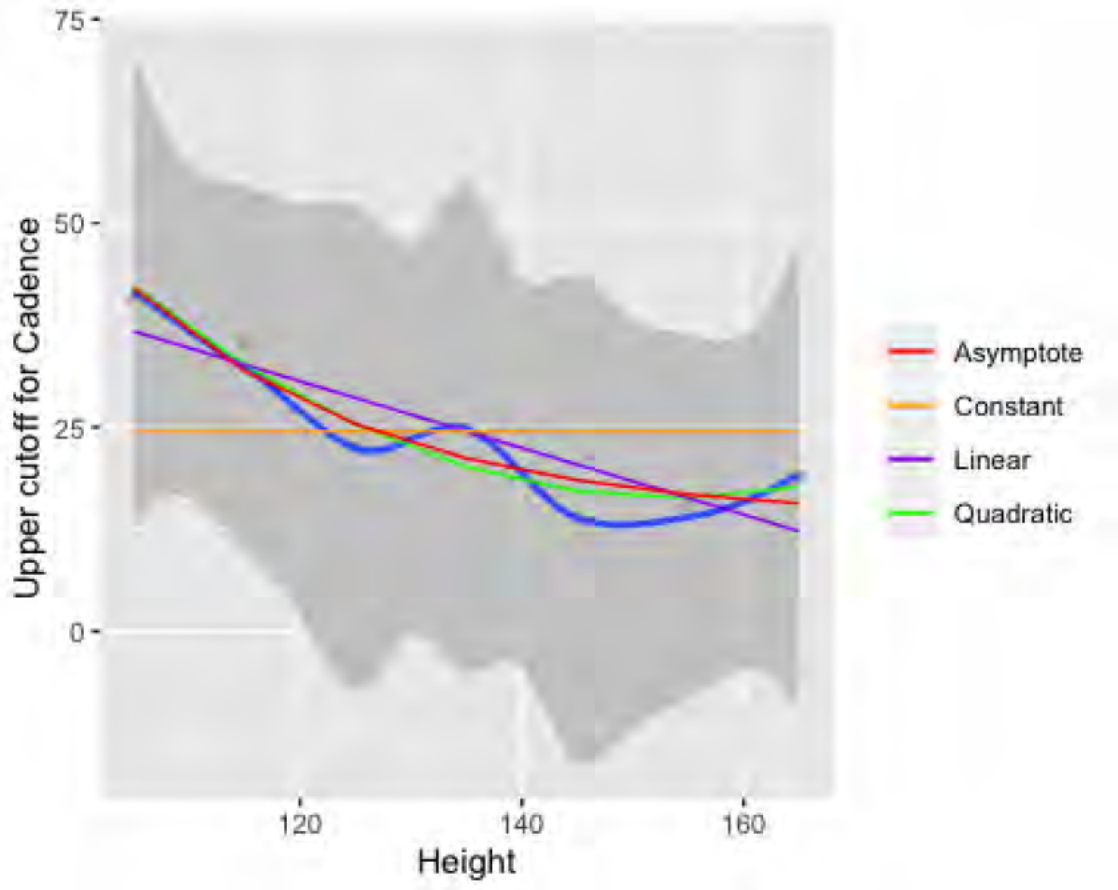
```
##                        AIC Order  deltaAIC
## Asymptotic Model 43.89846     2  1.980535
## Quadratic Model  41.91793     1  0.000000
## Linear Model     47.38944     3  5.471514
## ConstantModel    55.23956     4 13.321630
```

Quadratic is best, asymptotic is similar

```
# plot models to choose the best model based on AIC and theoretical plausibility

ModelPlot<-PlotModels(CurDataNE,"Height","UpperCutoff",paste("Upper cutoff for ",DependentVariableName,sep=""), NEUCOAsympModel, NEUCOQuadraticModel, NEUCOLinearModel, NEUCOConstantModel)
print(ModelPlot)
```

```
## `geom_smooth()` using method = 'loess' and formula 'y ~ x'
```




```
png(paste0(CurDir,"/", gsub(" ","", DependentVariableName), "/",DependentVariableName,"_UpperCutoffModelsNoExtremeValues.png"),width=20,height=15,units="cm",res=800)
ModelPlot
```

```
## `geom_smooth()` using method = 'loess' and formula 'y ~ x'
```

```
dev.off()

## quartz_off_screen
##                 2
```

Choose quadratic model

Upper cutoff: choose the best model from above and put on the right side of the equation below

```
# choose best model for upper cutoff
UpperCutoffModel<-UCOQuadraticModel
```

Do the same for model lower cutoff

Lower cutoff: choose the best model from above and put on the right side of the equation below

```
# choose best model for Lower cutoff
LowerCutoffModel<-LCOAsympModel
```

Set cutoffs in data

```
#
AllDataPptMeans<-AllDatNO %>%  dplyr::group_by(PID,Group,Age,Height)
%>% dplyr::summarise(PptMean=mean(Residual))

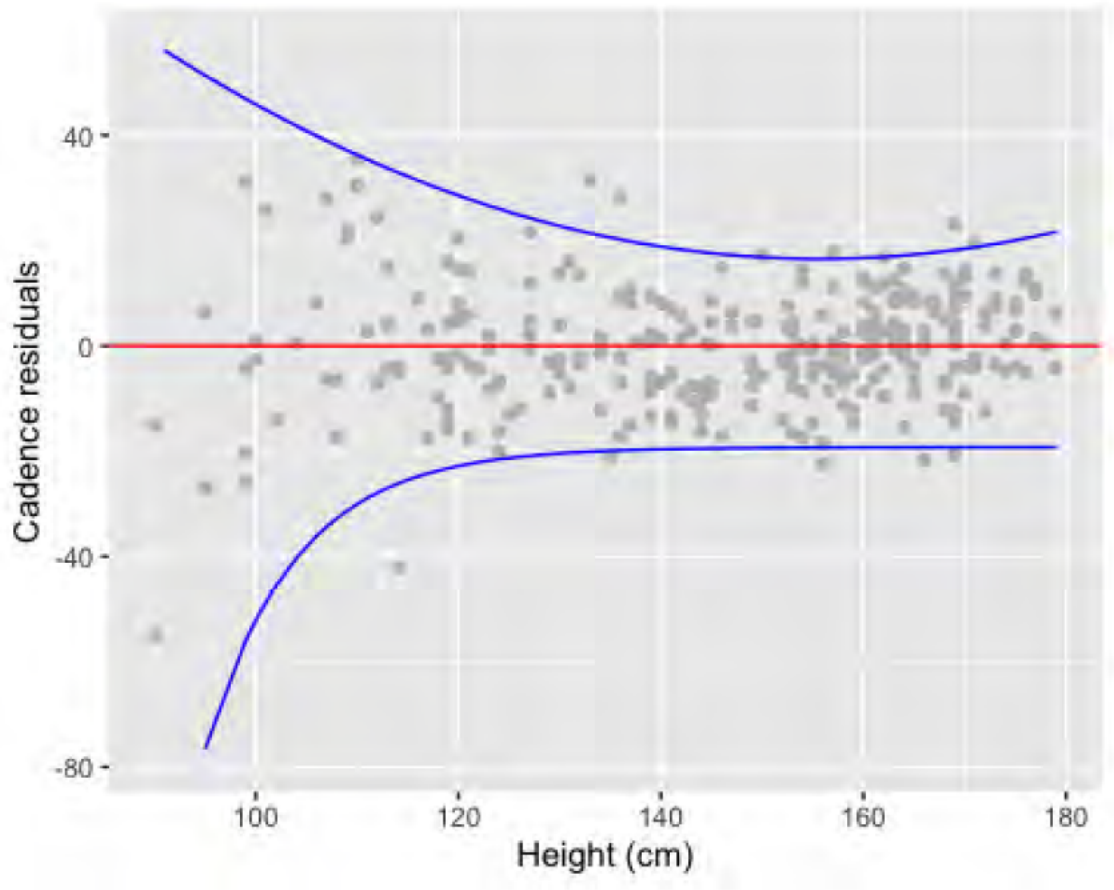
## `summarise()` has grouped output by 'PID', 'Group', 'Age'. You ca
n override using the `.groups` argument.

AllDataPptMeans$LowerCutoff<-predict(LowerCutoffModel,newdata=AllDat
aPptMeans)
AllDataPptMeans$UpperCutoff<-predict(UpperCutoffModel,newdata=AllDat
aPptMeans)

MyPlot<-ggplot(AllDataPptMeans[AllDataPptMeans$Group == 'c',],aes(x=
Height,y=PptMean))+geom_point(color="grey")
#MyPlot<-MyPlot + geom_point(data=AllDataPptMeans[AllDataPptMeans$Gr
oup!='c',],
#                            aes(x=Height,y=PptMean,color=Group))
MyPlot<-MyPlot + geom_line(data=AllDataPptMeans,aes(x=Height,y=Upper
Cutoff),color="blue")
MyPlot<-MyPlot + geom_line(data=AllDataPptMeans,aes(x=Height,y=Lower
```

```
Cutoff),color="blue")
MyPlot <- MyPlot + geom_hline(yintercept = 0,color='red')

MyPlot<-MyPlot + labs(x="Height (cm)", y=paste0(DependentVariableNam
e," residuals"))
MyPlot<-MyPlot + ylim(YLowerPlotLimit,YUpperPlotLimit)
MyPlot<-MyPlot + colScale
print(MyPlot)
```




```
png(paste0(CurDir,"/", gsub(" ","", DependentVariableName), "/",Depe
ndentVariableName,"_ControlsData_UpperLowerCutoffs.png"),width=20,he
ight=15,units="cm",res=800)
MyPlot
dev.off()

## quartz_off_screen
##                 2

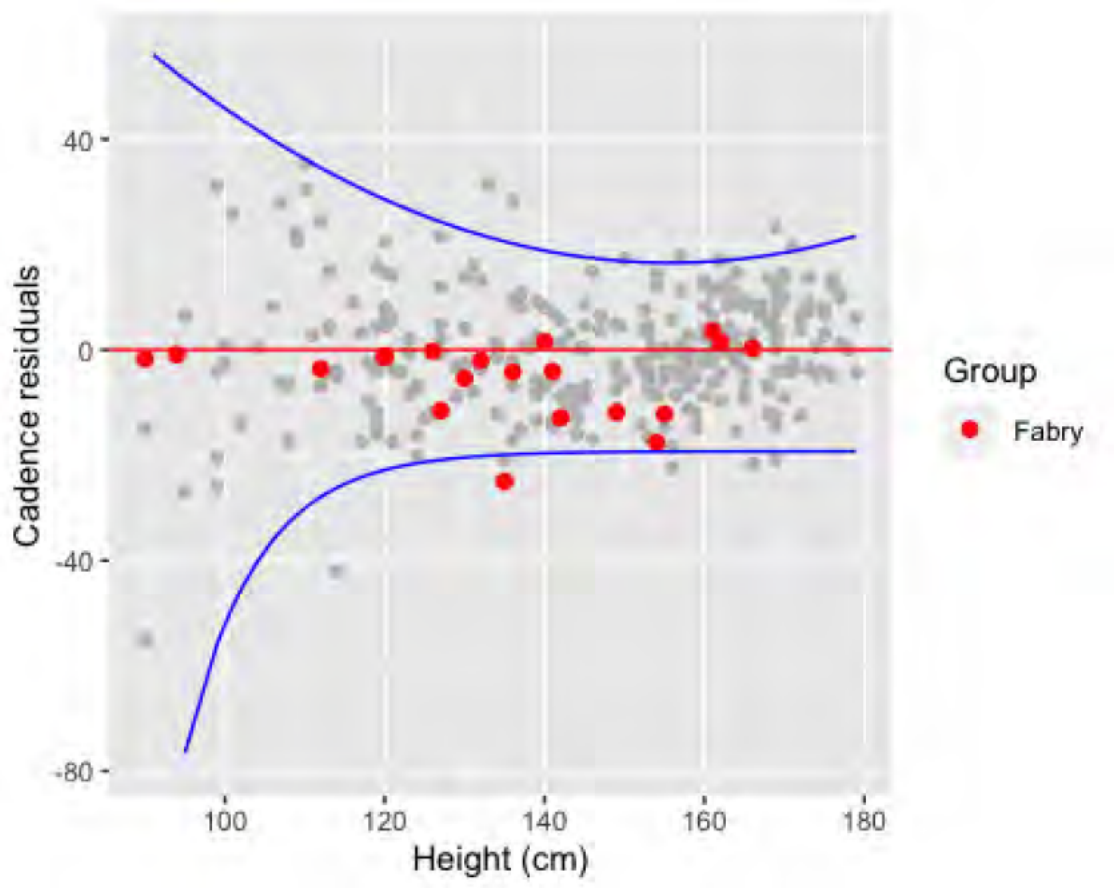
# plot controls and one group of patients

GroupName<-"Fabry"
MyPlot<-ggplot(AllDataPptMeans[AllDataPptMeans$Group == 'c',],aes(x=
Height,y=PptMean))+geom_point(color="grey")

MyPlot<-MyPlot + geom_point(data=AllDataPptMeans[AllDataPptMeans$Gro
```

```
up=='pf',],aes(x=Height,y=PptMean,color=Group),size=2)

MyPlot<-MyPlot + geom_line(data=AllDataPptMeans,aes(x=Height,y=Upper
Cutoff),color="blue")
MyPlot<-MyPlot + geom_line(data=AllDataPptMeans,aes(x=Height,y=Lower
Cutoff),color="blue")
MyPlot <- MyPlot + geom_hline(yintercept = 0,color='red')
MyPlot<-MyPlot + labs(x="Height (cm)", y=paste0(DependentVariableNam
e," residuals"))
MyPlot<-MyPlot + ylim(YLowerPlotLimit,YUpperPlotLimit)
MyPlot<-MyPlot + colScale
print(MyPlot)
```




```
png(paste0(CurDir,"/", gsub(" ","", DependentVariableName), "/",Depe
ndentVariableName,"_",GroupName,"_RawDataWithUpperLowerCutoffs.png")
,width=20,height=15,units="cm",res=800)
MyPlot
dev.off()

## quartz_off_screen
##                 2

# plot controls and the three other groups of patients

GroupName<-"SmallGroups"
```

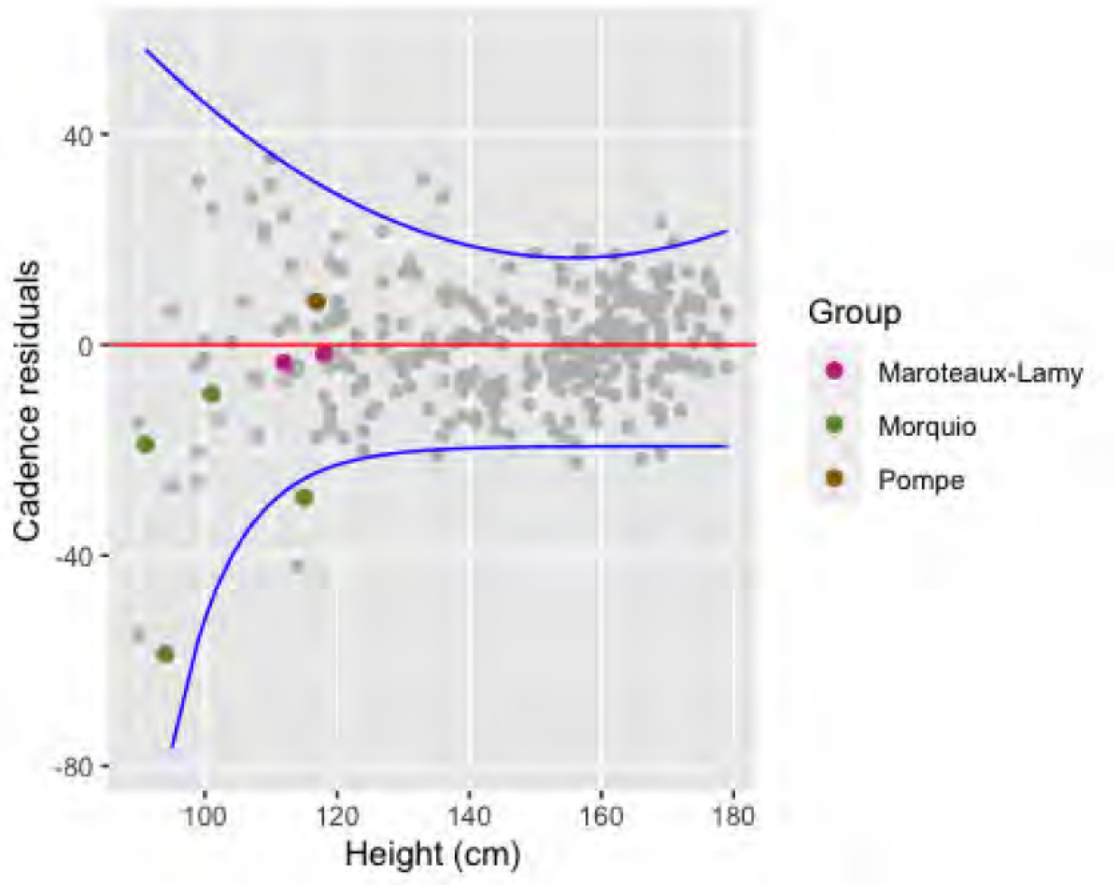
```
MyPlot<-ggplot(AllDataPptMeans[AllDataPptMeans$Group == 'c',],aes(x=
Height,y=PptMean))+geom_point(color= "grey")
MyPlot<-MyPlot + geom_point(data=AllDataPptMeans[(AllDataPptMeans$Gr
oup == 'pl') | (AllDataPptMeans$Group == 'pp') | (AllDataPptMeans$Gr
oup == 'pm'),],
                            aes(x=Height,y=PptMean,color= Group),siz
e=2)


MyPlot<-MyPlot + geom_line(data=AllDataPptMeans,aes(x=Height,y=Upper
Cutoff),color="blue")
MyPlot<-MyPlot + geom_line(data=AllDataPptMeans,aes(x=Height,y=Lower
Cutoff),color="blue")

MyPlot <- MyPlot + geom_hline(yintercept = 0,color='red')

MyPlot<-MyPlot + labs(x="Height (cm)", y=paste0(DependentVariableNam
e," residuals"))

MyPlot<-MyPlot + ylim(YLowerPlotLimit,YUpperPlotLimit)
MyPlot<-MyPlot + colScale
print(MyPlot)
```




```
png(paste0(CurDir,"/", gsub(" ","", DependentVariableName), "/",Depe
ndentVariableName,"_",GroupName,"_RawDataWithUpperLowerCutoffs.png")
```

```
,width=20,height=15,units="cm",res=800)
MyPlot
dev.off()

## quartz_off_screen
##                 2

AllDataPptMeans$SScore<-CalculateStandardScore(AllDataPptMeans$PptMe
an, AllDataPptMeans$LowerCutoff, AllDataPptMeans$UpperCutoff, PCutof
f)
# uses the cutoff that is closest to the ppt score (in this case Ppt
Mean)

# mark ppts outside the normal range
AllDataPptMeans$OutsideRange<-ifelse((AllDataPptMeans$PptMean < AllD
ataPptMeans$UpperCutoff) &
                                       (AllDataPptMeans$PptMean > Al
lDataPptMeans$LowerCutoff),0,1)

# list patient ppts outside the normal range
PatientsWithAbnormalValues<-AllDataPptMeans[(AllDataPptMeans$Outside
Range == 1) & (AllDataPptMeans$Group != "c"),]
AbValueTable<-PatientsWithAbnormalValues %>% select(PID,Group,Age,He
ight,PptMean,SScore,LowerCutoff,UpperCutoff)
AbValueTable<-AbValueTable[order(AbValueTable$Group),]
print(AbValueTable)

## # A tibble: 6 x 8
## # Groups:   PID, Group, Age [6]
##   PID         Group   Age Height PptMean SScore LowerCutoff Upper
Cutoff
##   <chr>       <chr> <int>  <dbl>   <dbl>  <dbl>       <dbl>
<dbl>
## 1 Fabry_50019 pf        8    135   -25.0  -2.46       -19.9
20.6
## 2 MPSI_10006  ph       12    139   -27.0  -2.69       -19.7
19.2
## 3 MPSIV_30016 pm        9    115   -29.0  -2.23       -25.5
32.2
## 4 NPC_NPC03   pn       10    145   -38.4  -3.86       -19.5
17.6
## 5 NPC_NPC04   pn        8    120   -73.2  -6.29       -22.8
28.6
## 6 NPC_NPC11   pn        8    119   -23.7  -2.00       -23.2
29.3

# list patient ppts NOT outside the normal range

PatientsWithNormValues<-AllDataPptMeans[(AllDataPptMeans$OutsideRang
e == 0) & (AllDataPptMeans$Group != "c"),]
NormValuesTable<-PatientsWithNormValues %>% select(PID,Group,Age,Hei
```

```
ght,PptMean,SScore,LowerCutoff,UpperCutoff)
NormValuesTable<-NormValuesTable[order(NormValuesTable$Group),]
print(NormValuesTable)

# get means of values inside the normal range

SelectedGroup<-"pf"
GroupName<-"Fabry"
NormMean<-mean(NormValuesTable[NormValuesTable$Group == SelectedGrou
p,]$PptMean)
print(paste("Mean for values inside the normal range for ",Dependent
VariableName," in ",GroupName,": ",NormMean))

## [1] "Mean for values inside the normal range for  Cadence  in  Fa
bry :  -4.41508725975089"
```

D. Balance R code example (jerk):

Analysis of a balance parameter example script

```
library(dplyr)

##
## Attaching package: 'dplyr'

## The following objects are masked from 'package:stats':
##
##     filter, lag

## The following objects are masked from 'package:base':
##
##     intersect, setdiff, setequal, union

library(tidyr)
library(nlme)

##
## Attaching package: 'nlme'

## The following object is masked from 'package:dplyr':
##
##     collapse

library(lme4)

## Loading required package: Matrix

##
## Attaching package: 'Matrix'

## The following objects are masked from 'package:tidyr':
##
##     expand, pack, unpack

##
## Attaching package: 'lme4'

## The following object is masked from 'package:nlme':
##
##     lmList

library(ggplot2)
library(nls2)

## Loading required package: proto

library(kableExtra)
```

```
##
## Attaching package: 'kableExtra'

## The following object is masked from 'package:dplyr':
##
##     group_rows

library(gridExtra)

##
## Attaching package: 'gridExtra'

## The following object is masked from 'package:dplyr':
##
##     combine

library(coin) # for permutation tests

## Loading required package: survival

library(parallel)

# choose one
# andrew's mac
DataHome<-"/Users/olsonac-admin/Documents/current/DanaAlsaqer/Balanc
e/RawData"
# others
# DataHome<-HomeDir

GData<-read.csv(paste0(DataHome,"/Nov2019AllPptRMSJerkResultsWithPpt
Info.csv"))
head(GData)

##    TrialID            PID EyeCond Trial        RMS      RMSAP
RMSML
## 1 Y7S1 EC1 KES_Year7_Y7S1      EC     1 0.04221446 0.03569217 0.0
2254173
## 2 Y7S1 EC2 KES_Year7_Y7S1      EC     2 0.04575802 0.03555601 0.0
2880220
## 3 Y7S1 EC3 KES_Year7_Y7S1      EC     3 0.04195830 0.03439719 0.0
2402773
## 4 Y7S1 EO1 KES_Year7_Y7S1      EO     1 0.03441567 0.02730185 0.0
2095346
## 5 Y7S1 EO2 KES_Year7_Y7S1      EO     2 0.03315305 0.02530283 0.0
2142175
## 6 Y7S1 EO3 KES_Year7_Y7S1      EO     3 0.03473704 0.02759438 0.0
2110005
##      JerkAP    JerkML   JerkOA  RawJerk TotalTime      NJS  Sourc
eID Group   ID
## 1 0.7974297 0.8864152 1.192487 39.48343  27.76562 427562.8 KES_Ye
ar7     c Y7S1
```

```
## 2 0.8199426 1.1508387 1.413698 54.85062  27.44531 451626.0 KES_Ye
ar7     c Y7S1
## 3 0.7898449 0.8505048 1.158833 36.52043  27.19531 392798.8 KES_Ye
ar7     c Y7S1
## 4 0.7178833 0.8390600 1.104428 36.03063  29.53906 584866.0 KES_Ye
ar7     c Y7S1
## 5 0.8104479 0.8713284 1.189268 41.88933  29.61719 658980.7 KES_Ye
ar7     c Y7S1
## 6 0.7908646 0.9212994 1.212190 40.48899  27.55469 516237.3 KES_Ye
ar7     c Y7S1
##   Age Height
## 1  12    156
## 2  12    156
## 3  12    156
## 4  12    156
## 5  12    156
## 6  12    156

# for running on a machine with more than one core to speed up
# the double bootstrap
NumCores<-detectCores()

# make sure that variable types are correct after reading data
GData$PID<-as.factor(GData$PID)
GData<-GData[GData$Group != "?",]
GData$Group<-factor(GData$Group)
GData$Age<-as.numeric(as.character(GData$Age))
GData$Height<-as.numeric(as.character(GData$Height))
GData$EyeCond<-factor(GData$EyeCond,levels=c("EO","EC"))
GData$RMS<-as.numeric(as.character(GData$RMS))
GData$RMSAP<-as.numeric(as.character(GData$RMSAP))
GData$RMSML<-as.numeric(as.character(GData$RMSML))
GData$Jerk<-as.numeric(as.character(GData$JerkAP))
GData$NormJerk<-as.numeric(as.character(GData$JerkOA))
levels(GData$Group)

## [1] "c"  "pf" "ph" "pl" "pm" "pn" "pp"

# map colors,shapes and sizes to different group labels (see 'breaks
')
# for plots for plots.  Associates a group label with a color, shape
and size,
# and a text name that will be used for legends
#
# Once set here plots by group use the correct colors, shapes, sizes
and names
# (e.g. 'color=Group' will set the colors for groups as they are map
ped here)

# create a custom color scale for patients and controls
```

```
myColors <- c("#AAAAAA","#FF0000", "#663300", "#CC3399","#669933","#
0066FF","#996600")
mySizes<-c(1,2,2,2,2,2,2)
myShapes<-c(16,15,17,18,6,1,0)
names(myColors) <- c("c","pf","ph","pl","pm","pn","pp")
colScale <- scale_colour_manual(name = "Group",
                                values = myColors,
                                labels=c("control", "Fabry", "Hurler
", "Maroteaux-Lamy", "Morquio", "NP-C", "Pompe"),
                                breaks=c("c","pf","ph","pl","pm","pn
","pp")
                                )

fillScale <- scale_fill_manual(name = "Group",
                                values = myColors,
                                labels=c("control", "Fabry", "Hurler
", "Maroteaux-Lamy", "Morquio", "NP-C", "Pompe"),
                                breaks=c("c","pf","ph","pl","pm","pn
","pp")
                                )
sizeScale <- scale_size_manual(name = "Group",
                                values = mySizes,
                                labels=c("control", "Fabry", "Hurler
", "Maroteaux-Lamy", "Morquio", "NP-C", "Pompe"),
                                breaks=c("c","pf","ph","pl","pm","pn
","pp")
                                )
shapeScale <- scale_shape_manual(name = "Group",
                                values = myShapes,
                                labels=c("control", "Fabry", "Hurler
", "Maroteaux-Lamy", "Morquio", "NP-C", "Pompe"),
                                breaks=c("c","pf","ph","pl","pm","pn
","pp")
                                )

####################################
#
# define dependent variable here - this script is analyzing 'jerk'
#
####################################

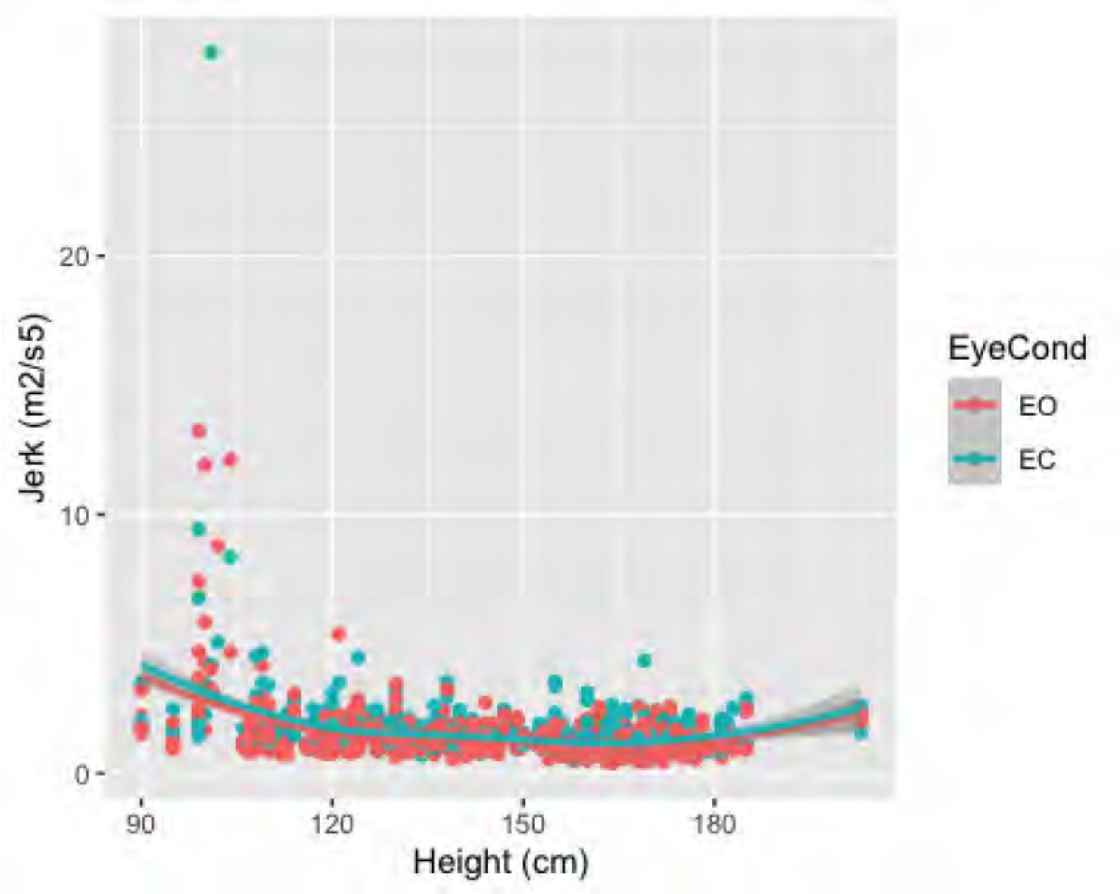
GData$DV<-GData$JerkOA
DependentVariableName<-"Jerk (m2/s5)"

# do age and height bins and separate patient and control data
GData$HtBin<-cut(GData$Height,breaks=10)  # bins every 10 cm
GData$HtBin<-CutMidpoints(GData$HtBin,1)
GData$AgeBin<-cut(GData$Age,breaks=c(0,5,8,11,15,17,30),right=TRUE)
GData$ObsID<-seq(1,length(GData[,1]))
```

```
# separate control and patient data
CData<-GData %>% filter(Group == "c")
PData<-GData %>% filter(Group != "c")

# plot control data with conditions in different colors (conditions
are
# 'eyes open' and 'eyes closed')
CPlot<-ggplot(CData,aes(x=Height,y=DV,group=EyeCond,color=EyeCond))+
geom_point()
CPlot<-CPlot + geom_smooth()
# CPlot<-CPlot+ylim(0,0.004) # use to zoom in or out
CPlot<-CPlot + labs(x="Height (cm)", y=DependentVariableName)
print(CPlot)

## `geom_smooth()` using method = 'loess' and formula 'y ~ x'
```




```
# plot all control data and add all patient groups or
# a single patient group
#
# first plot control data in grey
#
AllPlot<-ggplot(CData,aes(x=Height,y=DV,group=EyeCond))+geom_point(c
olor="grey")
AllPlot<-AllPlot + geom_smooth()
# CPlot<-CPlot+ylim(0,0.004) # use to zoom in or out
```

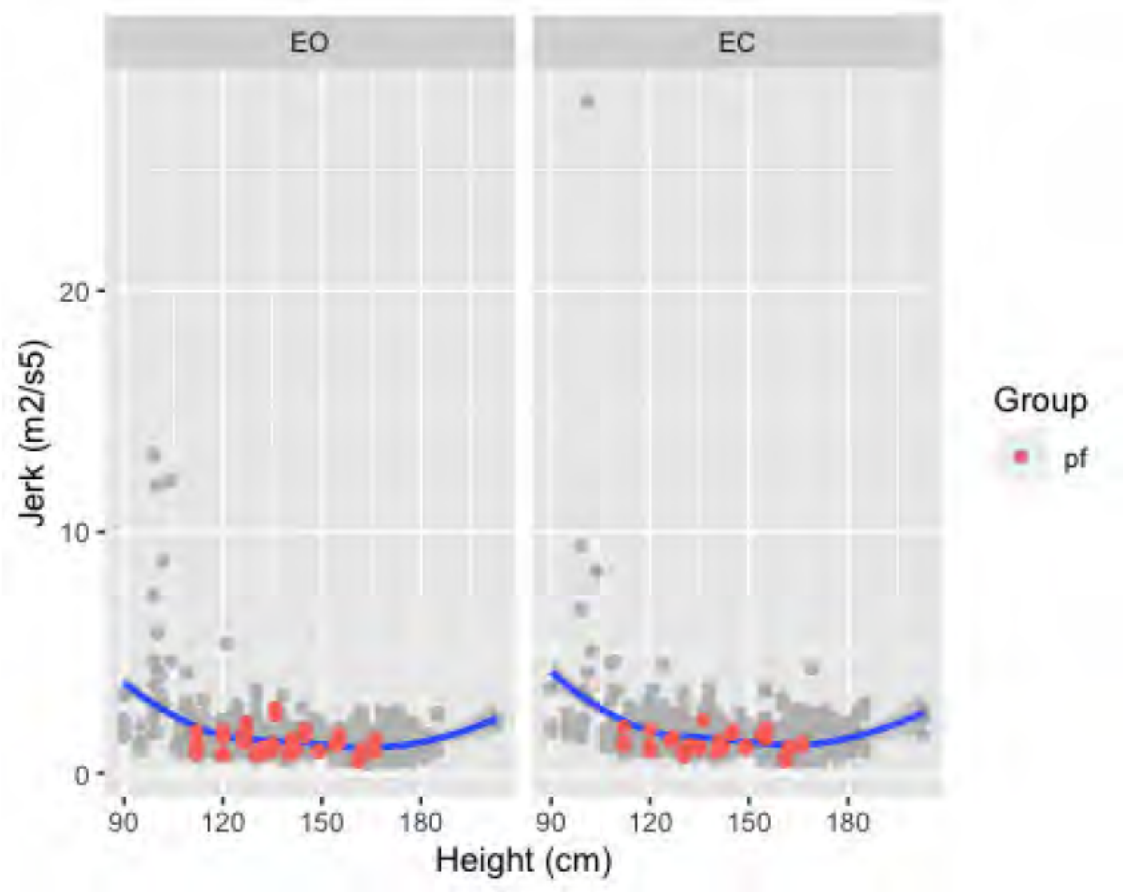
```
AllPlot<-AllPlot + labs(x="Height (cm)", y=DependentVariableName)

# to show all patient groups
#AllPlot<-AllPlot + geom_point(data=PData,aes(x=Height,y=DV,group=in
teraction(EyeCond,Group),color=Group)) + facet_grid(~EyeCond)

# to show just one patient group
AllPlot<-AllPlot + geom_point(data=PData[(PData$Group == "pf"),],aes
(x=Height,y=DV,group=interaction(EyeCond,Group),color=Group)) + face
t_grid(~EyeCond)

print(AllPlot)

## `geom_smooth()` using method = 'loess' and formula 'y ~ x'
```



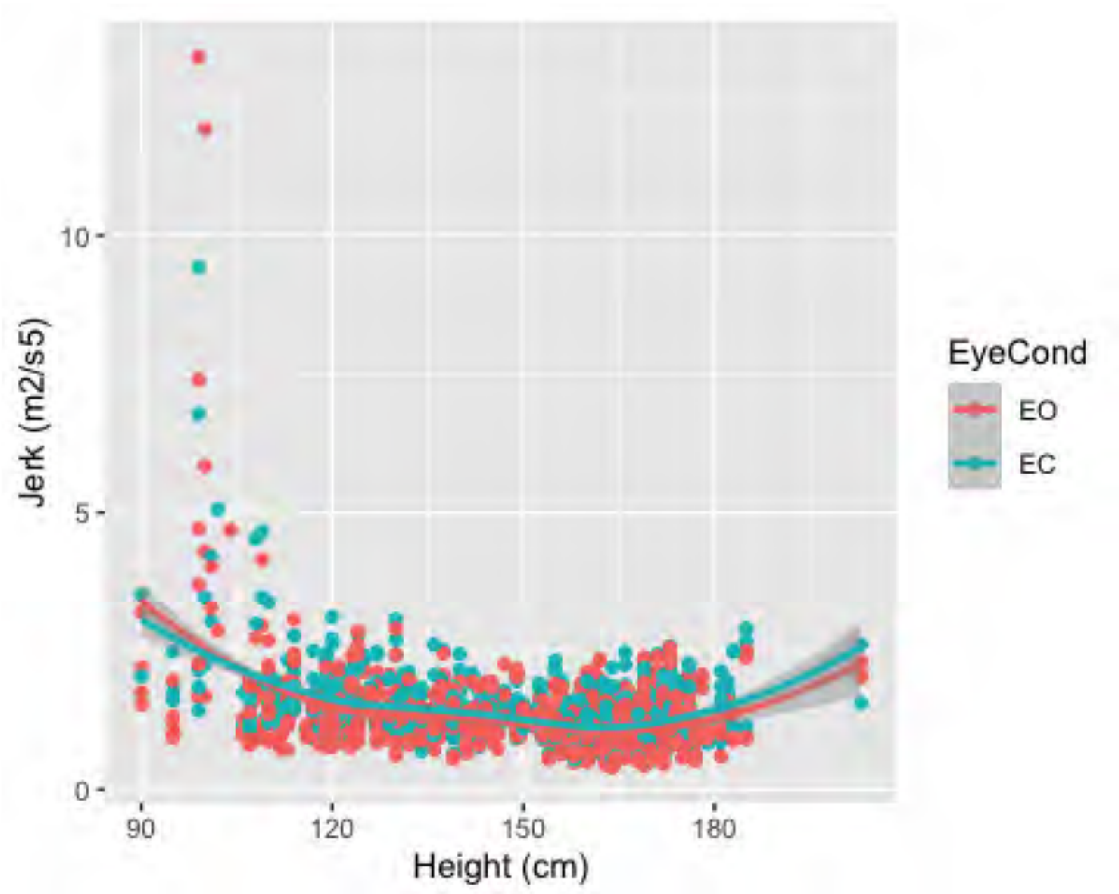

```
# mark outliers that are more than 3 SD from the
# mean for a height bin - report how many outliers there are
CDataOut<-MarkOutliers(CData,"DV","HtBin",3) # mark outlier rows
CDataNO<-CDataOut[CDataOut$DVOutlier == 0,] # keep only rows that ar
e not outliers

# report
print(paste("All control data N: ",length(CDataOut[,1])," w/o outlie
rs N: ",length(CDataNO[,1])," Number of outliers: ",length(CDataOut[
,1])-length(CDataNO[,1])))
```

```
## [1] "All control data N:  1835  w/o outliers N:  1809  Number of
outliers:  26"

# plot control data w/o outliers
CPlotNO<-ggplot(CDataNO,aes(x=Height,y=DV,group=EyeCond,color=EyeCon
d))+geom_point()
CPlotNO<-CPlotNO + geom_smooth()
# CPlot<-CPlot+ylim(0,0.004)
CPlotNO<-CPlotNO + labs(x="Height (cm)", y=DependentVariableName)
print(CPlotNO)

## `geom_smooth()` using method = 'loess' and formula 'y ~ x'
```




```
# get means and sd for each ppt
# look for outlier ppts

PptMeans<-CDataNO %>% dplyr::group_by(PID,HtBin) %>% dplyr::summaris
e(PptMean=mean(DV,na.rm=TRUE))

## `summarise()` has grouped output by 'PID'. You can override using
the `.groups` argument.

# mark individual participants whose mean is more than 3 SD from
# the average of the participant means (unusual whole participants)
PptMeanOutliers<-MarkOutliers(PptMeans,"PptMean","HtBin",3)
```

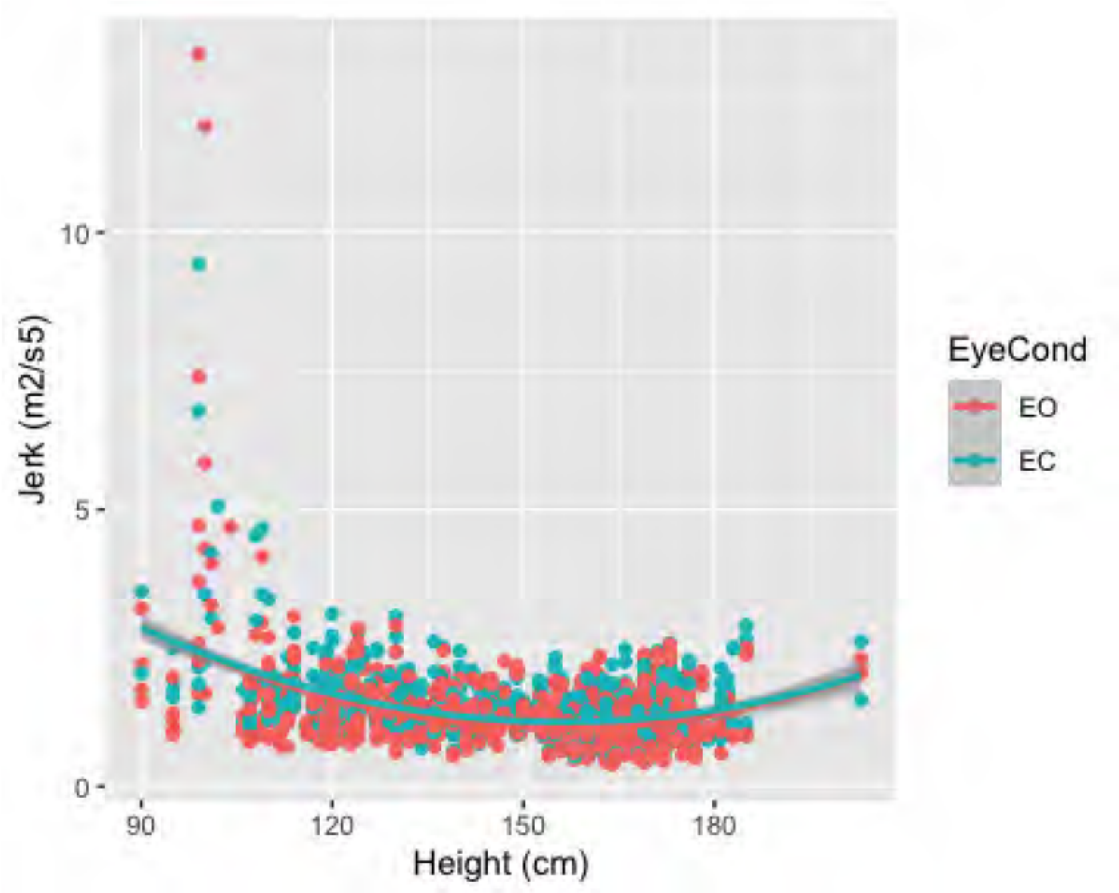
```
# report participants who are outliers
print(PptMeanOutliers[PptMeanOutliers$PptMeanOutlier == 1,])

## # A tibble: 0 x 9
## # Groups:   PID [0]
## # … with 9 variables: PID <fct>, HtBin <dbl>, PptMean <dbl>,
## #   ByMeanPptMean <dbl>, BySDPptMean <dbl>, Outlier <dbl>,
## #   PptMeanLowCutOff <dbl>, PptMeanHighCutOff <dbl>,
## #   PptMeanOutlier[,"PptMean"] <dbl>

# take outlier ppts out of control sample
PptOutlierPID<-as.character(PptMeanOutliers$PID[PptMeanOutliers$PptM
eanOutlier == 1])
# put all of the outlier participant IDs in a vector

# keep only participants who are not in the outlier participant vect
or
CDataNO<-CDataNO[!(CDataNO$PID %in% PptOutlierPID),]

# plot data once individual outlier trials and outlier participants
# have been removed
CPlotNO<-ggplot(CDataNO,aes(x=Height,y=DV,group=EyeCond,color=EyeCon
d))+geom_point()
CPlotNO<-CPlotNO + geom_smooth(method="lm",formula= y ~ I(x^2) + x)
# draw the line for a quadratic function fit to see if the shape is
non-linear
CPlotNO<-CPlotNO + labs(x="Height (cm)", y=DependentVariableName)
print(CPlotNO)
```



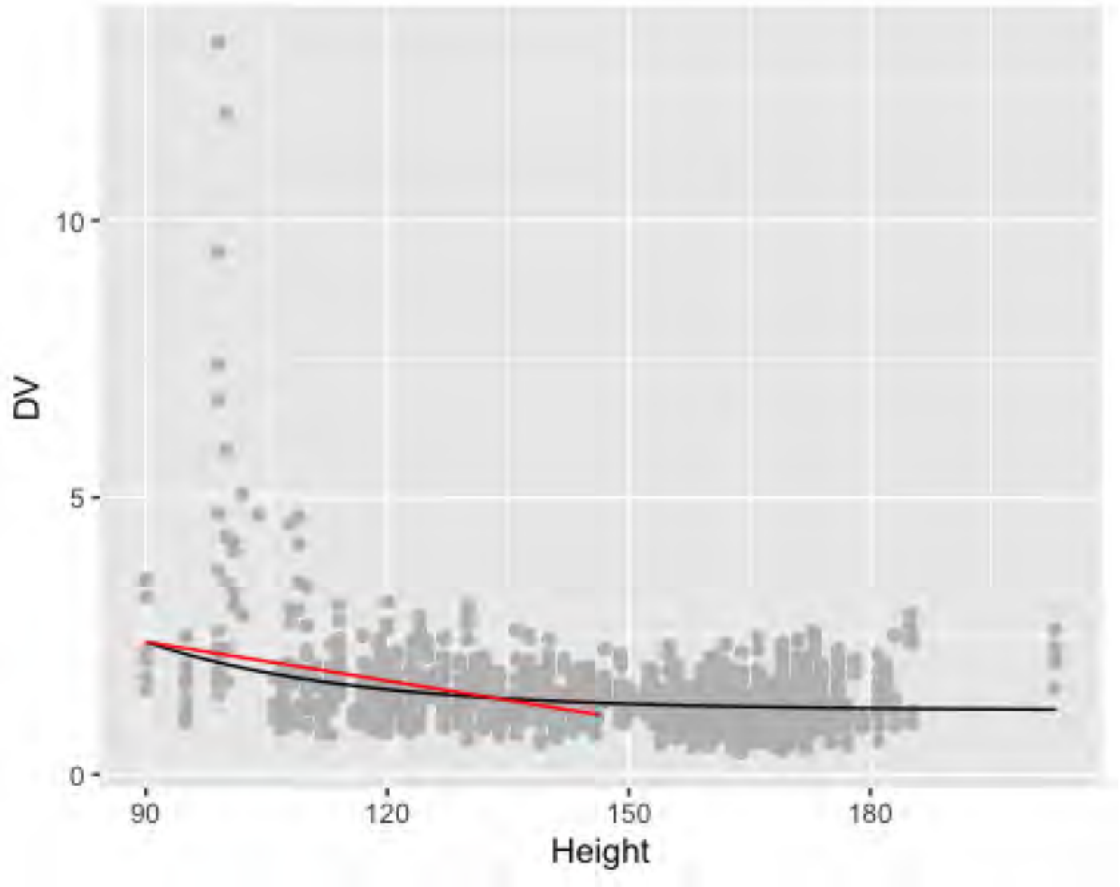

```
# do an asymptotic function fit -- need to find decent starting valu
es first

# set the range of starting values to explore
LrcStart<-0.1 # this would be a pretty flat function
LrcEnd<-5 # this would be a sharp corner
LrcStep<-0.1 # go between 0.5 and 5 in steps of 0.5

########################################
# AsmpPortion may need to be changed to get a good fit
########################################
AsympPortion <- 0.5 # portion of the curve that is curved

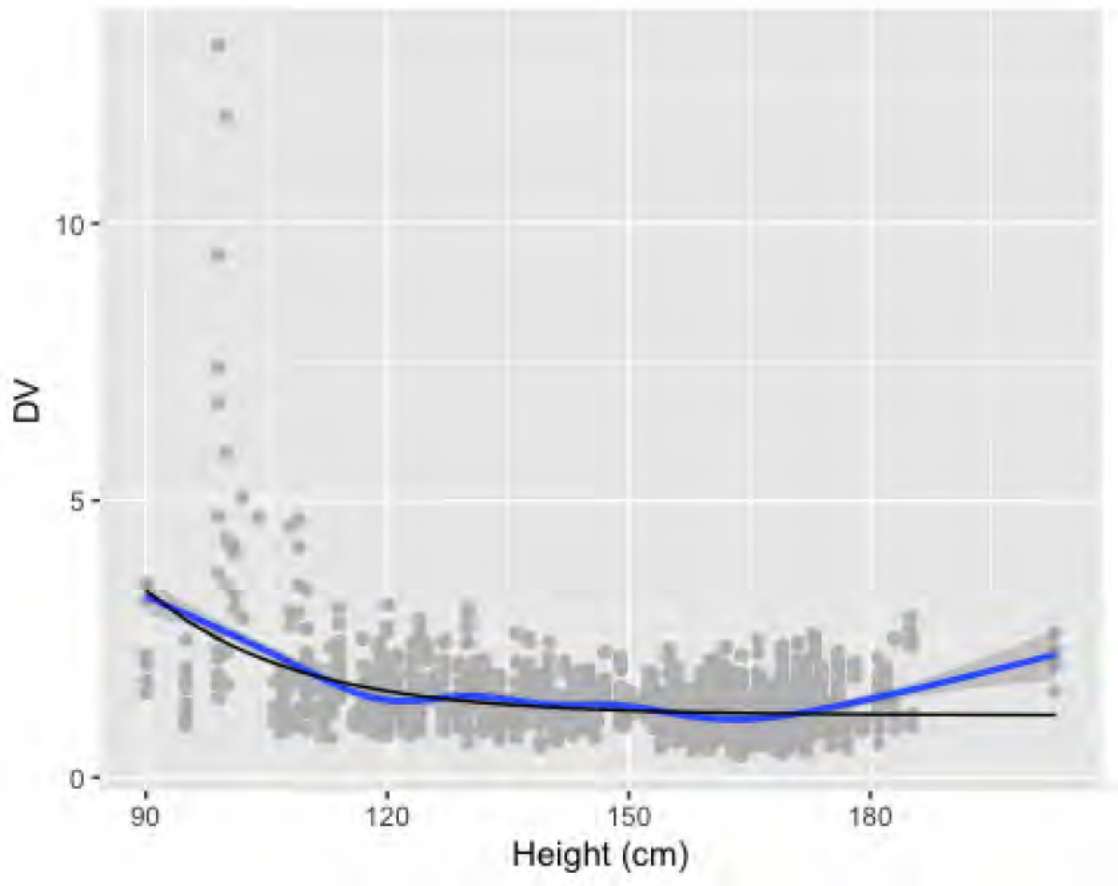
YName<-"DV"
XName<-"Height"

# plot the starting value function to check how it looks as a starti
ng value
# whether asymptotic fits converge are very sensitive to starting va
lues
AStartList<-PlotStartingAsympFunction(CDataNO,XName,YName,LrcStart,L
rcEnd,LrcStep,AsympPortion)
print(AStartList$Plot)
```




```
# fit an asymptotic function and plot the function against the point
s
AModelList<-FitAsymptoteModel(CDataNO,"Height","DV",AStartList$Start
Values)
AsympModel<-AModelList$Model
print(AModelList$Plot)
```

```
## `geom_smooth()` using method = 'gam' and formula 'y ~ s(x, bs = "
cs")'
```




```
# report the asymptotic function parameter values
print(AsympModel)

## Nonlinear regression model
##   model: DV ~ Asym + (R0 - Asym) * exp(-exp(lrc) * (Height - XOff
set)/XRange)
##    data: MyData
##  Asym    R0   lrc
## 1.123 3.383 1.825
##  residual sum-of-squares: 763
##
## Number of iterations to convergence: 10
## Achieved convergence tolerance: 7.094e-06

# fit quadratic, linear and constant models
QuadraticModel<-lm(DV ~ Height + I(Height^2),data=CDataNO)
LinearModel<-lm(DV ~ Height,data=CDataNO)
ConstantModel<-lm(DV ~ 1,data=CDataNO)
# no reason why these shouldn't converge

# compare results for asymptotic, quadratic, linear and constant mod
els using AIC
AICResult<-GetAICResult(AsympModel,QuadraticModel,LinearModel,Consta
ntModel)
```

```
##  Asymptotic model: 3580.17234481749
## Quadratic Model: 3560.23690302605
##  Linear Model: 3724.88828316754
##  ConstantModel: 3918.82699857763
```

```
kable(AICResult,row.names=TRUE)
```

AIC

Order

deltaAIC

Asymptotic Model

3580.172

2

19.93544

Quadratic Model

3560.237

1

0.00000

Linear Model

3724.888

3

164.65138

ConstantModel

3918.827

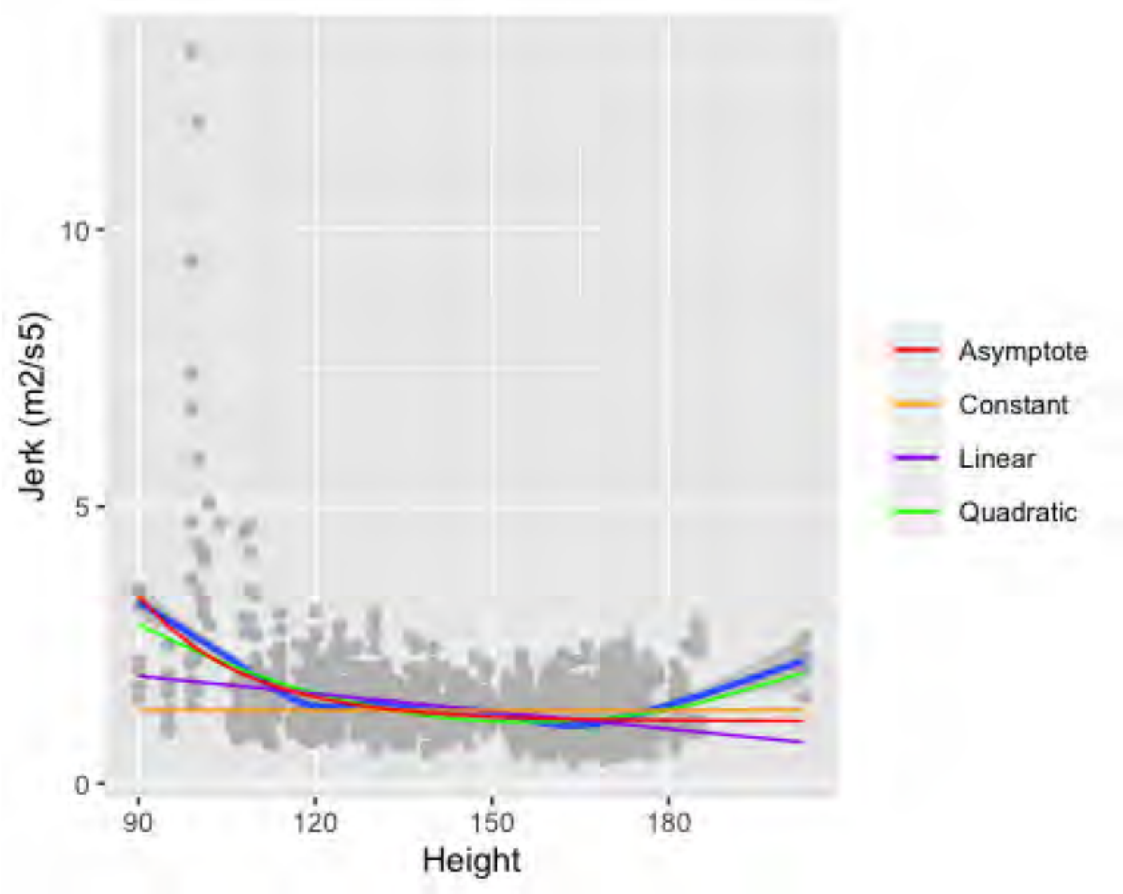
4

358.59010

```
# plot models to choose the best model based on AIC and theoretical plausibility

ModelPlot<-PlotModels(CDataNO,"Height","DV",DependentVariableName, AsympModel, QuadraticModel, LinearModel, ConstantModel)
print(ModelPlot)
```

```
## `geom_smooth()` using method = 'gam' and formula 'y ~ s(x, bs = "cs")'
```



Be aware of the possibility that, for example, quadratic is better than asymptotic, but just because of a small number of tall participants. Often performance getting worse at taller values (esp when driven by a few points) is not theoretically plausible, and the asymptotic version can be preferred on theoretical grounds (and because fit in the middle of the data may be forced downward by upward curve at the end).

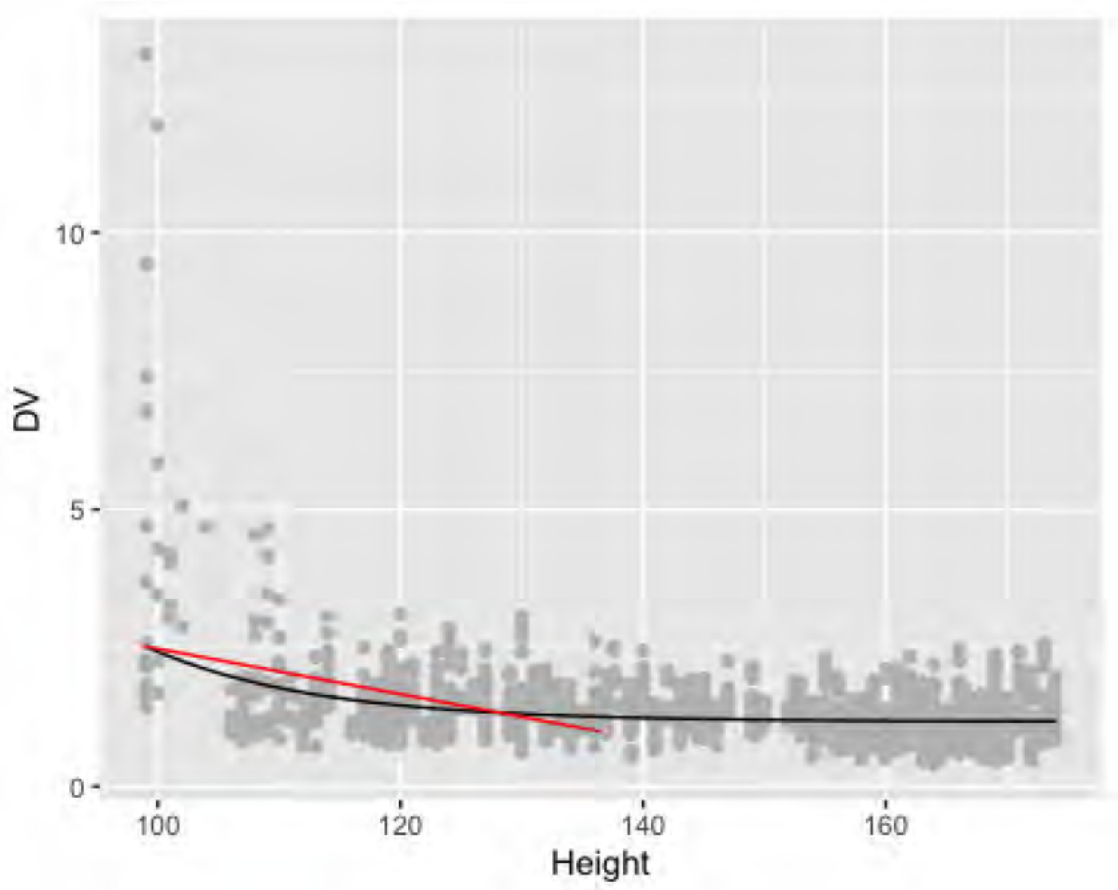
```
# Fit models without the extreme, small N points -- make sure best m
odel is consistent in both analyses

CDataNONE<-CDataNO[(CDataNO$Height > 95) & (CDataNO$Height < 175),]
# CDataNONE<-CDataNO[CDataNO$Height < 175,] # use if only excluding
tall participants

# adjust values here (95 / 175) if the range isn't right

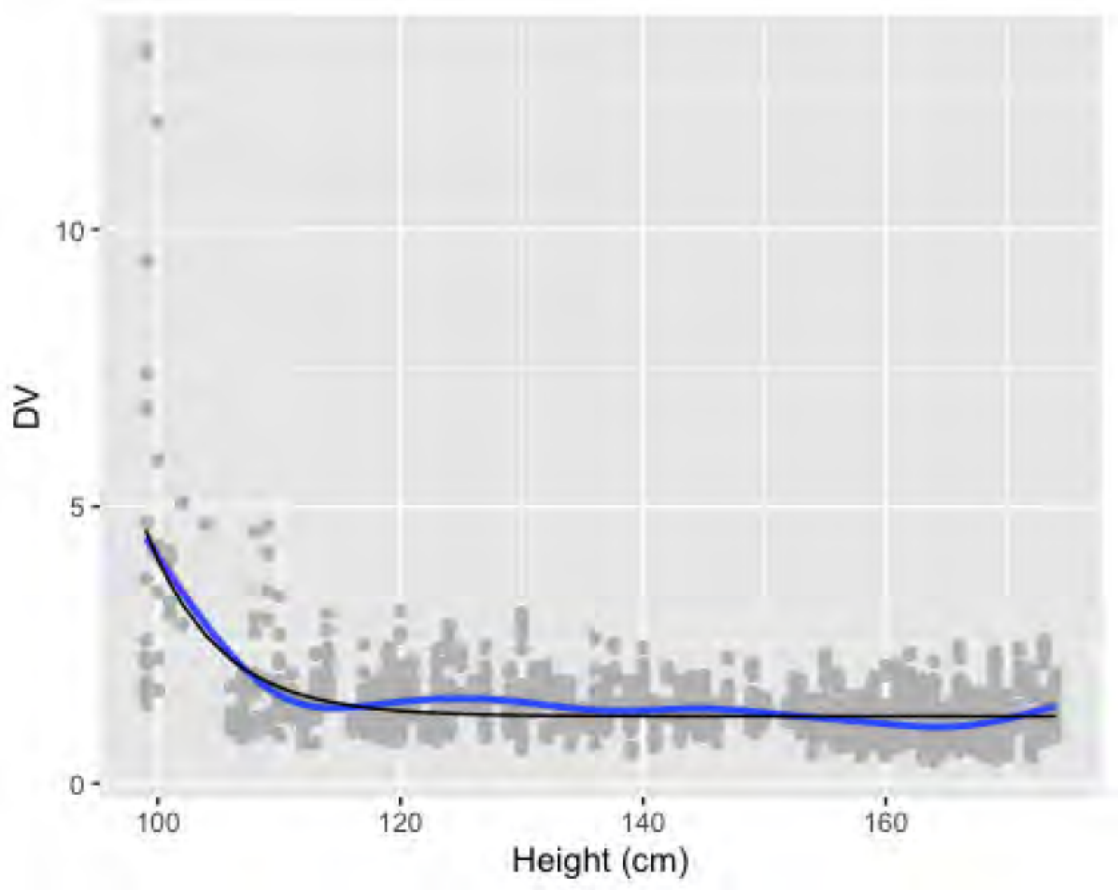
# AsympPortion <- 0.5 # portion of the curve that is curved -- try v
alue from above first

NEAStartList<-PlotStartingAsympFunction(CDataNONE,XName,YName,LrcSta
rt,LrcEnd,LrcStep,AsympPortion)
print(NEAStartList$Plot)
```




```
NEAModelList<-FitAsymptoteModel(CDataNONE,"Height","DV",NEAStartList
$StartValues)
NEAsympModel<-NEAModelList$Model
print(NEAModelList$Plot)
```

```
## `geom_smooth()` using method = 'gam' and formula 'y ~ s(x, bs = "
cs")'
```




```
NEQuadraticModel<-lm(DV ~ Height + I(Height^2),data=CDataNONE)
NELinearModel<-lm(DV ~ Height,data=CDataNONE)
NEConstantModel<-lm(DV ~ 1,data=CDataNONE)
# no reason why these shouldn't converge

# compare models again, but this time without the shortest and talle
st participants
NEAICResult<-GetAICResult(NEAsympModel,NEQuadraticModel,NELinearMode
l,NEConstantModel)

##  Asymptotic model: 3043.34577324892
## Quadratic Model: 3276.15483918257
##  Linear Model: 3389.83472680858
##  ConstantModel: 3634.48131721102

kable(NEAICResult,row.names=TRUE)
```

AIC

Order

deltaAIC

Asymptotic Model

3043.346

1

0.0000

Quadratic Model

3276.155

2

232.8091

Linear Model

3389.835

3

346.4890

ConstantModel

3634.481

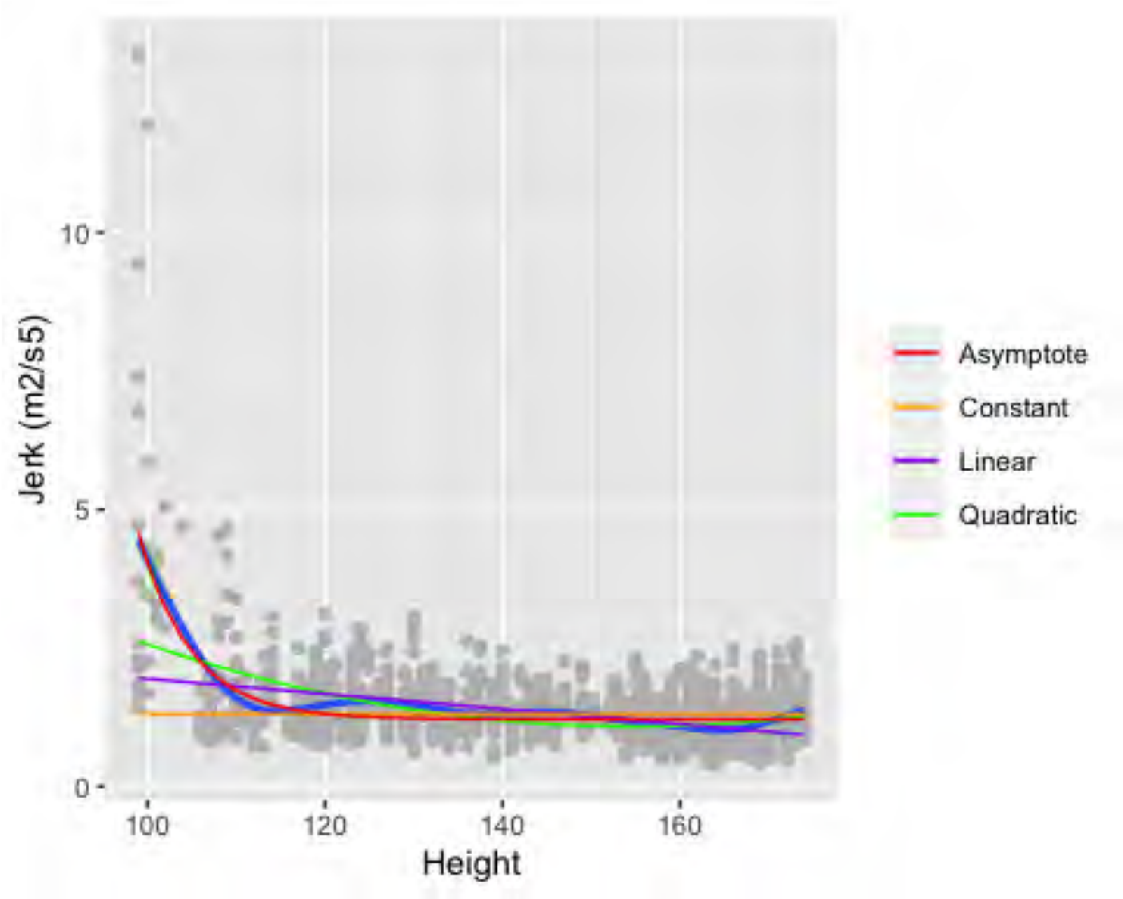
4

591.1355

```
# plot models to choose the best model based on AIC and theoretical plausibility

NEModelPlot<-PlotModels(CDataNONE,"Height","DV",DependentVariableName, NEAsy
mpModel, NEQuadraticModel, NELinearModel, NEConstantModel)
print(NEModelPlot)

## `geom_smooth()` using method = 'gam' and formula 'y ~ s(x, bs = "cs")'
```

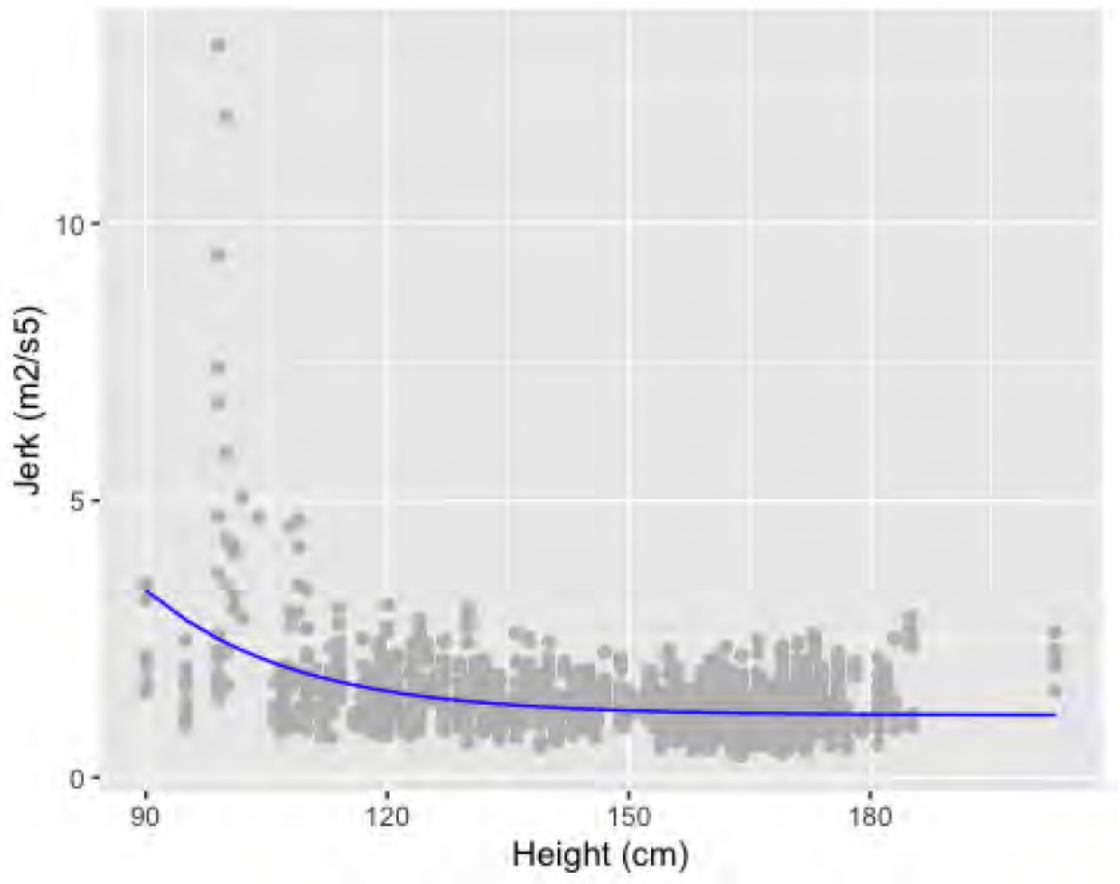


Compare results for full dataset and dataset without a small number of the shortest and tallest participants. The results should be consistent.

```
############################################################
#
# Must set best model here based on the previous section
#
############################################################

BestModel<-AsympModel
# plot model
CDataNO$PredDV<-fitted(BestModel)

# plot control values in grey and a blue line for the best function
CPlotNO<-ggplot(CDataNO,aes(x=Height,y=DV))+geom_point(color="grey")
CPlotNO<-CPlotNO + geom_line(aes(x=CDataNO$Height,y=CDataNO$PredDV),
color="blue")
CPlotNO<-CPlotNO + labs(x="Height (cm)", y=DependentVariableName)
print(CPlotNO)
```

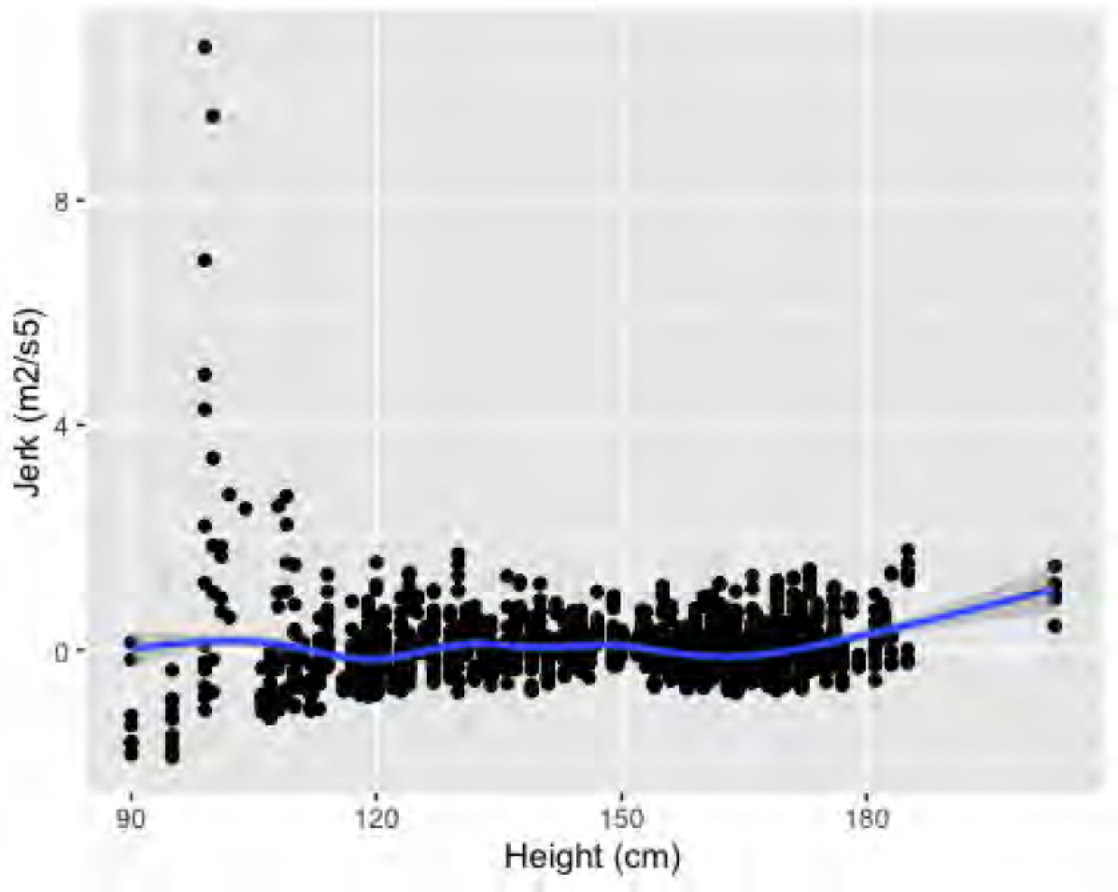



```
# calculate residuals for control data
CDataNO$Residual<-CDataNO$DV-CDataNO$PredDV

# calculate residuals for all data (including patients)
AllDatNO<-rbind(CDataNO[,1:length(PData[1,])],PData)
AllDatNO$PredDV<-predict(BestModel,newdata=AllDatNO)
AllDatNO$Residual<-AllDatNO$DV-AllDatNO$PredDV

# plot residuals
CPlotRes<-ggplot(CDataNO,aes(x=Height,y=Residual))+geom_point()
CPlotRes<-CPlotRes + geom_smooth()
# CPlot<-CPlot+ylim(0,0.004)
CPlotRes<-CPlotRes + labs(x="Height (cm)", y=DependentVariableName)
print(CPlotRes)

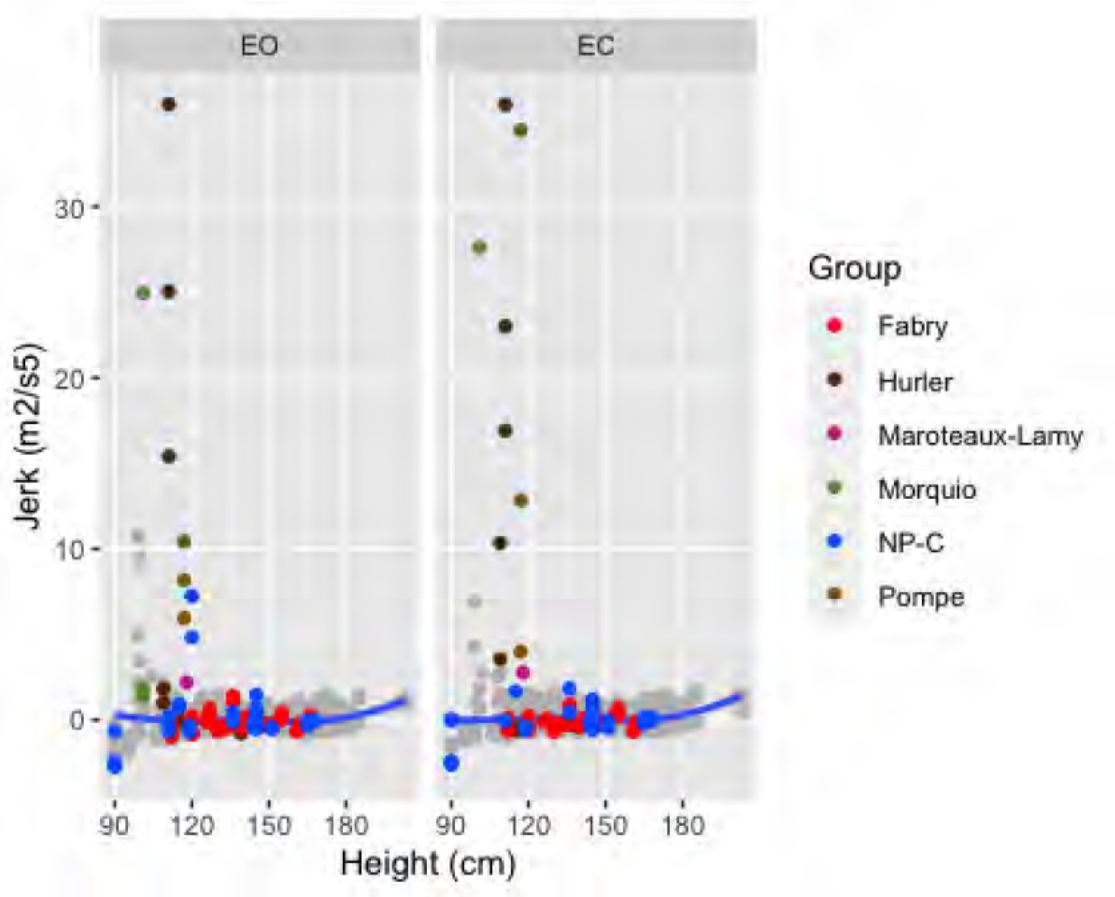
## `geom_smooth()` using method = 'gam' and formula 'y ~ s(x, bs = "
cs")'
```




```
# plot residuals for all data - including patients
AllPlotRes<-ggplot(CDataNO,aes(x=Height,y=Residual))+geom_point(colo
r="grey")
AllPlotRes<-AllPlotRes + geom_smooth()

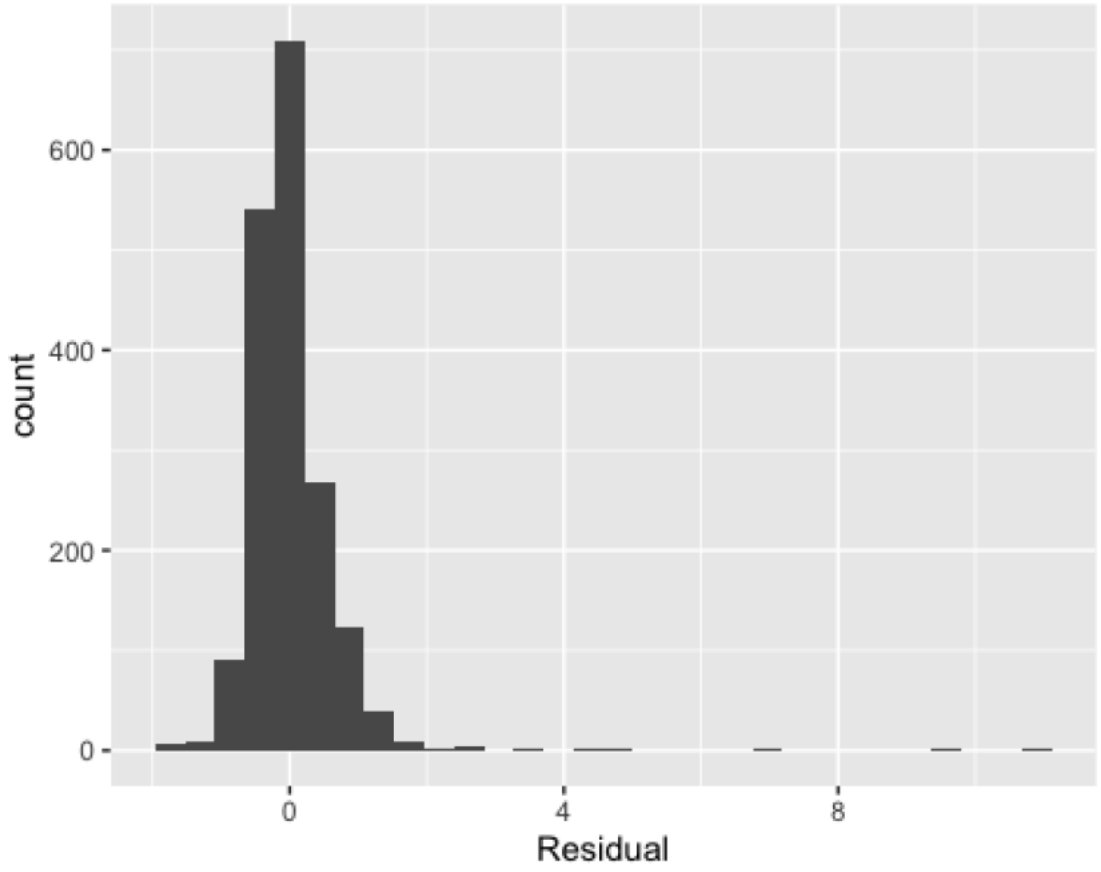
AllPlotRes<-AllPlotRes + geom_point(data=AllDatNO[AllDatNO$Group !=
"c",],aes(x=Height,y=Residual,group=Group,color=Group))
AllPlotRes<-AllPlotRes + labs(x="Height (cm)", y=DependentVariableNa
me)
AllPlotRes<-AllPlotRes + facet_grid(~EyeCond)
AllPlotRes<-AllPlotRes + colScale
print(AllPlotRes)

## `geom_smooth()` using method = 'loess' and formula 'y ~ x'
```




```
RDistPlot<-ggplot(CDataNO,aes(x=Residual))+geom_histogram()
RDistPlot<-RDistPlot
print(RDistPlot)

## `stat_bin()` using `bins = 30`. Pick better value with `binwidth`
.
```



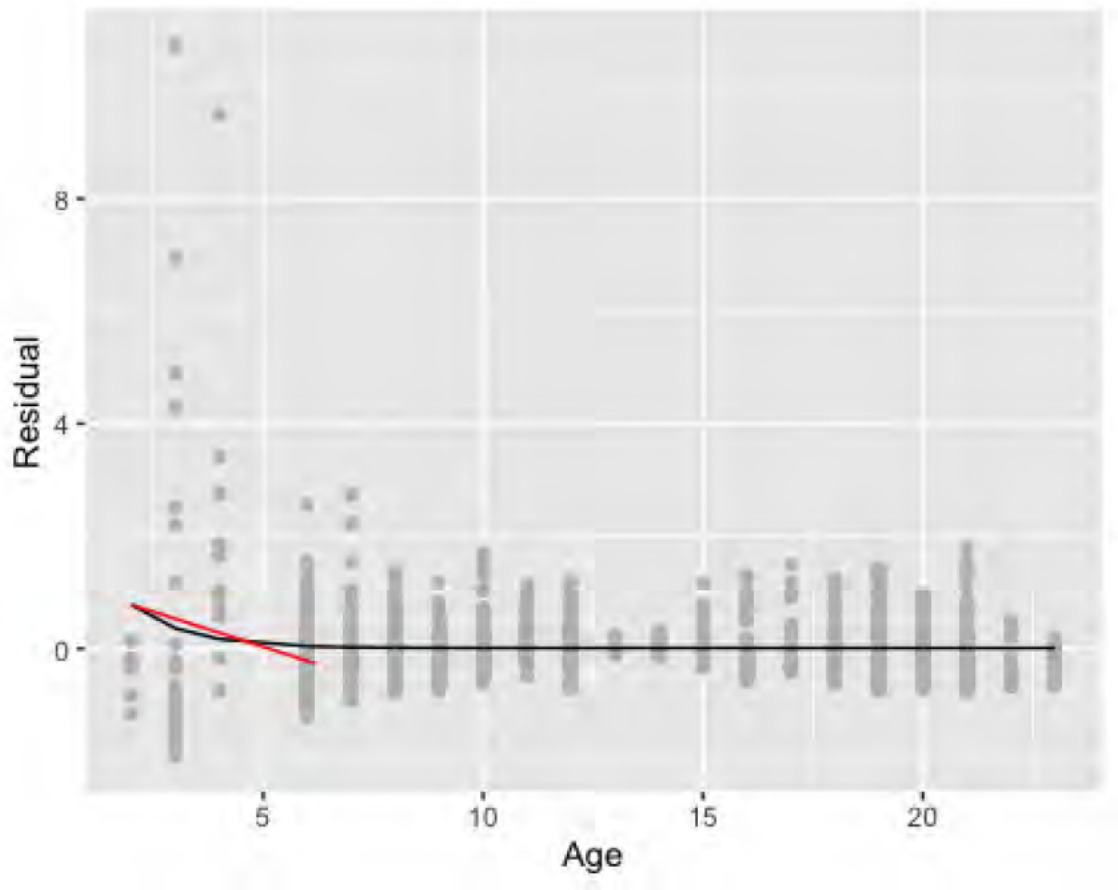
We are looking for a roughly normal distribution of residuals here.

```
# See if there is an additional effect of age once the effect of hei
ght
# has been removed.  This process mirrors the one we have done for h
eight above.
# Fit quadratic, asymptotic, linear and constant functions based on
age to the
# residuals from height.  See if there is any additional contributio
n based on
# age.  If so, re-do residuals with the effect of age removed.  If n
ot, keep
# residuals just based on height.

LrcStart<-0.1 # this would be a pretty flat function
LrcEnd<-5 # this would be a sharp corner
LrcStep<-0.1 # go between 0.5 and 5 in steps of 0.5
AsympPortion <- 0.2 # portion of the curve that is curved
YName<-"Residual"
XName<-"Age"

RAStartList<-PlotStartingAsympFunction(CDataNO,XName,YName,LrcStart,
```

```
LrcEnd,LrcStep,AsympPortion)
print(RAStartList$Plot)
```

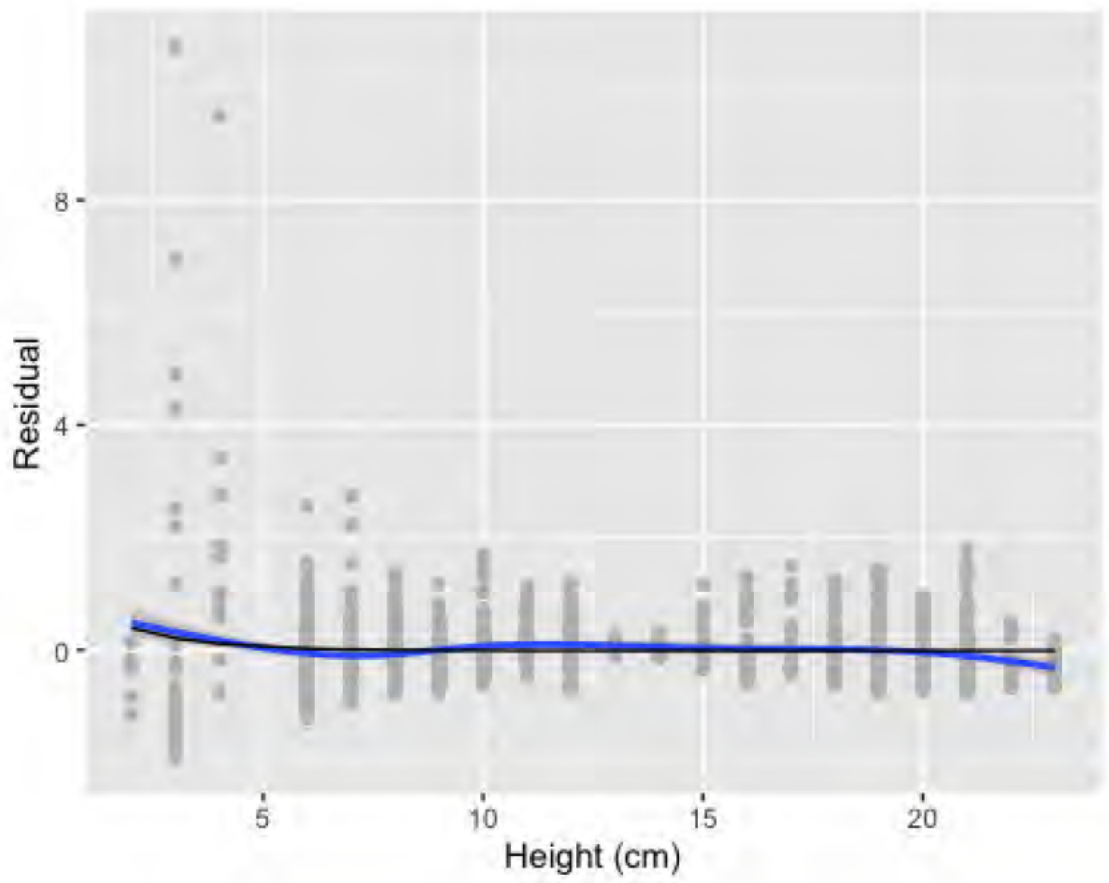



```
# asymnptotic function starting values for residuals fit
```

Check that this is a theoretically plausible shape if Age is shown to be a factor below

```
# check if there is any effect of age once height has been removed
# This means we fit a model with age to the residuals from height
RAModelList<-FitAsymptoteModel(CDataNO,"Age","Residual",RAStartList$
StartValues)
RAsympModel<-RAModelList$Model
print(RAModelList$Plot)

## `geom_smooth()` using method = 'gam' and formula 'y ~ s(x, bs = "
cs")'
```




```
RQuadraticModel<-lm(Residual ~ Age + I(Age^2),data=CDataNO)
RLinearModel<-lm(Residual~ Age,data=CDataNO)
RConstantModel<-lm(Residual ~ 1,data=CDataNO)
# no reason why these shouldn't converge

RAICResult<-GetAICResult(RAsympModel,RQuadraticModel,RLinearModel,RC
onstantModel)

##  Asymptotic model: 3574.19559816668
## Quadratic Model: 3569.9650806151
##  Linear Model: 3573.24757034496
##  ConstantModel: 3576.17234481749

kable(RAICResult,row.names=TRUE)
```

AIC

Order

deltaAIC

Asymptotic Model

3574.196

2

4.230518

Quadratic Model

3569.965

3

0.000000

Linear Model

3573.248

1

3.282490

ConstantModel

3576.172

4

6.207264

```
cat("Constant model intercept is: ",RConstantModel$coefficients[1])

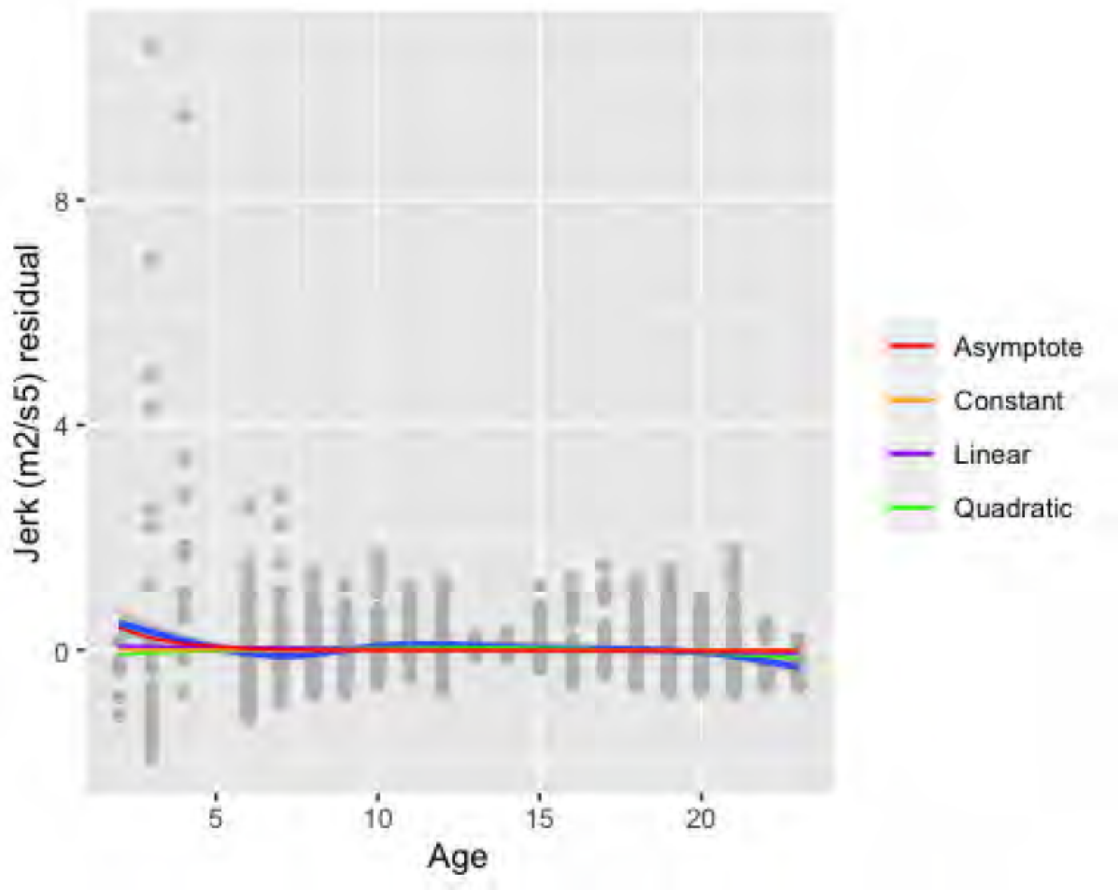
## Constant model intercept is:  -6.758022e-10
```

A constant model should have an intercept close to zero if there is no influence of age after the influence of height has been removed

```
# plot models to help choose the best model based on AIC and theoret
ical plausibility

RModelPlot<-PlotModels(CDataNO,"Age","Residual",paste(DependentVaria
bleName," residual",sep=""), RAsympModel, RQuadraticModel, RLinearMo
del, RConstantModel)
print(RModelPlot)

## `geom_smooth()` using method = 'gam' and formula 'y ~ s(x, bs = "
cs")'
```




```
# test alternative models if necessary
anova(RLinearModel,RConstantModel)

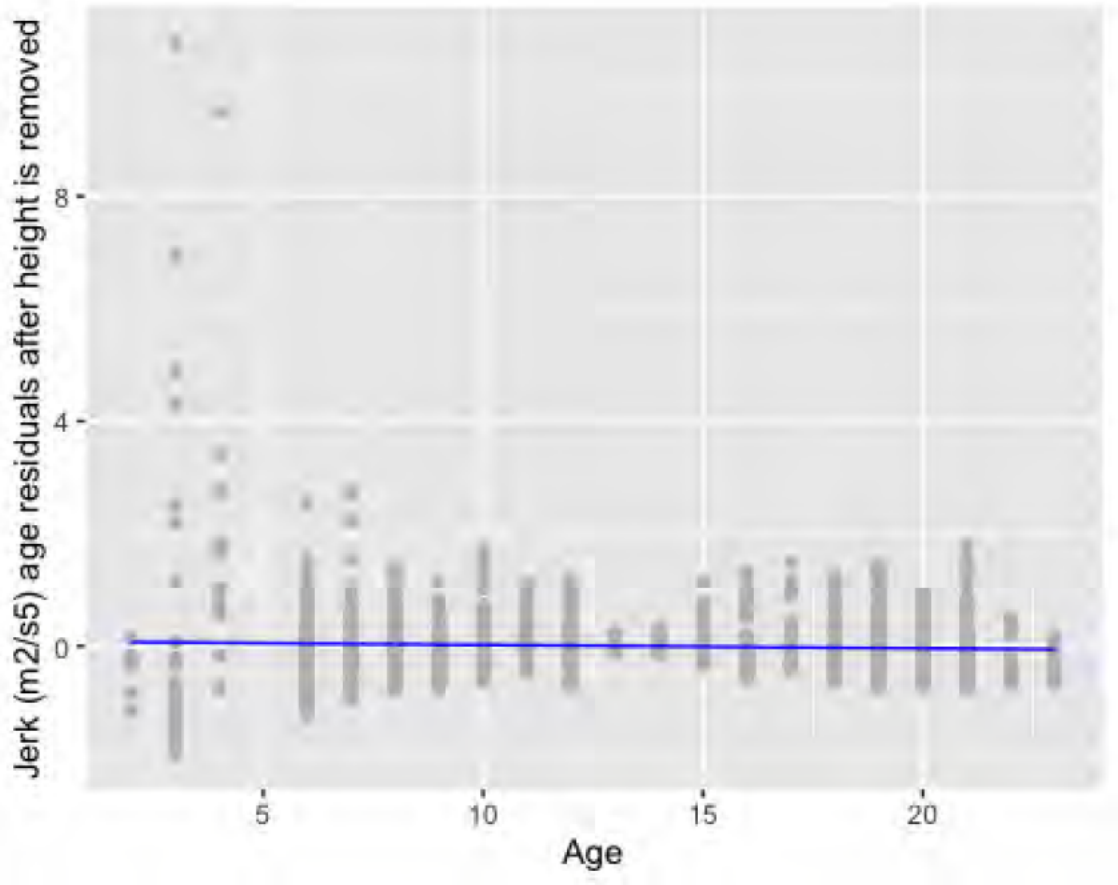
## Analysis of Variance Table
##
## Model 1: Residual ~ Age
## Model 2: Residual ~ 1
##   Res.Df    RSS Df Sum of Sq     F  Pr(>F)
## 1   1807 760.97
## 2   1808 763.05 -1   -2.0745 4.926 0.02658 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

#################################################################
#
#  use only if Constant model is not best above -
#    if ConstantModel is best, skip to down below
#  This removes the effect of age and returns residuals after the ef
fect
#  of both age and height have been removed
#################################################################

BestModel<-RLinearModel
# plot model
```

```
CDataNO$PredDV<-fitted(BestModel) # this is age residuals on top of
height residuals

# plot the additional effect of age on height residuals
CPlotNO<-ggplot(CDataNO,aes(x=Age,y=Residual))+geom_point(color="gre
y")
CPlotNO<-CPlotNO + geom_line(aes(x=CDataNO$Age,y=CDataNO$PredDV),col
or="blue")
CPlotNO<-CPlotNO + labs(x="Age", y=paste0(DependentVariableName," ag
e residuals after height is removed"))
print(CPlotNO)
```



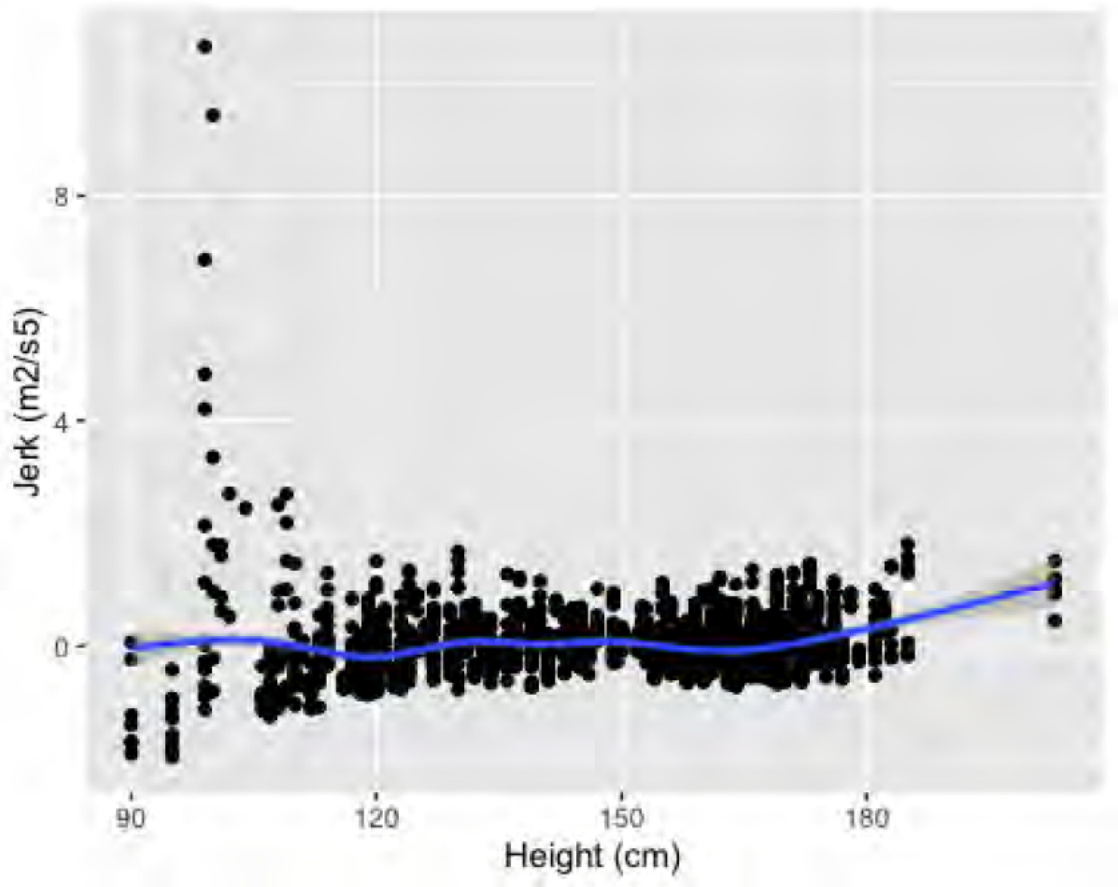
If age has an effect, use the following sections (otherwise, skip down to marked location)

```
# calculate residuals for control data
CDataNO$Residual<-CDataNO$Residual-CDataNO$PredDV

# calculate residuals for all data (including patients)
AllDatNO$PredDV<-predict(BestModel,newdata=AllDatNO)
AllDatNO$Residual<-AllDatNO$Residual-AllDatNO$PredDV

# plot  new residuals - these have effects of both age and height re
moved
CPlotRes<-ggplot(CDataNO,aes(x=Height,y=Residual))+geom_point()
CPlotRes<-CPlotRes + geom_smooth()
# CPlot<-CPlot+ylim(0,0.004)
CPlotRes<-CPlotRes + labs(x="Height (cm)", y=DependentVariableName)
print(CPlotRes)

## `geom_smooth()` using method = 'gam' and formula 'y ~ s(x, bs = "
cs")'
```




```
# make a table of differences between EC and EO for each  control pa
rticipant
PptTableRaw<-CDataNO %>% dplyr::group_by(PID,EyeCond,Group, Height)
%>% dplyr::summarise(MeanResid=mean(Residual))
```

```
## `summarise()` has grouped output by 'PID', 'EyeCond', 'Group'. Yo
u can override using the `.groups` argument.
```

```
PptData<-PptTableRaw %>% pivot_wider(names_from = EyeCond, values_fr
om = MeanResid) # put EC in one column and EO in another column
PptData<-PptData[!(is.na(PptData$EC) | is.na(PptData$EO)),] # use on
ly ppts that have both EC and EO values
PptData$EyeCondDiff<-PptData$EC - PptData$EO # take the difference b
etween EC/EO
head(PptData)
```

```
## # A tibble: 6 x 6
## # Groups:   PID, Group [6]
##   PID                 Group Height     EO     EC EyeCondDiff
##   <fct>               <fct>  <dbl>  <dbl>  <dbl>       <dbl>
## 1 EdgbastonNursery_H1 c         99  7.74   5.54       -2.20
## 2 EdgbastonNursery_H3 c         90 -1.81  -1.56        0.244
## 3 FirstSchool_Y1S1    c        120 -0.114  0.229       0.342
## 4 FirstSchool_Y1S2    c        109  1.01   1.38        0.371
## 5 FirstSchool_Y1S3    c        119 -0.215  0.518       0.733
## 6 FirstSchool_Y1S4    c        125  0.210  0.580       0.370
```

```
# effect of eye condition in controls?

M1<-lmer(Residual ~ EyeCond + (1|PID),data=CDataNO,REML=FALSE)
M2<-lmer(Residual ~ 1 + (1|PID),data=CDataNO,REML=FALSE)

# test effect
anova(M1,M2)
```

```
## Data: CDataNO
## Models:
## M2: Residual ~ 1 + (1 | PID)
## M1: Residual ~ EyeCond + (1 | PID)
##    npar    AIC    BIC  logLik deviance  Chisq Df Pr(>Chisq)
## M2    3 2121.7 2138.2 -1057.8   2115.7
## M1    4 2079.1 2101.1 -1035.5   2071.1 44.558  1   2.47e-11 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Effect of eye condition

```
# need these later for plotting
EOControlValue<-fixed.effects(M1)[2]
ECControlValue<-fixed.effects(M1)[1]

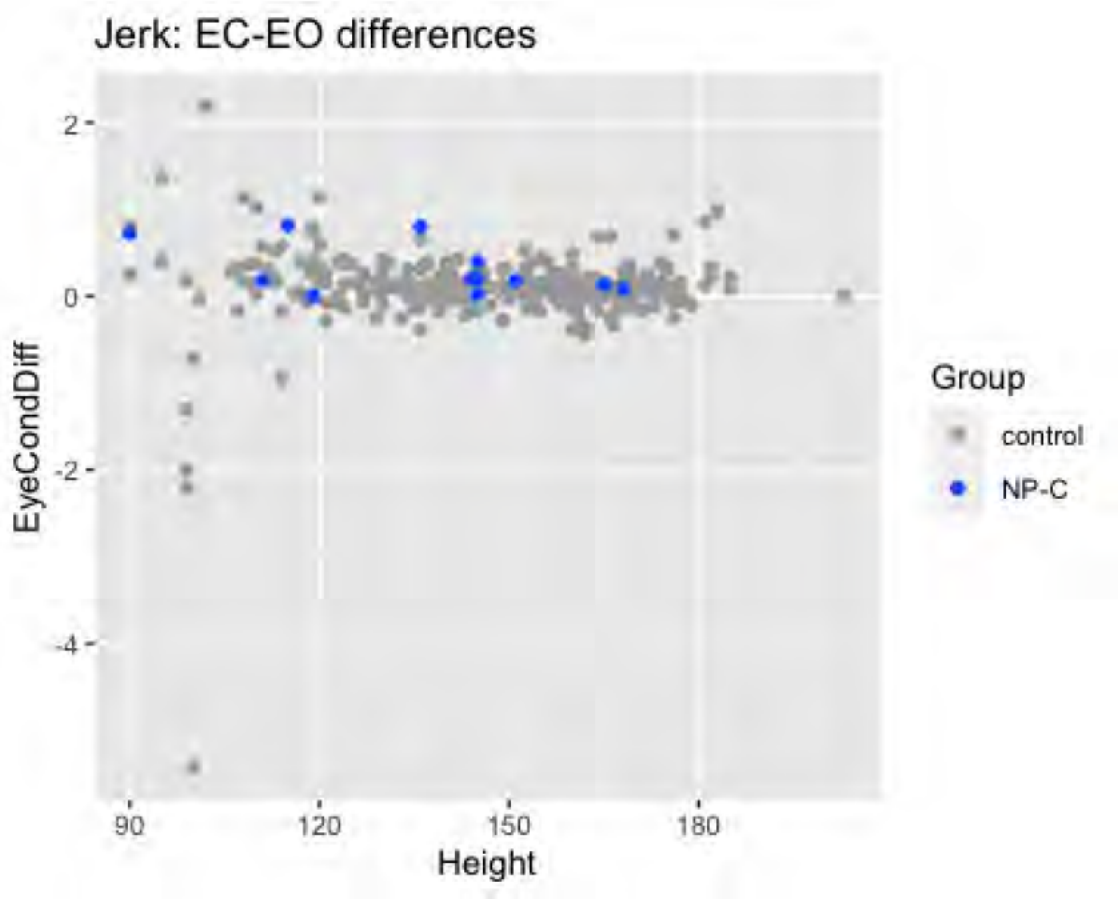
# get condition means -- which condition has higher value?
EyeCondMeans<-CDataNO %>% dplyr::group_by(EyeCond) %>% dplyr::summar
ise(ECMean=mean(Residual))
print(EyeCondMeans)
```

```
## # A tibble: 2 x 2
##   EyeCond  ECMean
## * <fct>     <dbl>
## 1 EO      -0.0504
## 2 EC       0.0523
```

EO is lower

```
# plot all groups and put EO and EC conditions on separate plots
PPlot<-ggplot(AllDatNO[AllDatNO$Group == "c",], aes(x=Height, y=Resi
dual, group=Group, color=Group))+geom_point(color="grey")
PPlot<-PPlot + geom_point(data=AllDatNO[AllDatNO$Group != "c",],aes(
x=Height, y=Residual, group=Group, color=Group))
PPlot<-PPlot + facet_wrap( ~ EyeCond,nrow=1)
PPlot<-PPlot + labs(x="Height (cm)", y=DependentVariableName)
PPlot<-PPlot + colScale
print(PPlot)
```

```
# plot EO-EC differences
CPlot<-ggplot(PptTable[PptTable$Group == "c",], aes(x=Height,y=EyeCo
ndDiff,color=Group)) + geom_point()
CPlot<-CPlot + geom_point(data=PptTable[PptTable$Group == PatientGro
upCode,],aes(x=Height, y=EyeCondDiff)) # separate controls and patie
nts so patients are plotted on top of controls
CPlot<-CPlot + colScale
CPlot<-CPlot + ggtitle("Jerk: EC-EO differences")
print(CPlot)
```



Another way of showing this result - scatterplot of EO/EC differences, separated by group

```
# print a table of patient values
PptTablePatOnly<-PptTableLong[PptTableLong$Group == PatientGroupCode
,]
# print(PptTablePatOnly)
```

Bootstrap analysis

```
# do a double bootstrap confidence interval for the mean EO/EC diffe
rence
# This is for patients only
PData<-PptTable %>% filter(Group == PatientGroupCode)
PDataN<-length(unique(PData$PID))
PatECEOBootstrapDiff<-DoubleBootstrapCIForMeanParallel(PData$EyeCond
Diff,2000,500,Alpha=0.05,NumCores=NumCores)
print(PatECEOBootstrapDiff$CI)

## [1] 0.1445137 0.7803295

# do a double bootstrap confidence interval for the EO mean, patient
s only
PatEOBootstrap<-DoubleBootstrapCIForMeanParallel(PData$EO,2000,500,A
```

```
lpha=0.05,NumCores=NumCores)
print(PatEOBootstrap$CI)

## [1] -0.96683144  0.01838718

# do a double bootstrap confidence interval for the EC mean, patient
s only
PatECBootstrap<-DoubleBootstrapCIForMeanParallel(PData$EC,2000,500,A
lpha=0.05,NumCores=NumCores)
print(PatECBootstrap$CI)

## [1] -0.4184356  0.5556434

# do a double bootstrap confidence interval for
# EO/EC differences in controls only
# the bootstrap samples the same number of values as in the patient
sample
# (it does NOT use a sample of the size of the whole control group,
which
# would have less variance).  This keeps the control sample on the s
ame footing
# as the patient bootstrap sample

CData<-PptData %>% filter(Group == "c")
ContECEOBootstrapDiff<-DoubleBootstrapCIForMeanSetNParallel(CData$Ey
eCondDiff,PDataN,2000,500,Alpha=0.05,NumCores=NumCores)
print(ContECEOBootstrapDiff$CI)

## [1] -0.2658813  0.3024146

# do a double bootstrap confidence interval for the EC mean - contro
ls only
# N for each control bootstrap sample = size of patient sample
ContECBootstrap<-DoubleBootstrapCIForMeanSetNParallel(CData$EC,PData
N,2000,500,Alpha=0.05,NumCores=NumCores)

# saveRDS(ContECBootstrap,"RMSControlECBootstrap.RData")
print(ContECBootstrap$CI)

## [1] -0.2056721  0.6797539

# do a double bootstrap confidence interval for the EO mean - contro
ls only
# N for each control bootstrap sample = size of patient sample
ContEOBootstrap<-DoubleBootstrapCIForMeanSetNParallel(CData$EO,PData
N,2000,500,Alpha=0.05,NumCores=NumCores)
# saveRDS(ContEOBootstrap,"RMSControlEOBootstrap.RData")
print(ContEOBootstrap$CI)

## [1] -0.3202922  0.6544376
```

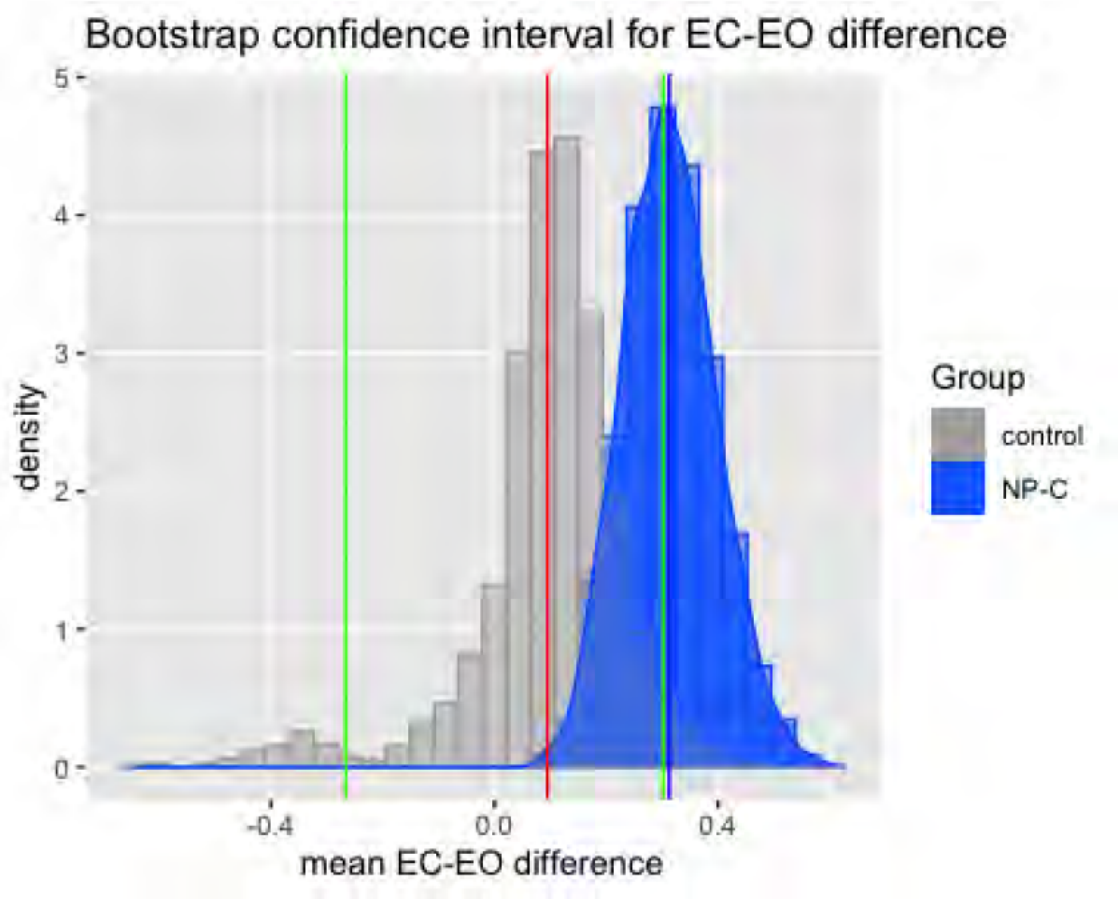
```
# Plot EC/EO difference

# put patient bootstrap values in a dataframe for plotting
PatDF<-data.frame(BootMeans=PatECEOBootstrapDiff$BootMeans,Group=fac
tor(PatientGroupCode,levels=names(myColors)))
# put control bootstrap values in a dataframe for plotting
ContDF<-data.frame(BootMeans=ContECEOBootstrapDiff$BootMeans,Group=f
actor("c",levels=names(myColors)))

CMean<-mean(ContDF$BootMeans) # control mean of bootstrap means
MeanPatBootMeans<-mean(PatDF$BootMeans) # patient mean of bootstrap
means

# do plot
# do histogram for bootstrap patient means first
DCIPlot<-ggplot(PatDF,aes(x=BootMeans,y=..density..,fill=Group,color
=Group))+geom_histogram(alpha=0.5)+ geom_density(alpha=0.5)
# add histogram for bootstrap control means
DCIPlot<-DCIPlot + geom_histogram(data=ContDF,aes(x=BootMeans,y=..de
nsity..,fill="c",color="c"),alpha=0.5)+geom_density(alpha=0.5)
# add a line marking the mean of patient bootstrap means
DCIPlot <- DCIPlot + geom_vline(xintercept=MeanPatBootMeans,color="b
lue")
# add lines  marking the boundaries of CI for control bootstrap mean
s
DCIPlot <- DCIPlot + geom_vline(xintercept=ContECEOBootstrapDiff$CI[
1],color="green")
DCIPlot <- DCIPlot + geom_vline(xintercept=ContECEOBootstrapDiff$CI[
2],color="green")
# add a line marking the mean of control bootstrap means
DCIPlot <- DCIPlot + geom_vline(xintercept=CMean,color="red")
# add a title
DCIPlot <- DCIPlot + ggtitle("Bootstrap confidence interval for EC-E
O difference")
# put a title on the x axis
DCIPlot <- DCIPlot + fillScale + colScale + xlab("mean EC-EO differe
nce")
print(DCIPlot)
```

```
## `stat_bin()` using `bins = 30`. Pick better value with `binwidth`
.
## `stat_bin()` using `bins = 30`. Pick better value with `binwidth`
.
```



EC-EO difference is higher in NPC

```
# print bootstrap mean values for patients and controls
print(sprintf("Bootstrap mean difference for patients = %.3f",MeanPa
tBootMeans))

## [1] "Bootstrap mean difference for patients = 0.313"

print(sprintf("Bootstrap mean difference for controls = %.3f",CMean)
)

## [1] "Bootstrap mean difference for controls = 0.095"

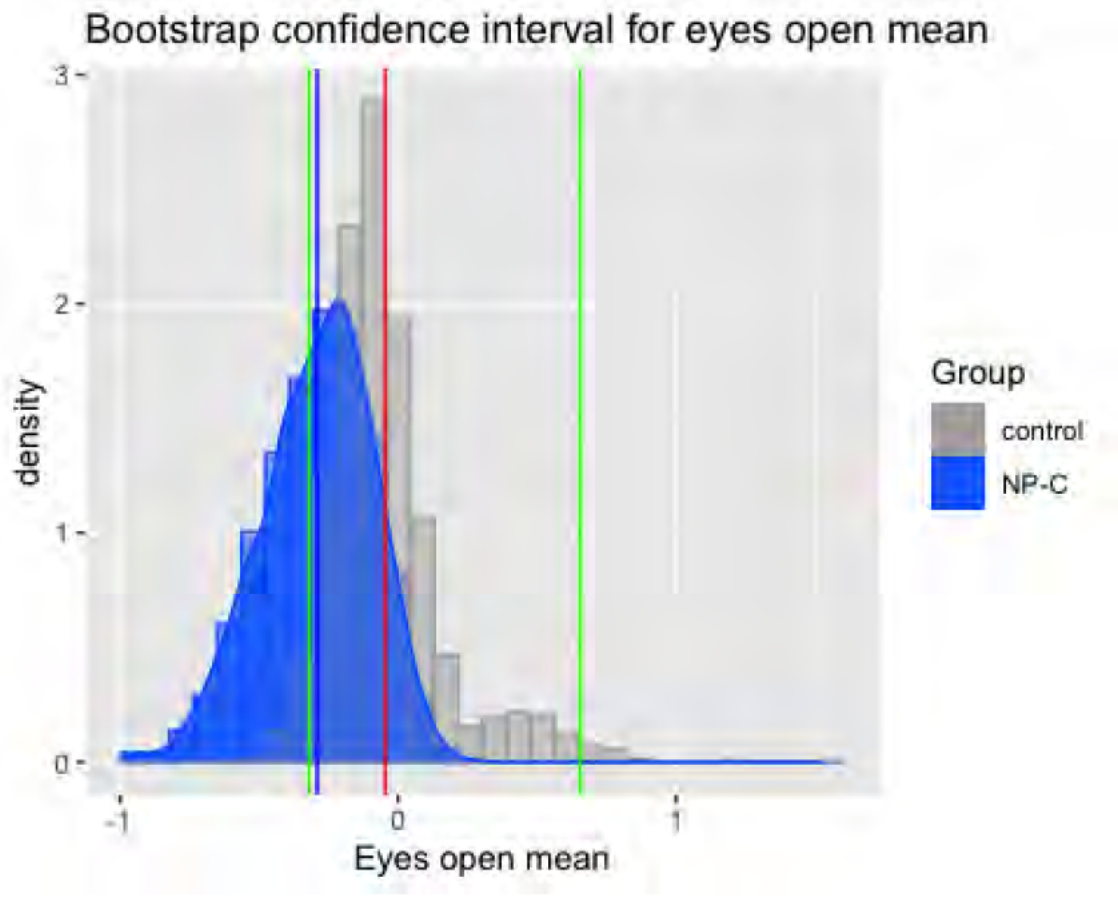
# make plots of bootstrap results for EO means
# (see plot details in example above)

# put patient bootstrap values in dataframes for plotting
EOPatDF<-data.frame(BootMeans=PatEOBootstrap$BootMeans,Group=factor(
PatientGroupCode,levels=names(myColors)))
# put
EOContDF<-data.frame(BootMeans=ContEOBootstrap$BootMeans,Group=facto
r("c",levels=names(myColors)))
```

```
EOCMean<-mean(EOContDF$BootMeans) # control mean of bootstrap means
EOMeanPatBootMeans<-mean(EOPatDF$BootMeans) # patient mean of bootst
rap means

# make the plot
DCIPlot<-ggplot(EOPatDF,aes(x=BootMeans,y=..density..,fill=Group,col
or=Group))+geom_histogram(alpha=0.5)+ geom_density(alpha=0.5)
DCIPlot<-DCIPlot + geom_histogram(data=EOContDF,aes(x=BootMeans,y=..
density..,fill="c",color="c"),alpha=0.5)+geom_density(alpha=0.5)
DCIPlot <- DCIPlot + geom_vline(xintercept=EOMeanPatBootMeans,color=
"blue")
DCIPlot <- DCIPlot + geom_vline(xintercept=ContEOBootstrap$CI[1],col
or="green")
DCIPlot <- DCIPlot + geom_vline(xintercept=ContEOBootstrap$CI[2],col
or="green")
DCIPlot <- DCIPlot + geom_vline(xintercept=EOCMean,color="red")
DCIPlot <- DCIPlot + ggtitle("Bootstrap confidence interval for eyes
open mean")
DCIPlot <- DCIPlot + fillScale + colScale + xlab("Eyes open mean")
print(DCIPlot)
```

```
## `stat_bin()` using `bins = 30`. Pick better value with `binwidth`
.
## `stat_bin()` using `bins = 30`. Pick better value with `binwidth`
.
```




```
# make plots of bootstrap results for EC means
# (see plot details in example above)

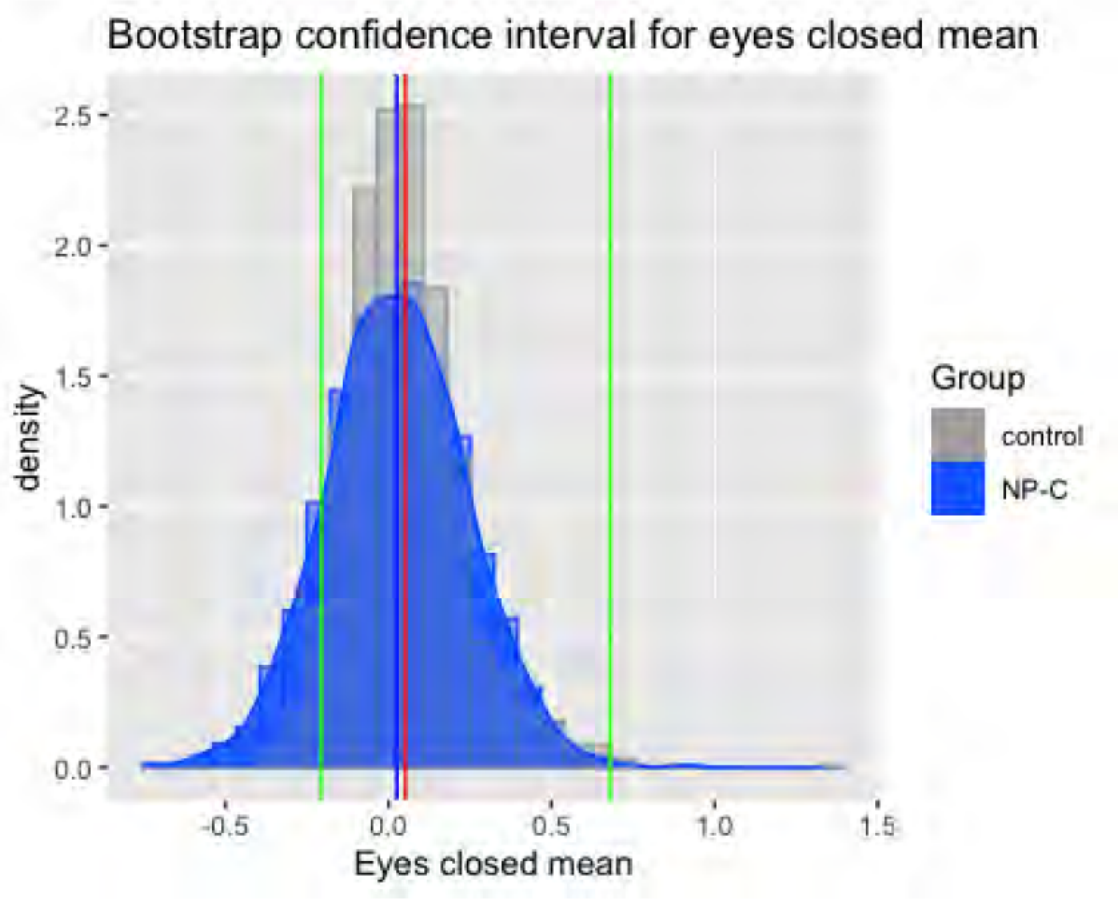
# put patient bootstrap values in dataframes for plotting
ECPatDF<-data.frame(BootMeans=PatECBootstrap$BootMeans,Group=factor(
PatientGroupCode,levels=names(myColors)))
# put
ECContDF<-data.frame(BootMeans=ContECBootstrap$BootMeans,Group=facto
r("c",levels=names(myColors)))

ECCMean<-mean(ECContDF$BootMeans) # control mean of bootstrap means
ECMeanPatBootMeans<-mean(ECPatDF$BootMeans) # patient mean of bootst
rap means

DCIPlot<-ggplot(ECPatDF,aes(x=BootMeans,y=..density..,fill=Group,col
or=Group))+geom_histogram(alpha=0.5)+ geom_density(alpha=0.5)
DCIPlot<-DCIPlot + geom_histogram(data=ECContDF,aes(x=BootMeans,y=..
density..,fill="c",color="c"),alpha=0.5)+geom_density(alpha=0.5)
DCIPlot <- DCIPlot + geom_vline(xintercept=ECMeanPatBootMeans,color=
"blue")
DCIPlot <- DCIPlot + geom_vline(xintercept=ContECBootstrap$CI[1],col
or="green")
DCIPlot <- DCIPlot + geom_vline(xintercept=ContECBootstrap$CI[2],col
or="green")
DCIPlot <- DCIPlot + geom_vline(xintercept=ECCMean,color="red")
```

```
DCIPlot <- DCIPlot + ggtitle("Bootstrap confidence interval for eyes
closed mean")
DCIPlot <- DCIPlot + fillScale + colScale + xlab("Eyes closed mean")
print(DCIPlot)
```

```
## `stat_bin()` using `bins = 30`. Pick better value with `binwidth`
.
## `stat_bin()` using `bins = 30`. Pick better value with `binwidth`
.
```




```
#########################################################################
##
#
##### This section tests whether individual patients
##### are inside/outside the control range
#
#########################################################################
##

# get cutoffs of control range in order to classify individual patie
nts as
# inside or outside the control range

# first calculate mean values for control ppts
```

```
PptMeans<-CDataNO %>% dplyr::group_by(PID,Height,HtBin,EyeCond) %>%
dplyr::summarise(PptMean=mean(Residual))

## `summarise()` has grouped output by 'PID', 'Height', 'HtBin'. You
can override using the `.groups` argument.

head(PptMeans)

## # A tibble: 6 x 5
## # Groups:   PID, Height, HtBin [4]
##   PID                 Height HtBin EyeCond PptMean
##   <fct>                <dbl> <dbl> <fct>     <dbl>
## 1 EdgbastonNursery_H1     99  95.4 EO        7.74
## 2 EdgbastonNursery_H1     99  95.4 EC        5.54
## 3 EdgbastonNursery_H2    104 107   EO        2.44
## 4 EdgbastonNursery_H3     90  95.4 EO       -1.81
## 5 EdgbastonNursery_H3     90  95.4 EC       -1.56
## 6 FirstSchool_Y1S1       120 118.  EO       -0.114

# set the cutoff value for the prediction interval
# (e.g. 0.95 is for a 95% prediction interval -- analogous to a 95%
confidence interval)
PCutoff<-0.95

# get prediction intervals for each height bin based on ppt mean res
iduals
# EO condition only
PptMeansEO<-PptMeans[PptMeans$EyeCond == "EO",]
PIByHeightEO<-GroupedPredictionInterval(PptMeansEO,"PptMean","HtBin"
,PCutoff)
PIByHeightEO<-PIByHeightEO[!is.na(PIByHeightEO$MySD),]
print(PIByHeightEO)

## # A tibble: 9 x 7
##   HtBin    MyMean  MySD   MyN MyTCrit UpperCutoff LowerCutoff
##   <dbl>     <dbl> <dbl> <int>   <dbl>       <dbl>       <dbl>
## 1  95.4  0.988    3.21     11    2.23        8.45       -6.48
## 2 107   -0.263    1.00     15    2.14        1.96       -2.49
## 3 118.  -0.281    0.382    34    2.03        0.508      -1.07
## 4 130.  -0.00400  0.424    29    2.05        0.880      -0.888
## 5 140.  -0.000239 0.325    42    2.02        0.663      -0.663
## 6 152   -0.0123   0.271    43    2.02        0.541      -0.565
## 7 164.  -0.118    0.376    89    1.99        0.633      -0.869
## 8 174.   0.0325   0.500    29    2.05        1.07       -1.01
## 9 186    0.255    0.541     7    2.45        1.67       -1.16

# get prediction intervals for height bins based on ppt mean residua
ls
# EC condition only
PptMeansEC<-PptMeans[PptMeans$EyeCond == "EC",]
PIByHeightEC<-GroupedPredictionInterval(PptMeansEC,"PptMean","HtBin"
```

```
,PCutoff)
PIByHeightEC<-PIByHeightEC[!is.na(PIByHeightEC$MySD),]
print(PIByHeightEC)
```

```
## # A tibble: 9 x 7
##   HtBin  MyMean  MySD   MyN MyTCrit UpperCutoff LowerCutoff
##   <dbl>   <dbl> <dbl> <int>   <dbl>       <dbl>       <dbl>
## 1  95.4  0.199  1.96     11    2.23        4.76       -4.36
## 2 107    0.0394 1.14     14    2.16        2.59       -2.52
## 3 118.  -0.0689 0.417    34    2.03        0.792      -0.930
## 4 130.   0.113  0.440    29    2.05        1.03       -0.802
## 5 140.   0.0897 0.338    41    2.02        0.782      -0.602
## 6 152    0.0833 0.311    42    2.02        0.718      -0.552
## 7 164.  -0.0487 0.370    89    1.99        0.690      -0.787
## 8 174.   0.121  0.492    29    2.05        1.15       -0.903
## 9 186    0.657  0.553     7    2.45        2.10       -0.790
```

```
# rename HtBin to Height because when we apply the cutoff to the dat
a we will
# use each ppt's Height variable, so the model will need to predict
based on Height rather than HtBin
PIByHeightEO<-PIByHeightEO %>% dplyr::rename(Height=HtBin)
PIByHeightEC<-PIByHeightEC %>% dplyr::rename(Height=HtBin)
head(PIByHeightEO)
```

```
## # A tibble: 6 x 7
##   Height    MyMean  MySD   MyN MyTCrit UpperCutoff LowerCutoff
##    <dbl>     <dbl> <dbl> <int>   <dbl>       <dbl>       <dbl>
## 1   95.4  0.988    3.21     11    2.23        8.45       -6.48
## 2  107   -0.263    1.00     15    2.14        1.96       -2.49
## 3  118.  -0.281    0.382    34    2.03        0.508      -1.07
## 4  130.  -0.00400  0.424    29    2.05        0.880      -0.888
## 5  140.  -0.000239 0.325    42    2.02        0.663      -0.663
## 6  152   -0.0123   0.271    43    2.02        0.541      -0.565
```

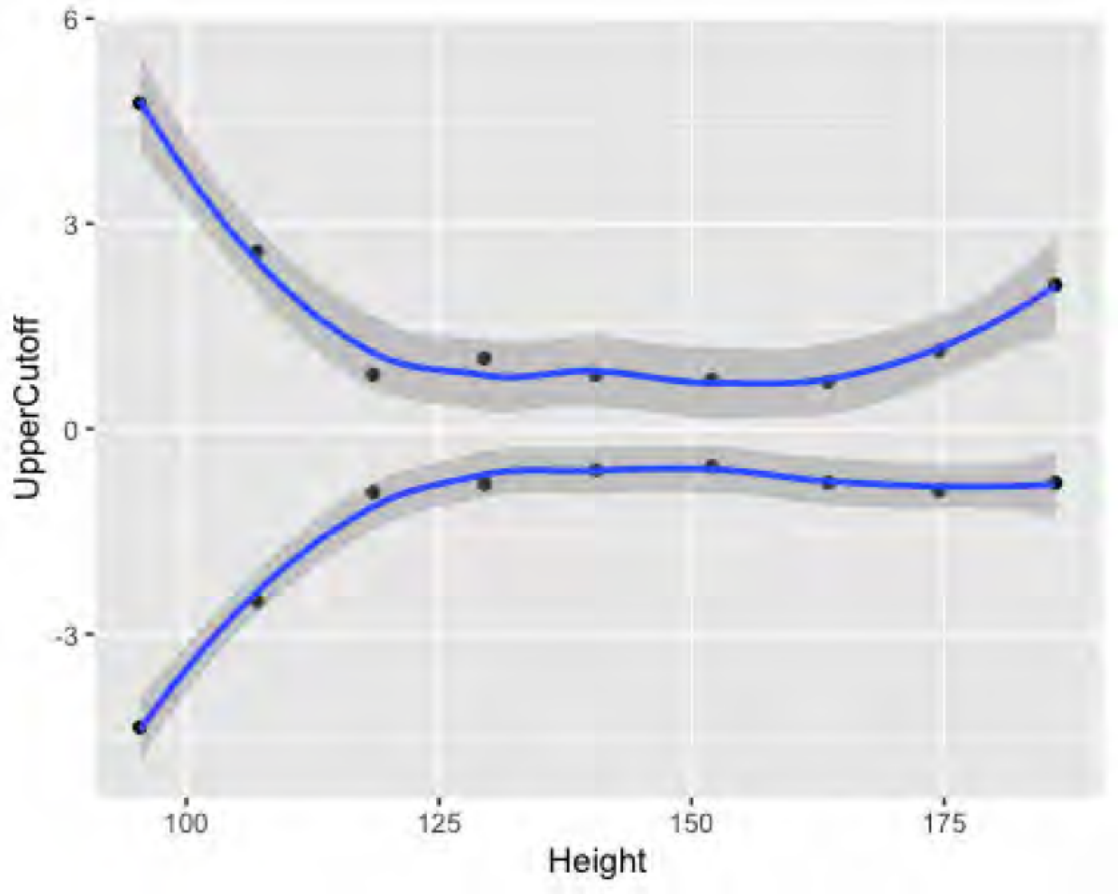
```
# ################################### EC data ####################
#############

# plot the eyes closed cutoff values for each bin in preparation for
fitting
# a smoothing function

CurData<-PIByHeightEC
ConditionName<-"Eyes closed"

CutoffPlot<-ggplot(CurData,aes(x=Height,y=UpperCutoff))+geom_point()
+geom_smooth()
CutoffPlot<-CutoffPlot + geom_point(aes(x=Height,y=LowerCutoff))+geo
m_smooth(aes(x=Height,y=LowerCutoff))
print(CutoffPlot)
```

```
## `geom_smooth()` using method = 'loess' and formula 'y ~ x'
## `geom_smooth()` using method = 'loess' and formula 'y ~ x'
```

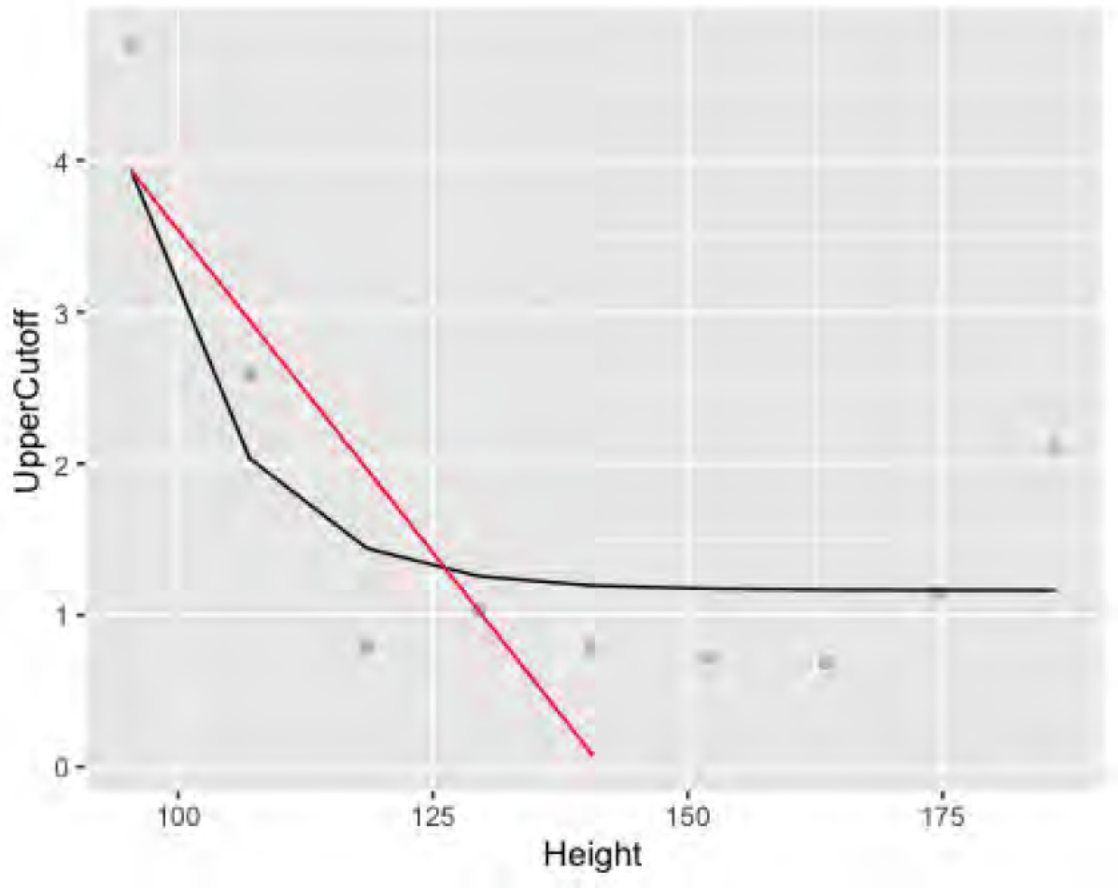



```
# fit a function to the upper cutoff points

# prepare starting values for an asymptotic fit as above
LrcStart<-0.1 # this would be a pretty flat function
LrcEnd<-5 # this would be a sharp corner
LrcStep<-0.1 # go between 0.5 and 5 in steps of 0.5

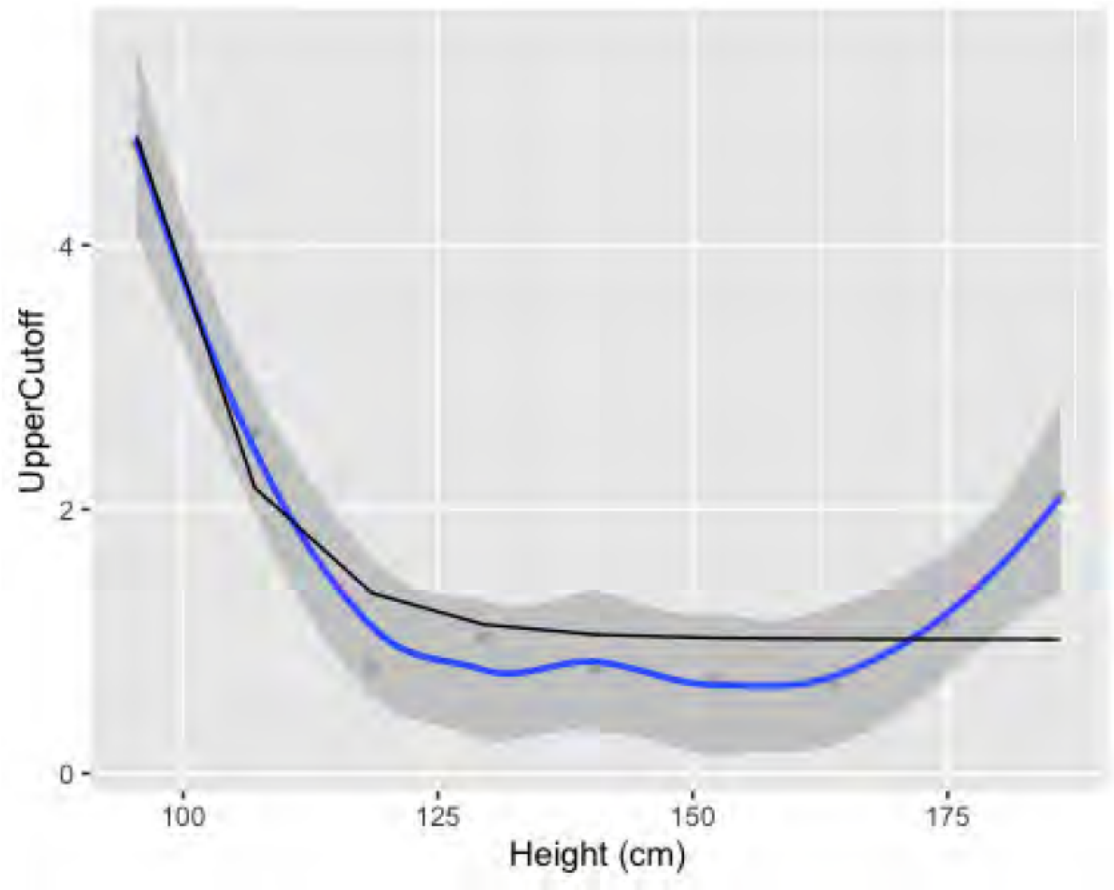
AsympPortion <- 0.5 # portion of the curve that is curved
# change this as necessary for a good starting fit
YName<-"UpperCutoff"
XName<-"Height"

# plot the starting asymptotic function to check if starting values
are OK
UCOAStartList<-PlotStartingAsympFunction(CurData,XName,YName,LrcStar
t,LrcEnd,LrcStep,AsympPortion)
print(UCOAStartList$Plot)
```




```
# fit an asymptotic function to the upper cutoff values
UCOAModelList<-FitAsymptoteModel(CurData,"Height","UpperCutoff",UCOA
StartList$StartValues)
if(!is.null(UCOAModelList)){ # did asymptotic model not fail?
  UCOAsympModel<-UCOAModelList$Model
  print(UCOAModelList$Plot)
} else{
  message("\nAsymptote model was not fit successfully")
}

## `geom_smooth()` using method = 'loess' and formula 'y ~ x'
```




```
# fit quadratic, linear and constant models to the upper cutoff
UCOQuadraticModel<-lm(UpperCutoff ~ Height + I(Height^2),data=CurDat
a)
UCOLinearModel<-lm(UpperCutoff ~ Height,data=CurData)
UCOConstantModel<-lm(UpperCutoff ~ 1,data=CurData)
# no reason why these shouldn't converge

# see which model is best based on reporting their AIC values
UCOAICResult<-GetAICResult(UCOAsympModel,UCOQuadraticModel,UCOLinear
Model,UCOConstantModel)

##  Asymptotic model: 20.0262040672084
## Quadratic Model: 15.6582070131618
##  Linear Model: 33.0702408185405
##  ConstantModel: 33.9523325399768

kable(UCOAICResult,row.names=TRUE)
```

AIC

Order

deltaAIC

Asymptotic Model

20.02620

2

4.367997

Quadratic Model

15.65821

1

0.000000

Linear Model

33.07024

3

17.412034

ConstantModel

33.95233

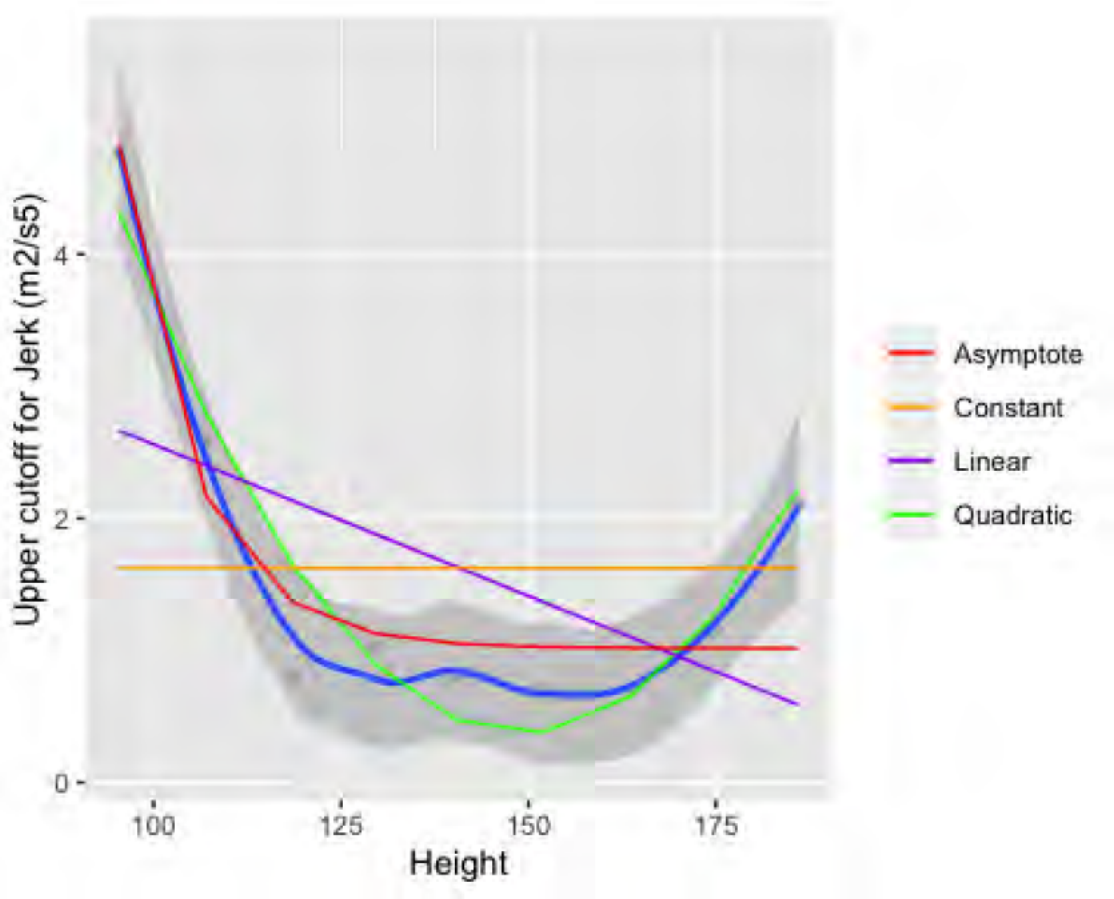
4

18.294125

```
# plot models to choose the best model based on AIC and theoretical plausibility

ModelPlot<-PlotModels(CurData,"Height","UpperCutoff",paste("Upper cutoff for ",DependentVariableName,sep=""), UCOAsympModel, UCOQuadraticModel, UCOLinearModel, UCOConstantModel)
print(ModelPlot)

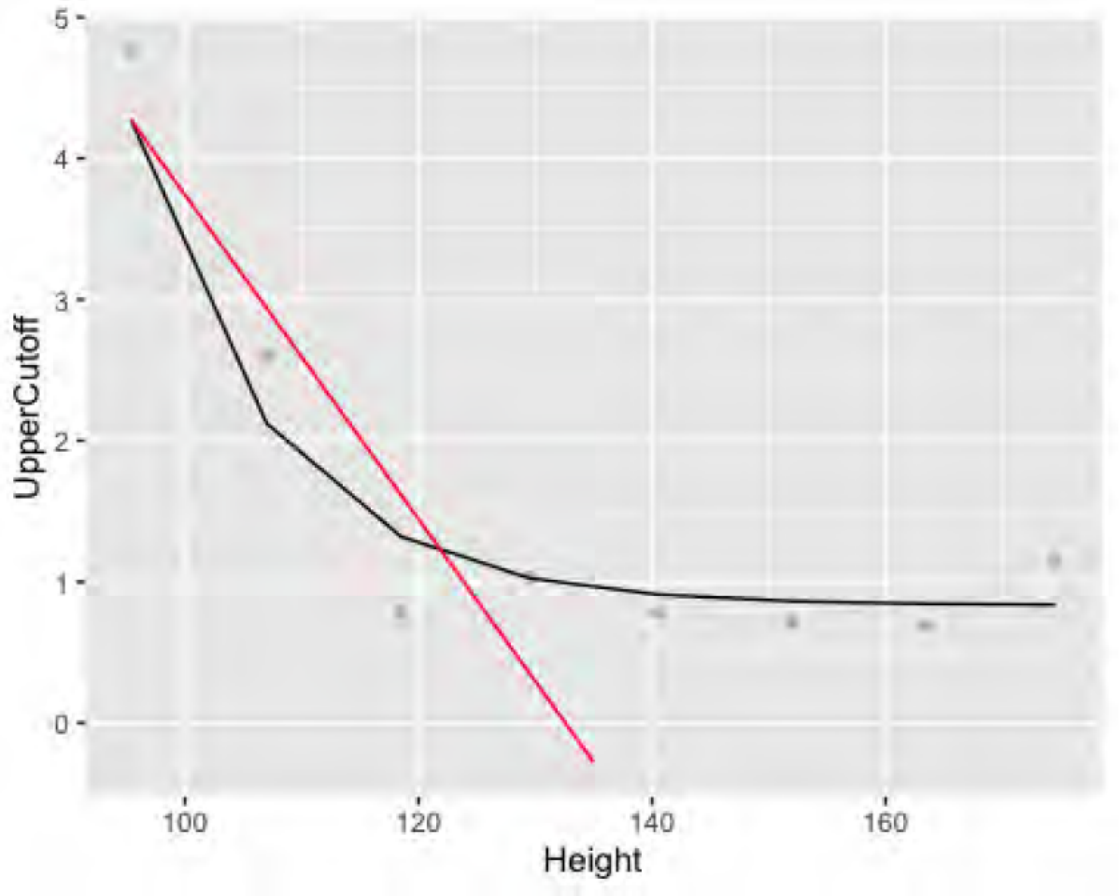
## `geom_smooth()` using method = 'loess' and formula 'y ~ x'
```




```
# Fit models without the extreme, small N points -- make sure best m
odel is consistent in both analyses

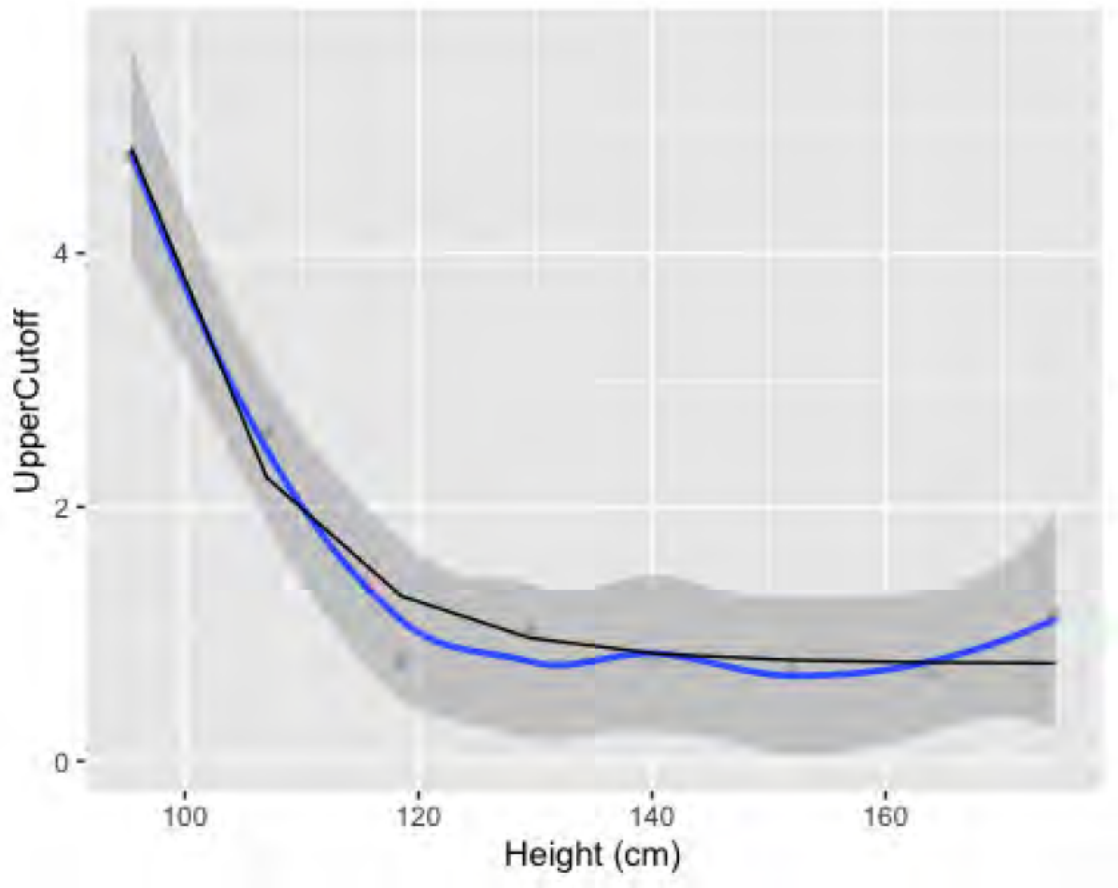
CurDataNE<-CurData[(CurData$Height > 95) & (CurData$Height < 175),]

NEUCOAStartList<-PlotStartingAsympFunction(CurDataNE,XName,YName,Lrc
Start,LrcEnd,LrcStep,AsympPortion)
print(NEUCOAStartList$Plot)
```




```
NEUCOAModelList<-FitAsymptoteModel(CurDataNE,"Height","UpperCutoff",
NEUCOAStartList$StartValues)
if(!is.null(NEUCOAModelList)){
  NEUCOAsympModel<-NEUCOAModelList$Model
  print(NEUCOAModelList$Plot)
}else{
  message("\nAsymptote model was not fit successfully")
}
```

```
## `geom_smooth()` using method = 'loess' and formula 'y ~ x'
```




```
NEUCOQuadraticModel<-lm(UpperCutoff ~ Height + I(Height^2),data=CurD
ataNE)
NEUCOLinearModel<-lm(UpperCutoff ~ Height,data=CurDataNE)
NEUCOConstantModel<-lm(UpperCutoff ~ 1,data=CurDataNE)
# no reason why these shouldn't converge

NEUCOAICResult<-GetAICResult(NEUCOAsympModel,NEUCOQuadraticModel,NEU
COLinearModel,NEUCOConstantModel)

##  Asymptotic model: 9.35873399086763
## Quadratic Model: 15.4837900484
##  Linear Model: 27.5868396506215
##  ConstantModel: 31.4240418034322

kable(NEUCOAICResult,row.names=TRUE)
```

AIC

Order

deltaAIC

Asymptotic Model

9.358734

1

0.000000

Quadratic Model

15.483790

2

6.125056

Linear Model

27.586840

3

18.228106

ConstantModel

31.424042

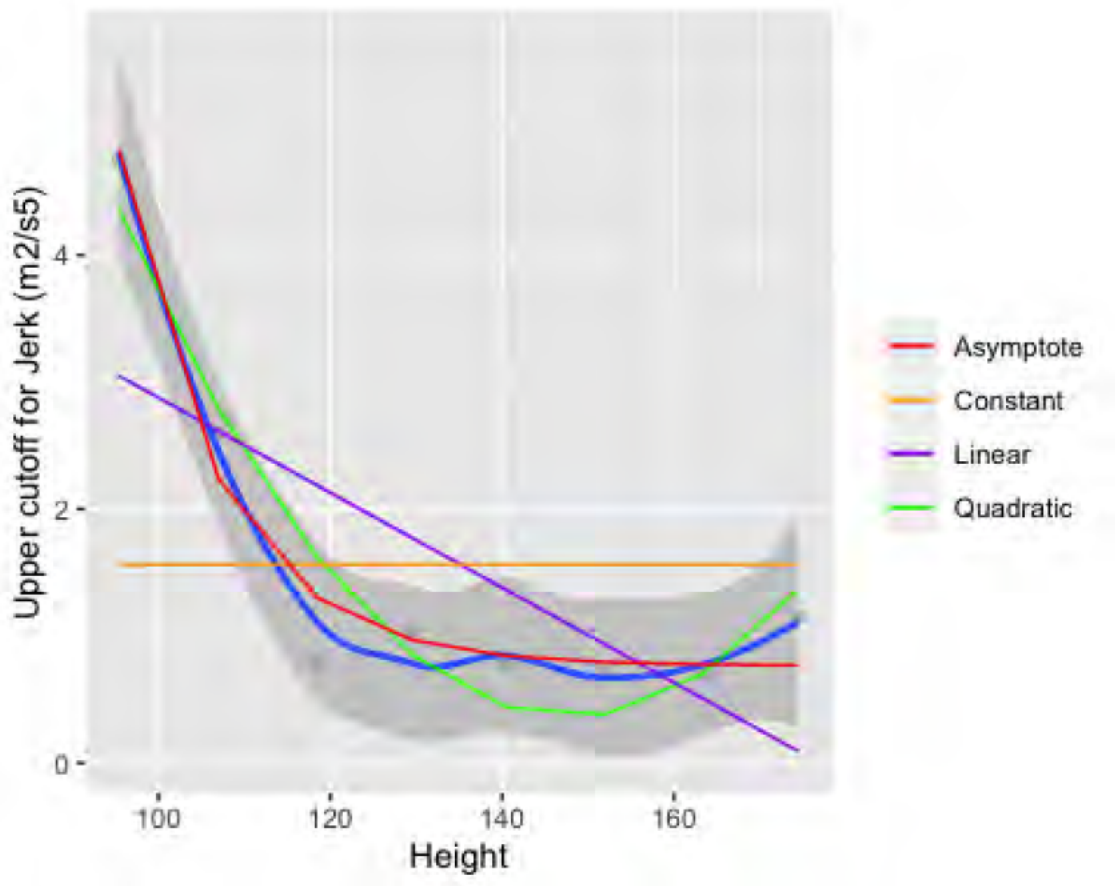
4

22.065308

```
# plot models to choose the best model based on AIC and theoretical
plausibility

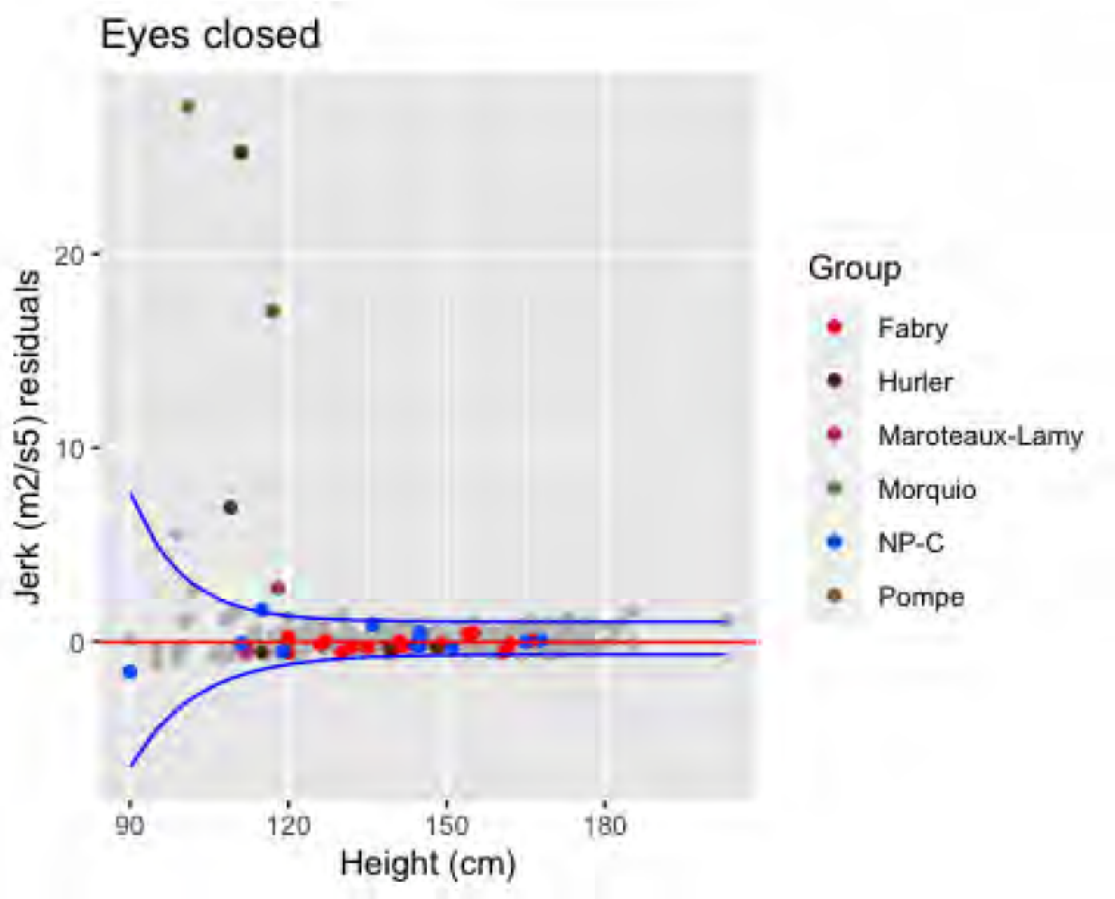
ModelPlot<-PlotModels(CurDataNE,"Height","UpperCutoff",paste("Upper
cutoff for ",DependentVariableName,sep=""), NEUCOAsympModel, NEUCOQu
adraticModel, NEUCOLinearModel, NEUCOConstantModel)
print(ModelPlot)

## `geom_smooth()` using method = 'loess' and formula 'y ~ x'
```




```
# choose best model for upper cutoff here based on plots and AIC val
ues
ECUpperCutoffModel<-UCOAsympModel

################################################
# model lower cutoff -- this repeats everything from above
# but applies it to the lower cutoff, rather than the upper one
################################################
```



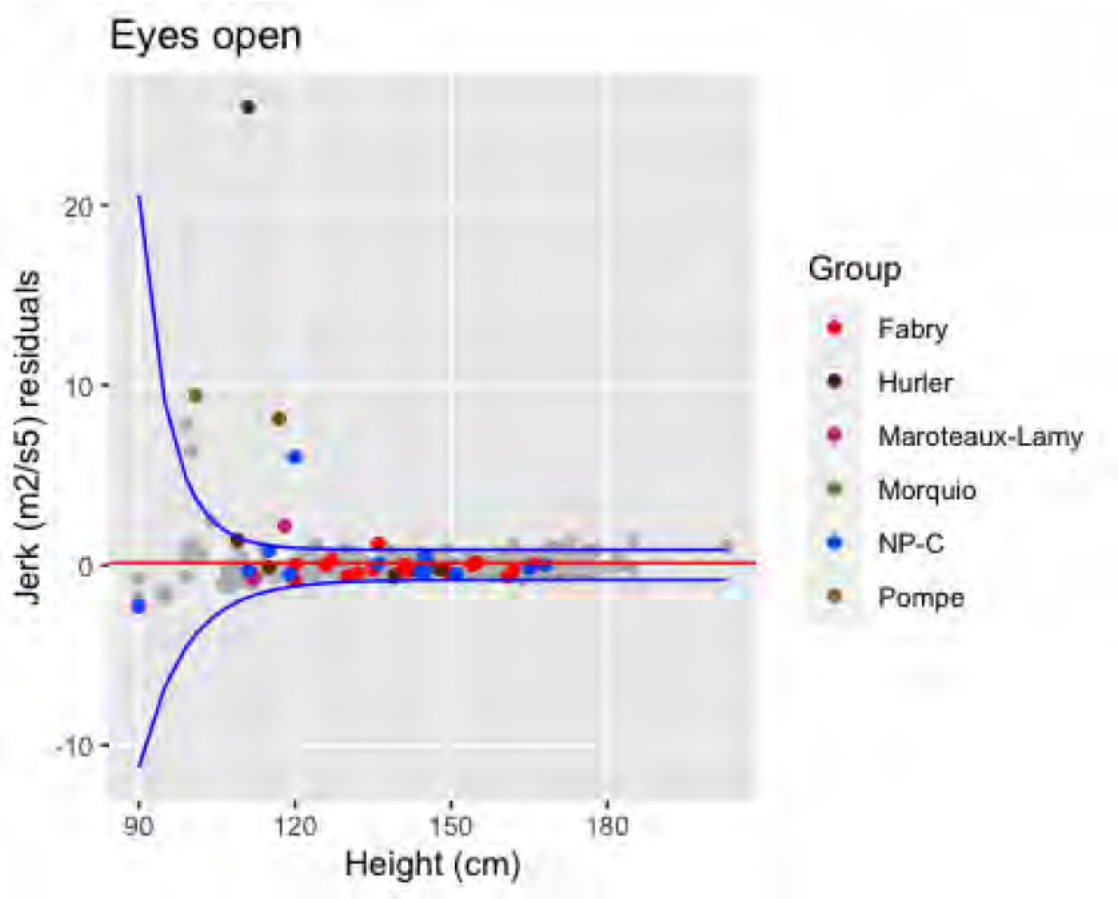

```
# calculate standard scores
ECAllDataPptMeans$SScore<-CalculateStandardScore(ECAllDataPptMeans$P
ptMean, ECAllDataPptMeans$LowerCutoff, ECAllDataPptMeans$UpperCutoff
, PCutoff)

# mark ppts outside the normal range
ECAllDataPptMeans$OutsideRange<-ifelse((ECAllDataPptMeans$PptMean <
ECAllDataPptMeans$UpperCutoff) &
                                        (ECAllDataPptMeans$PptMean
> ECAllDataPptMeans$LowerCutoff),0,1)

# save a list of all ppts with values outside the control range
PatientsWithAbnormalValues<-ECAllDataPptMeans[(ECAllDataPptMeans$Out
sideRange == 1) & (ECAllDataPptMeans$Group != "c"),]
# make a table with data from patients with values outside the contr
ol range
AbValueTable<-PatientsWithAbnormalValues %>% select(PID,Group,Age,He
ight,PptMean,SScore,LowerCutoff,UpperCutoff)
AbValueTable<-AbValueTable[order(AbValueTable$Group),]
print(AbValueTable)

# ################################### EO data ######################
#############
```

```
# do the same thing as above, but for the eyes-open data
```




```
# calculate standard scores
EOAllDataPptMeans$SScore<-CalculateStandardScore(EOAllDataPptMeans$P
ptMean, EOAllDataPptMeans$LowerCutoff, EOAllDataPptMeans$UpperCutoff
, PCutoff)

# mark ppts outside the normal range
EOAllDataPptMeans$OutsideRange<-ifelse((EOAllDataPptMeans$PptMean <
EOAllDataPptMeans$UpperCutoff) &
                                        (EOAllDataPptMeans$PptMean
> EOAllDataPptMeans$LowerCutoff),0,1)

PatientsWithAbnormalValues<-EOAllDataPptMeans[(EOAllDataPptMeans$Out
sideRange == 1) & (EOAllDataPptMeans$Group != "c"),]
AbValueTable<-PatientsWithAbnormalValues %>% select(PID,Group,Age,He
ight,PptMean,SScore,LowerCutoff,UpperCutoff)
AbValueTable<-AbValueTable[order(AbValueTable$Group),]
print(AbValueTable)
```

```
# list ppts NOT outside the normal range

PatientsWithNormValues<-EOAllDataPptMeans[(EOAllDataPptMeans$Outside
Range == 0) & (EOAllDataPptMeans$Group != "c"),]
NormValuesTable<-PatientsWithNormValues %>% select(PID,Group,Age,Hei
ght,PptMean,SScore,LowerCutoff,UpperCutoff)
NormValuesTable<-NormValuesTable[order(NormValuesTable$Group),]
print(NormValuesTable)

# list all ppts

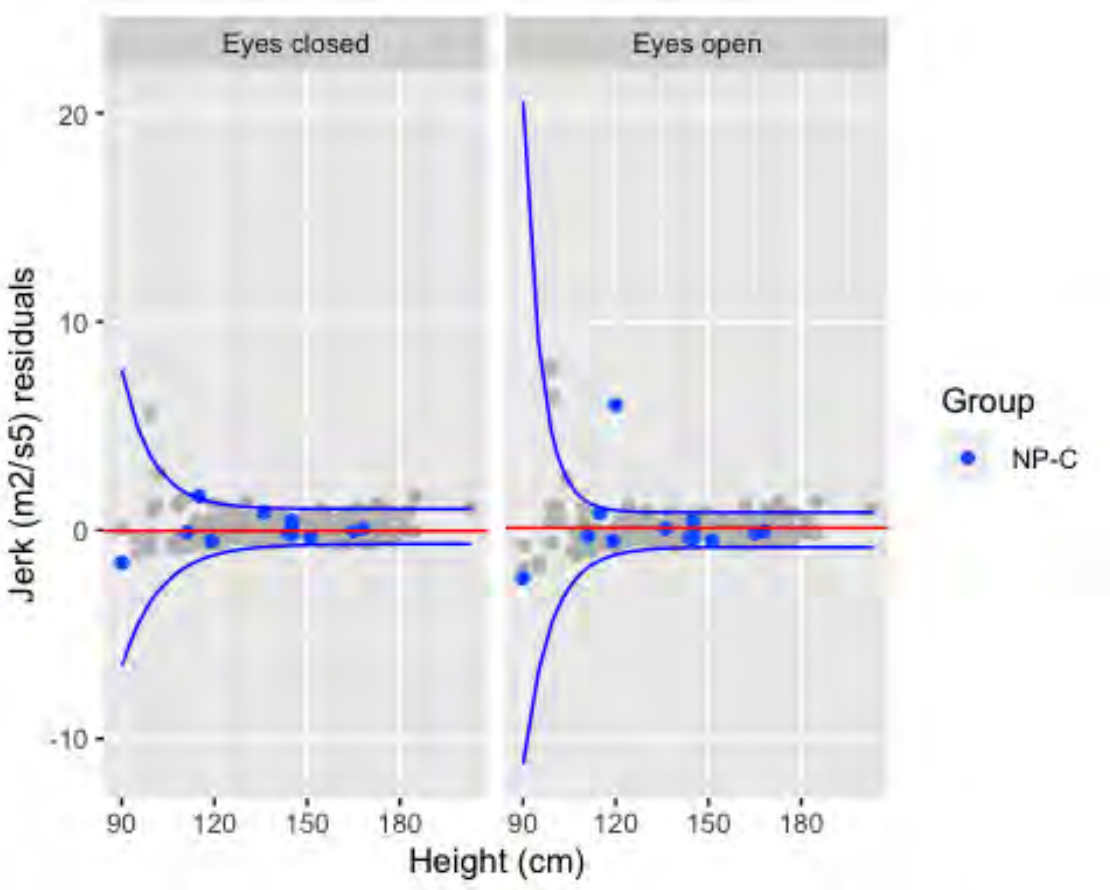
PatientsWithNormValues<-EOAllDataPptMeans[(EOAllDataPptMeans$Group !
= "c"),]
NormValuesTable<-PatientsWithNormValues %>% select(PID,Group,Age,Hei
ght,PptMean,SScore,LowerCutoff,UpperCutoff)
NormValuesTable<-NormValuesTable[order(NormValuesTable$Group),]
# print(NormValuesTable)

# plot EO and EC data on adjacent plots for one group
InterceptDF<-data.frame(Intercept=c(ECControlValue,EOControlValue),
Cond=c("Eyes closed","Eyes open"))
SelectedGroup<-"pn"

ECAllDataPptMeans$Cond<-"Eyes closed"
EOAllDataPptMeans$Cond<-"Eyes open"
PlotData<-rbind(ECAllDataPptMeans,EOAllDataPptMeans)

MyPlot<-ggplot(PlotData[PlotData$Group == 'c',],
               aes(x=Height,y=PptMean,group=Cond))+geom_point(color=
"grey")
MyPlot<-MyPlot + geom_point(data=PlotData[PlotData$Group==SelectedGr
oup,],
                            aes(x=Height,y=PptMean,group=Cond,color=
Group))

MyPlot<-MyPlot + geom_line(data=PlotData,aes(x=Height,y=UpperCutoff,
group=Cond),color="blue")
MyPlot<-MyPlot + geom_line(data=PlotData,aes(x=Height,y=LowerCutoff,
group=Cond),color="blue")
MyPlot <- MyPlot + geom_hline(data=InterceptDF,aes(yintercept = Inte
rcept, group=Cond),color='red')
MyPlot<-MyPlot + labs(x="Height (cm)", y=paste0(DependentVariableNam
e," residuals"))
MyPlot<-MyPlot + facet_wrap(~ Cond)
MyPlot<-MyPlot + colScale
print(MyPlot)
```


Eyes closed
Eyes open
20
10
0
-10
Jerk (m2/s5) residuals
90
120
150
180
Height (cm)
Group
NP-C

Appendix 3

A. NP-C patient gait figures:

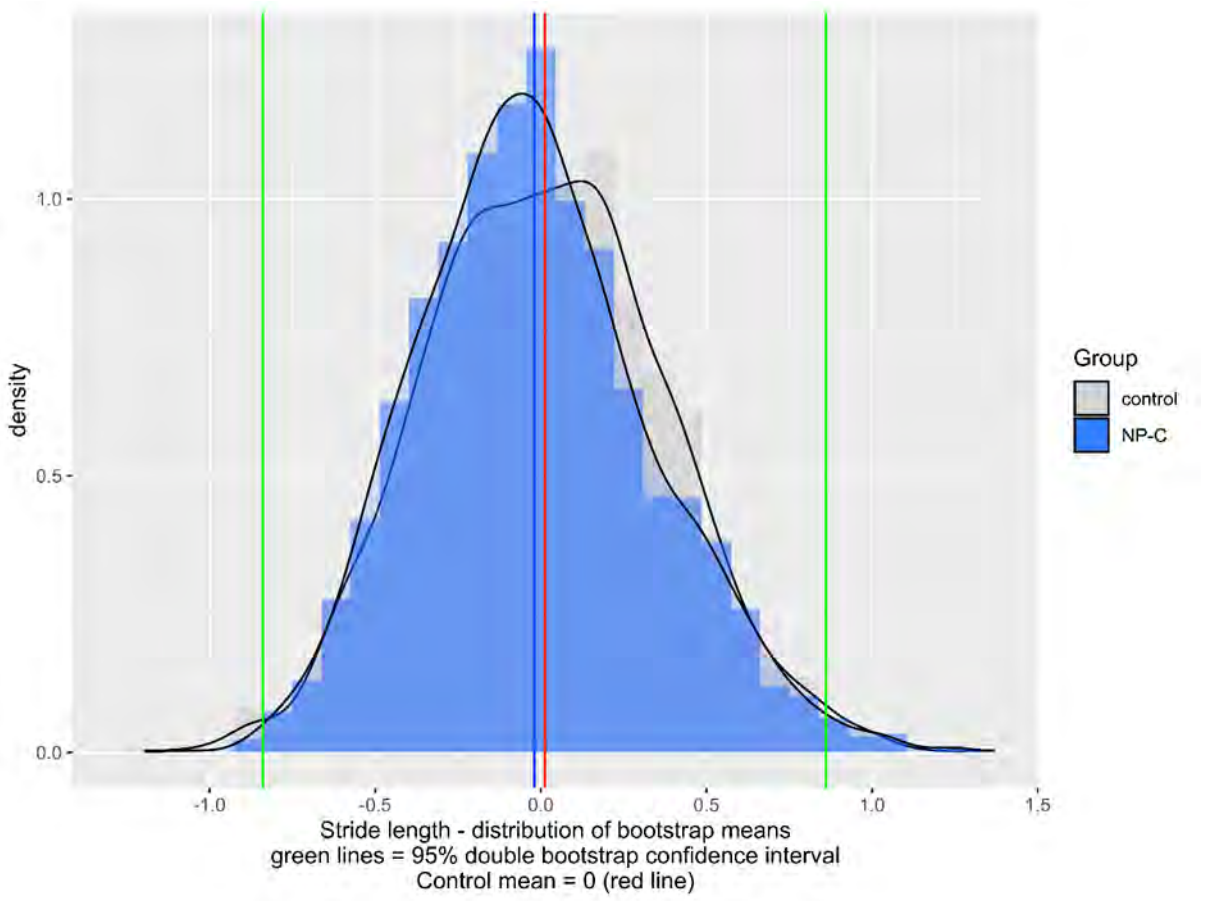


Figure 3.A1: The distribution of bootstrap means for NP-C patients and controls in stride length after removing the extreme values. Green lines are the 95% confidence intervals. Red line is the control mean. Blue line is the patients mean.

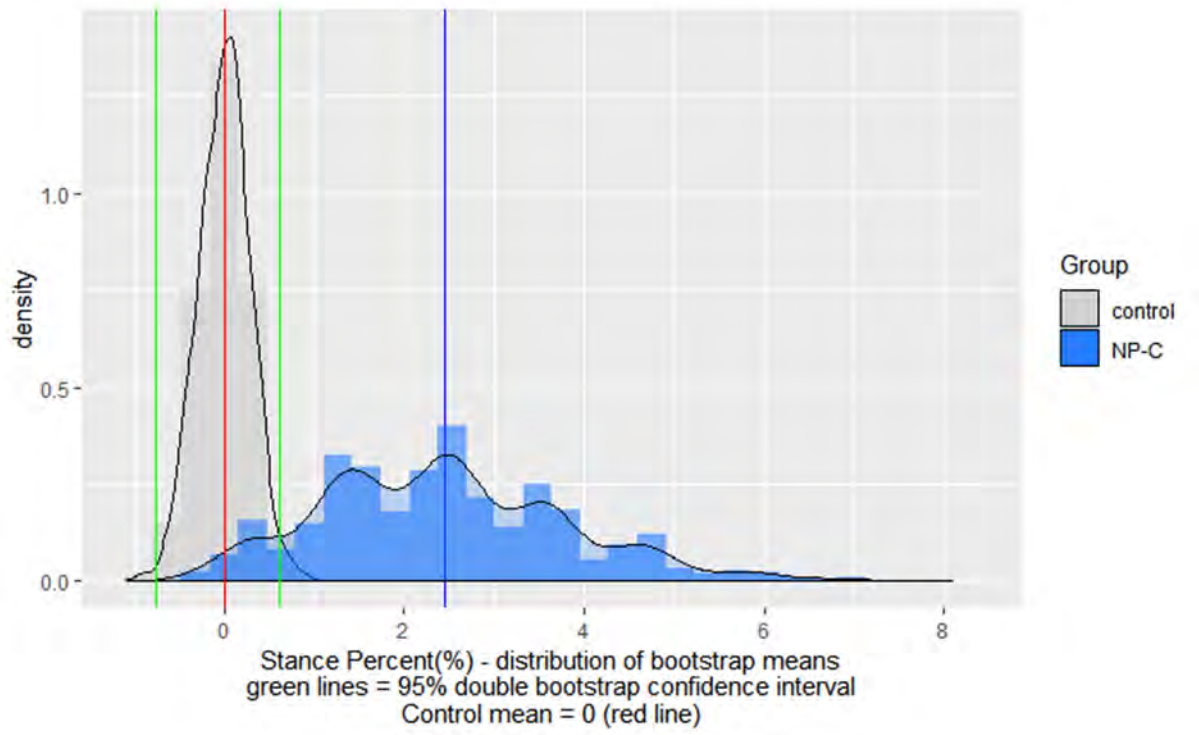


Figure 3.A2: The distribution of bootstrap means for NP-C patients and controls in stance percentage. Green lines are the 95% confidence intervals. Red line is the control mean. Blue line is the patients mean.

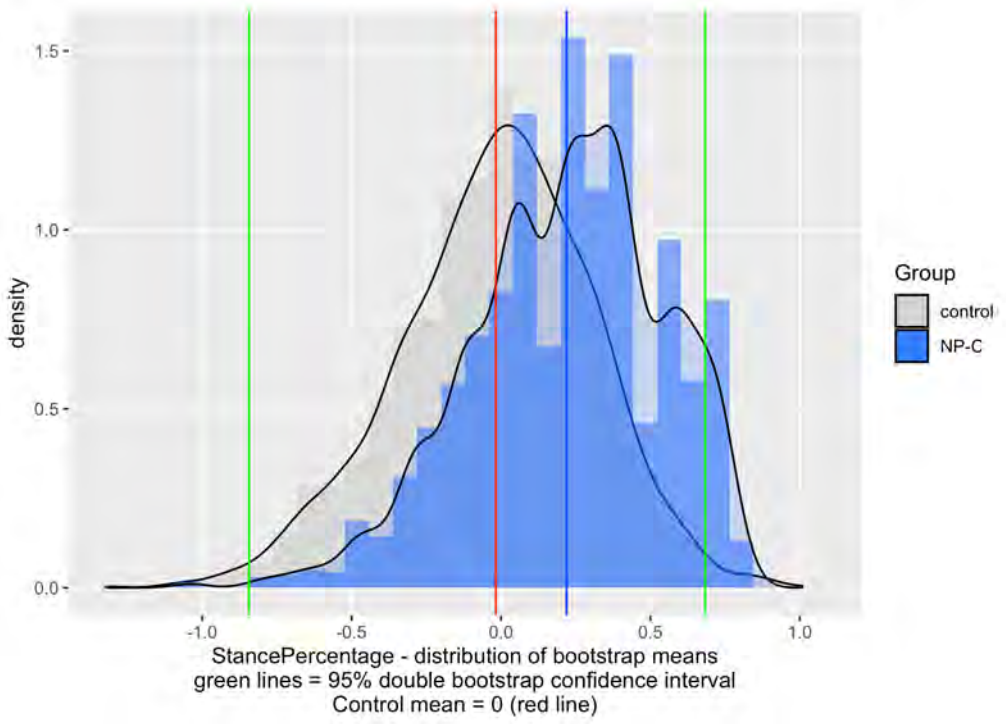


Figure 3.A3: The distribution of bootstrap means for NP-C patients and controls in stance percentage after removing the extreme values. Green lines are the 95% confidence intervals. Red line is the control mean. Blue line is the patients mean.

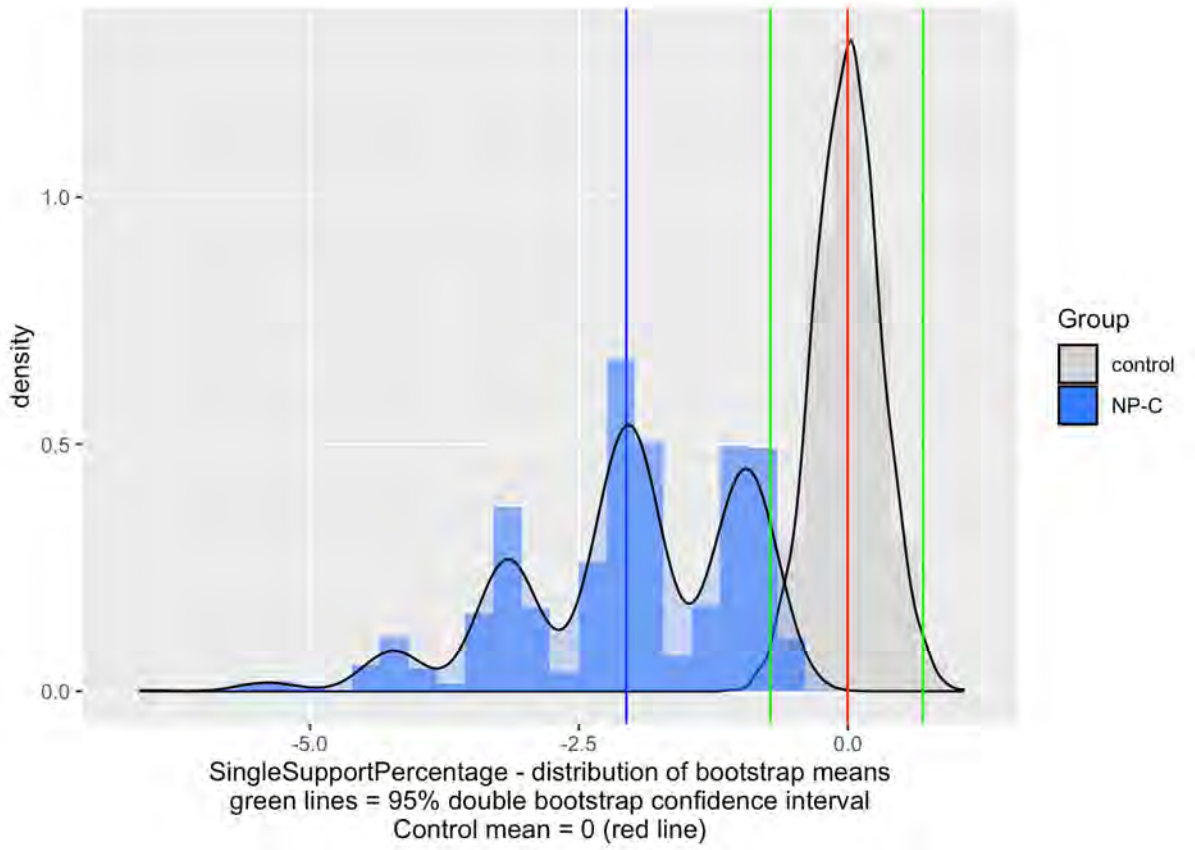


Figure 3.A4: The distribution of bootstrap means for NP-C patients and controls in single support percentage. Green lines are the 95% confidence intervals. Red line is the control mean. Blue line is the patients mean.

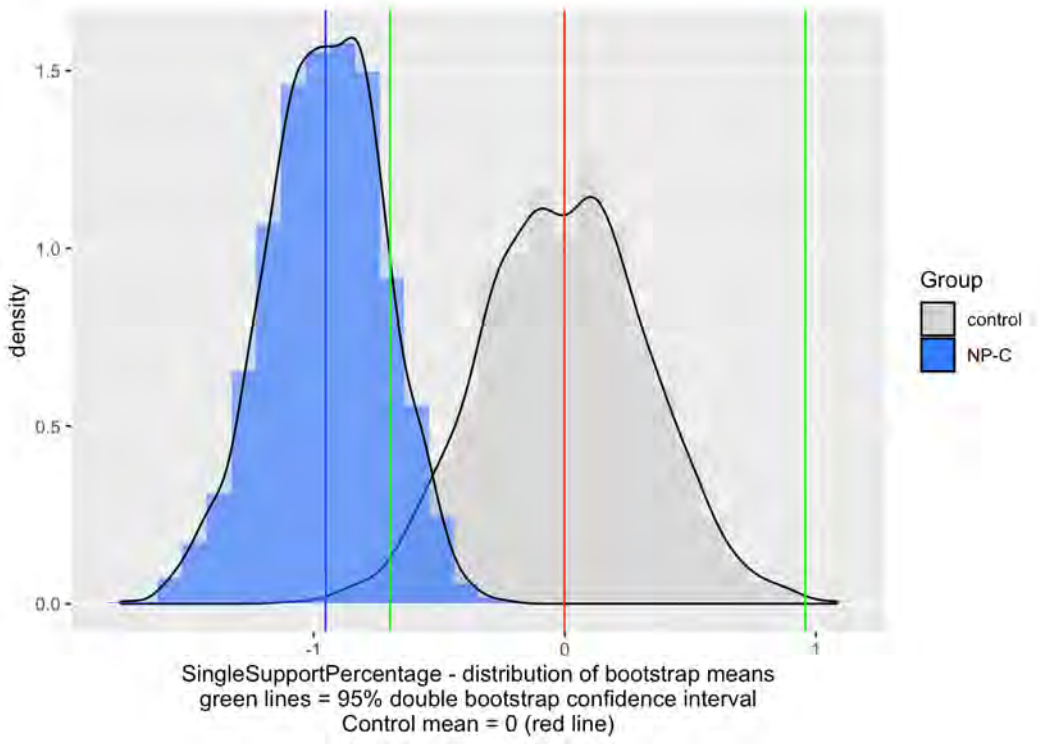


Figure 3.A5: The distribution of bootstrap means for NP-C patients and controls in single support percentage after removing the extreme patient value. Green lines are the 95% confidence intervals. Red line is the control mean. Blue line is the patients mean.

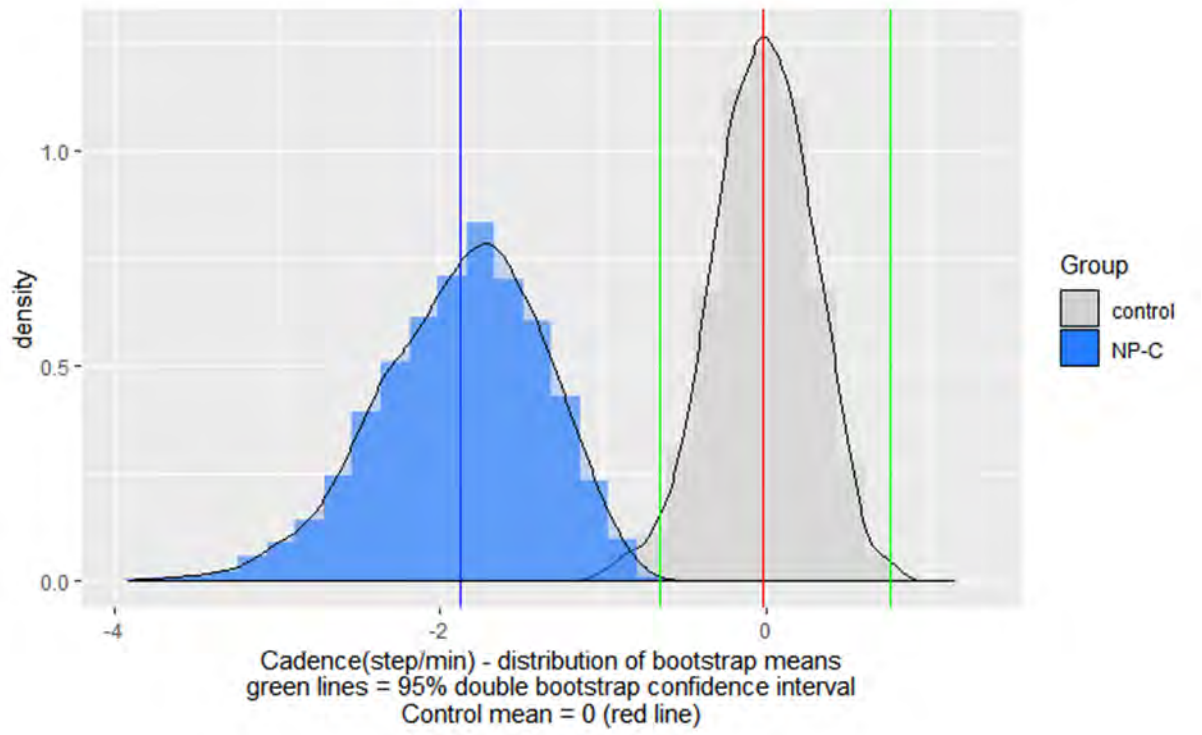


Figure 3.A6: The distribution of bootstrap means for NP-C patients and controls in cadence. Green lines are the 95% confidence intervals. Red line is the control mean. Blue line is the patients mean.

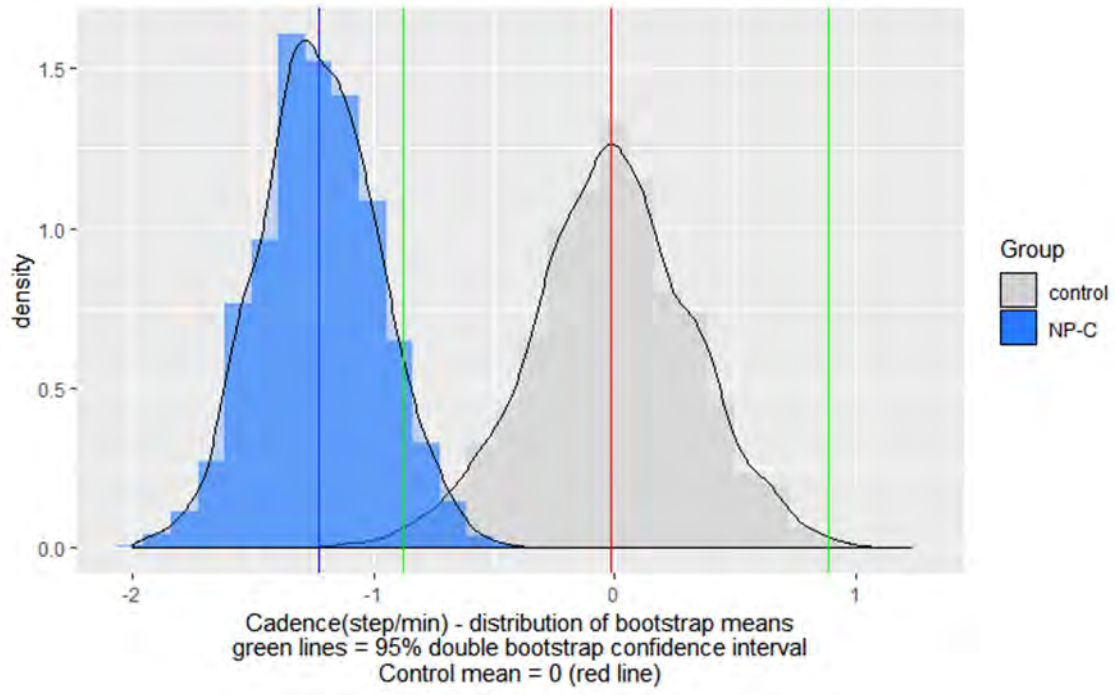


Figure 3.A7: The distribution of bootstrap means for NP-C patients and controls in cadence after removing the extreme patients‟ values. Green lines are the 95% confidence intervals. Red line is the control mean. Blue line is the patients mean.

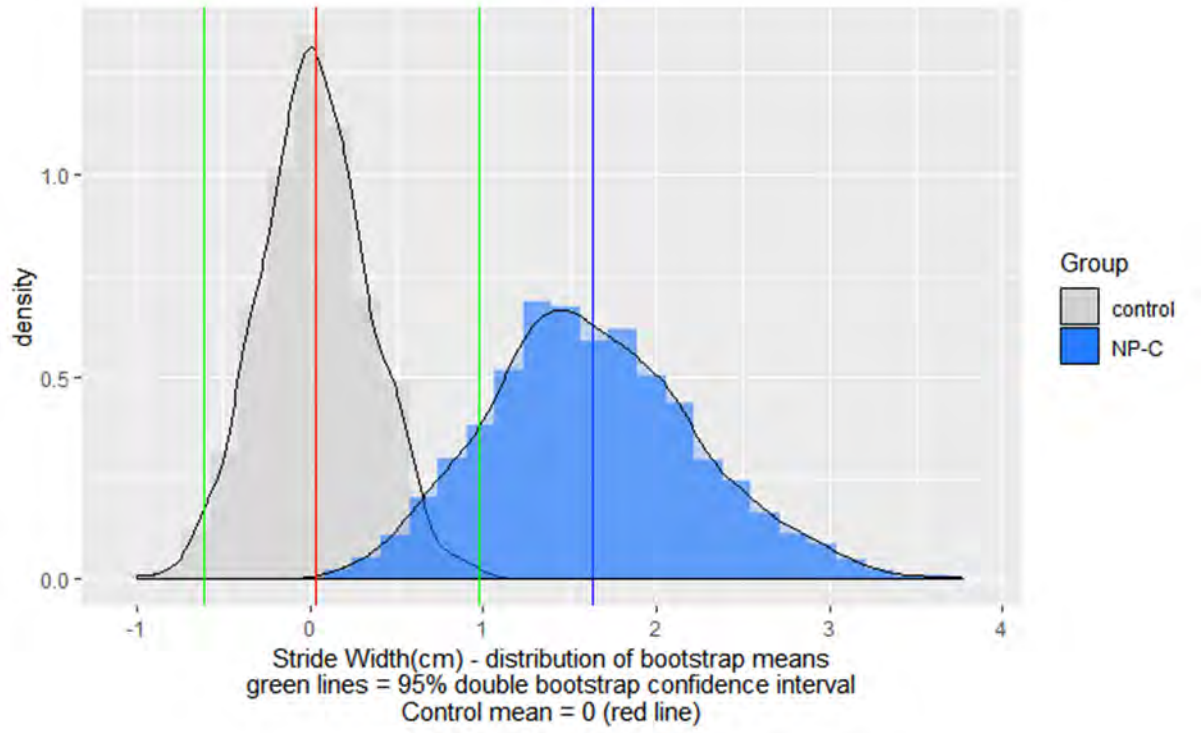


Figure 3.A8: The distribution of bootstrap means for NP-C patients and controls in stride width. Green lines are the 95% confidence intervals. Red line is the control mean. Blue line is the patients mean.

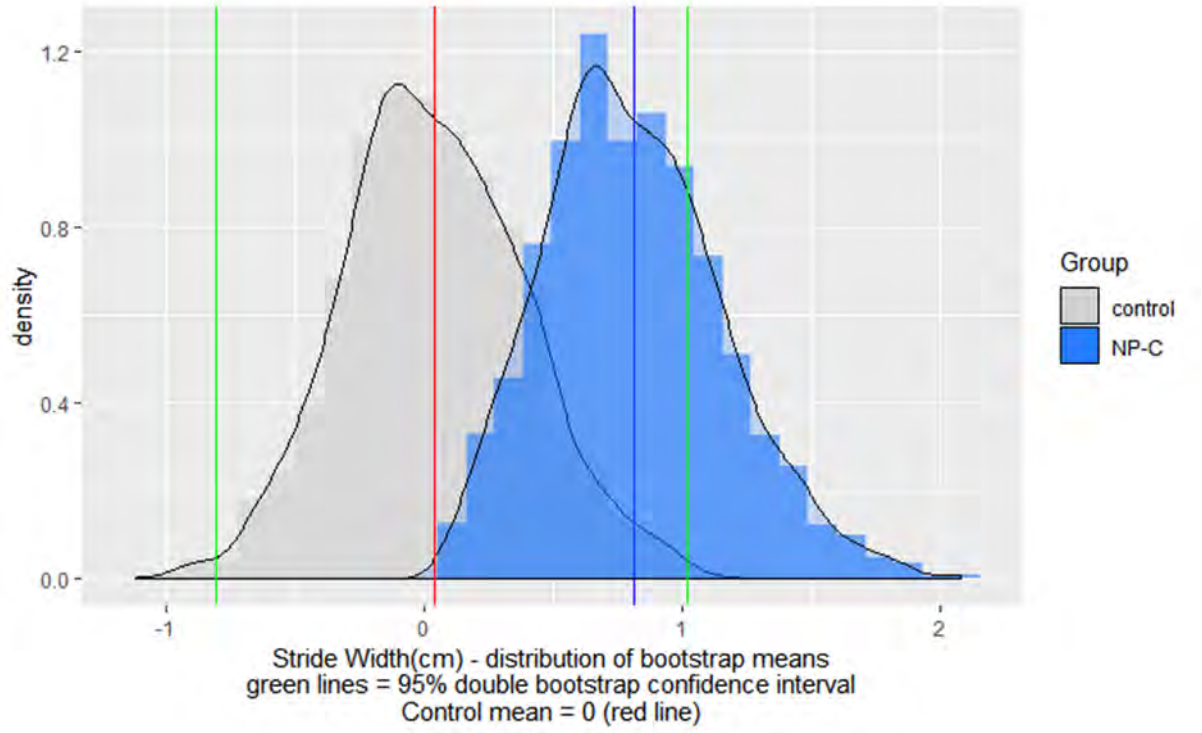


Figure 3.A9: The distribution of bootstrap means for NP-C patients and controls in stride width after removing the extreme patients‟ values. Green lines are the 95% confidence intervals. Red line is the control mean. Blue line is the patients mean.

B. *Fabry patient gait figures:*

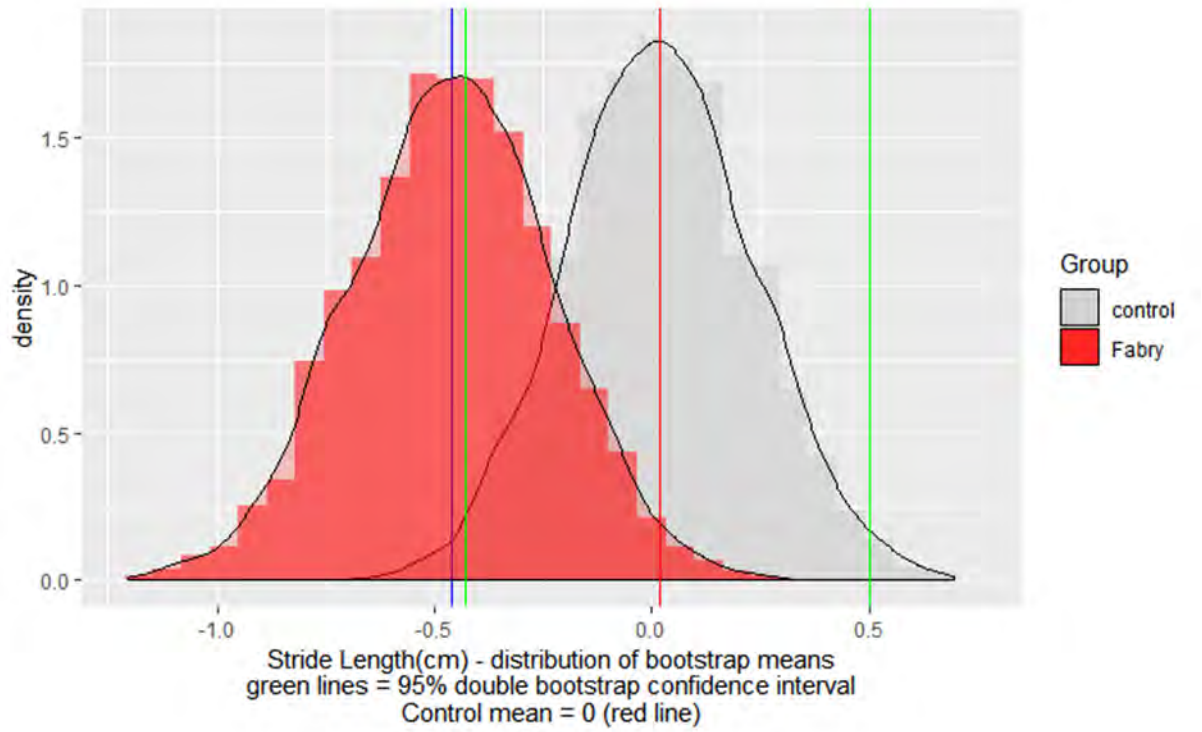


Figure 3.B1: The distribution of bootstrap means for Fabry patients and controls in stride length. Green lines are the 95% confidence intervals. Red line is the control mean. Blue line is the patients mean.

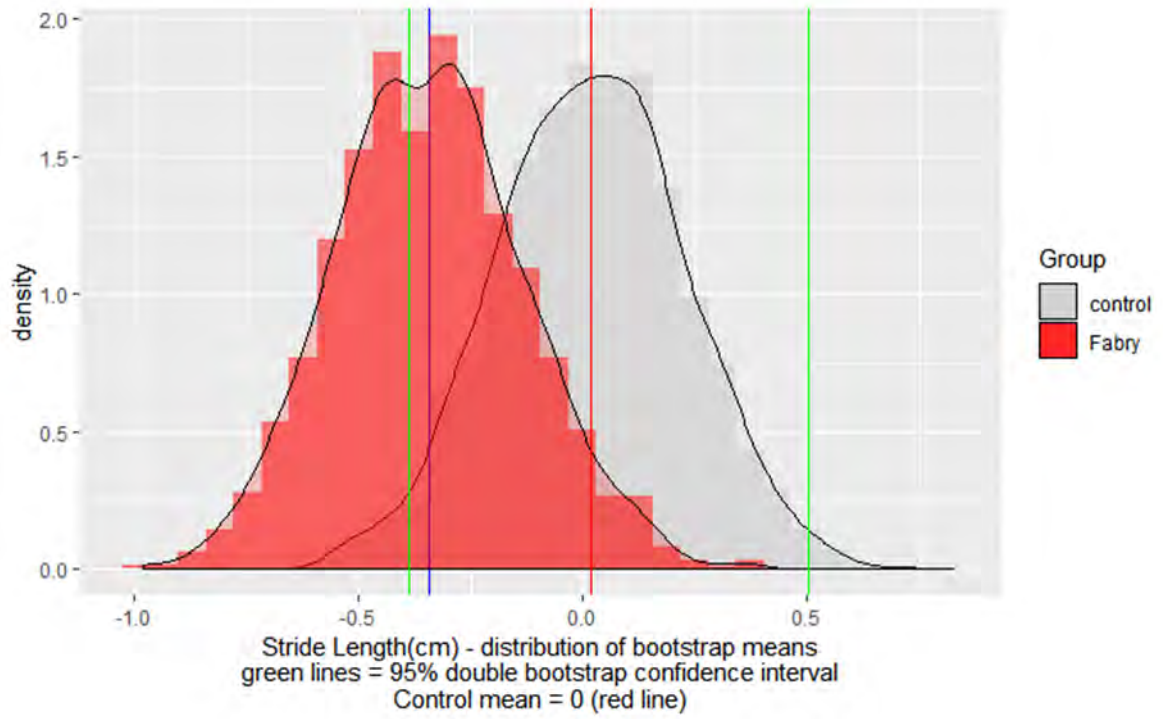


Figure 3.B2: The distribution of bootstrap means for Fabry patients and controls in stride length after removing the patient extreme value. Green lines are the 95% confidence intervals. Red line is the control mean. Blue line is the patients mean.

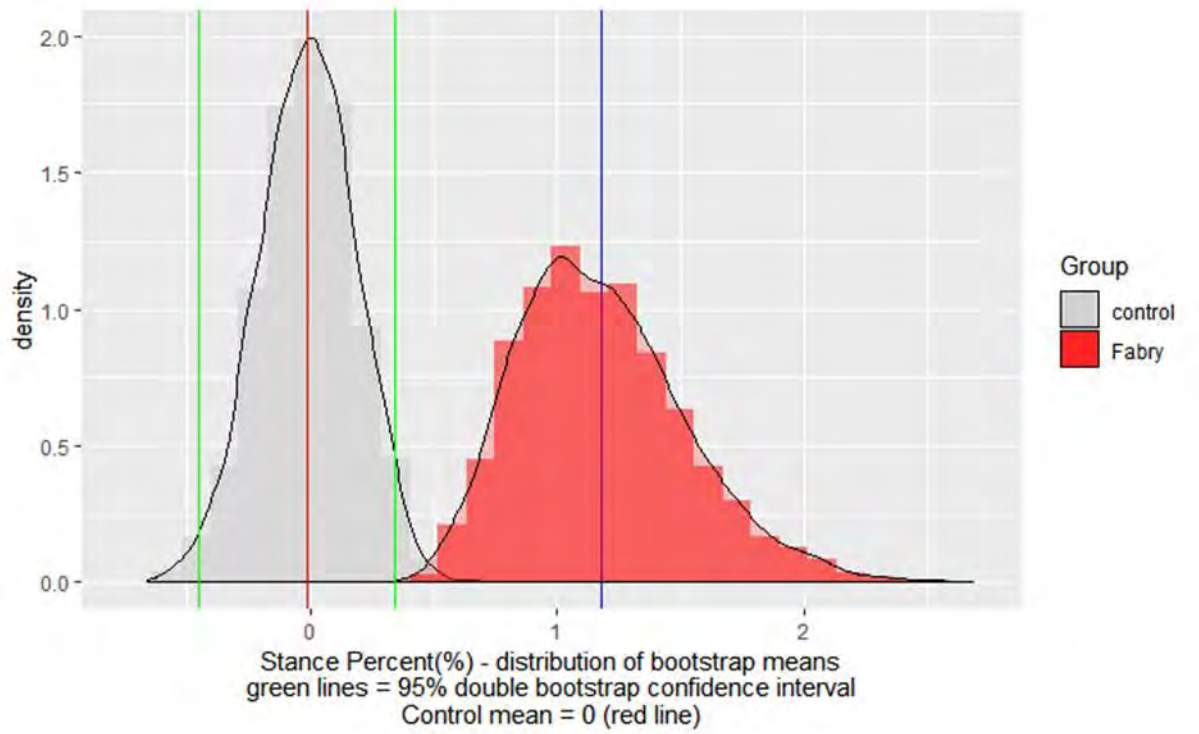


Figure 3.B3: The distribution of bootstrap means for Fabry patients and controls in stance percentage. Green lines are the 95% confidence intervals. Red line is the control mean. Blue line is the patients mean.

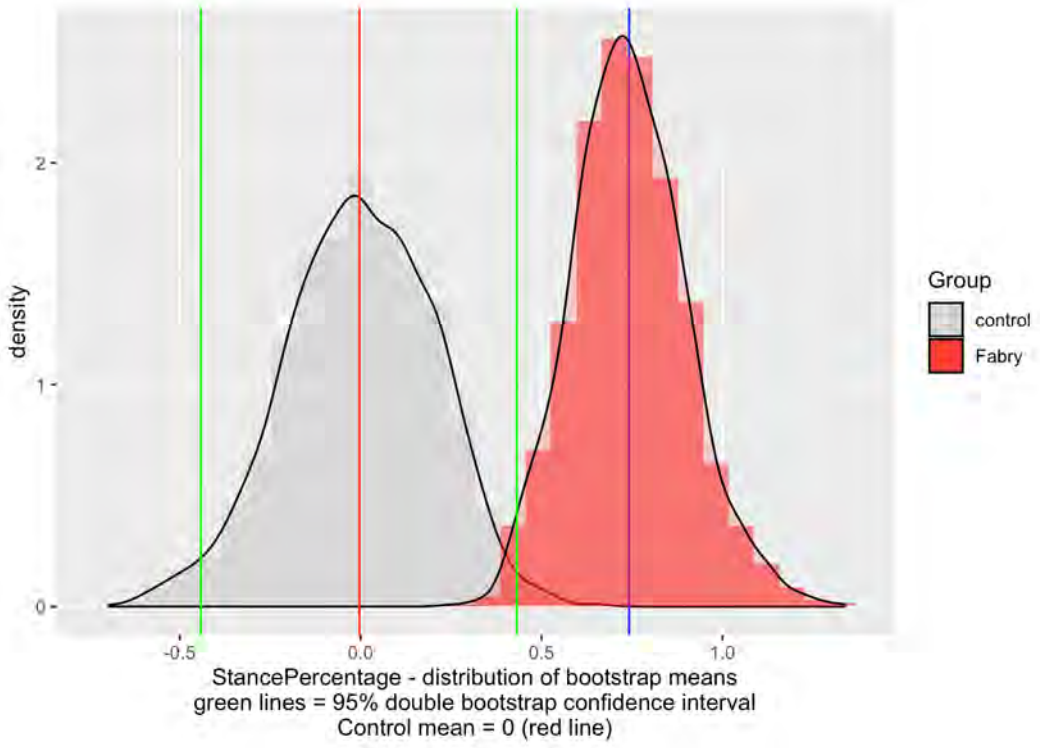


Figure 3.B4: The distribution of bootstrap means for Fabry patients and controls in stance percentage after removing the extreme patients‟ values. Green lines are the 95% confidence intervals. Red line is the control mean. Blue line is the patients mean.

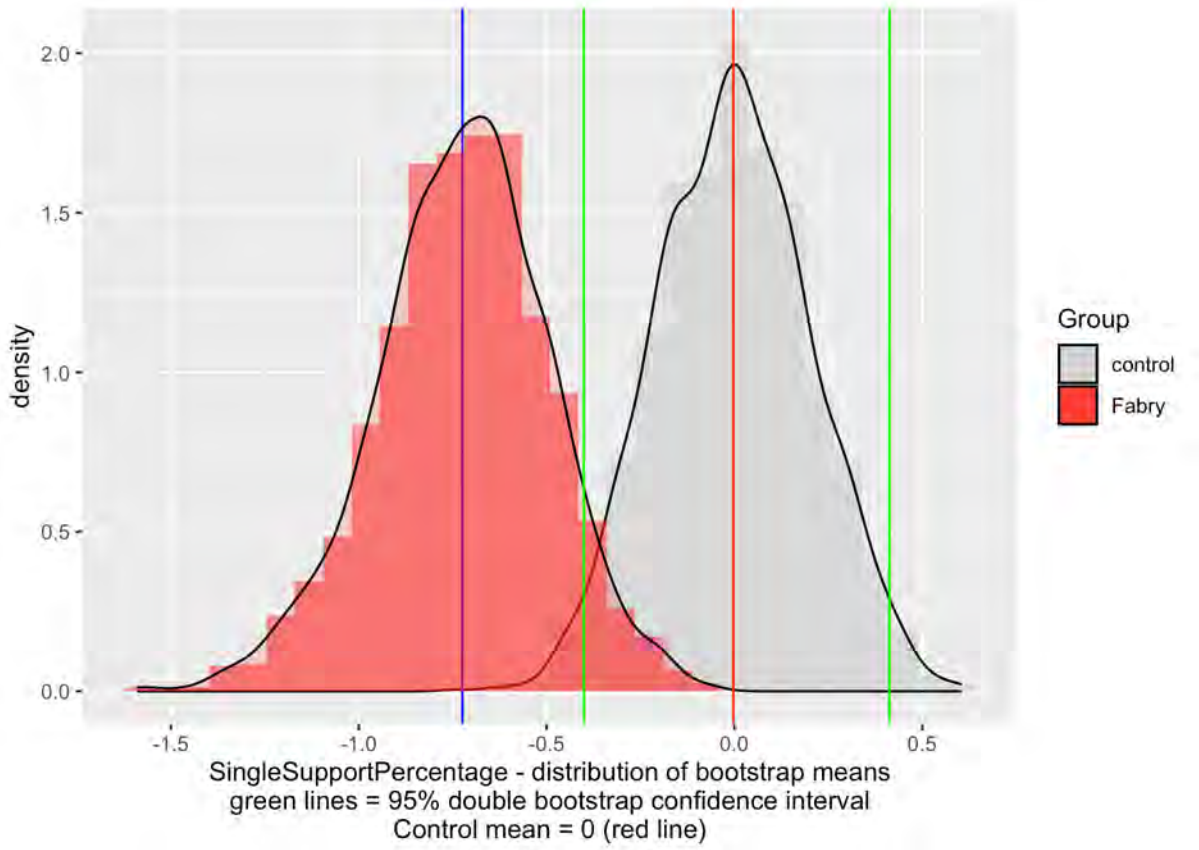


Figure 3.B5: The distribution of bootstrap means for Fabry patients and controls in single support percentage. Green lines are the 95% confidence intervals. Red line is the control mean. Blue line is the patients mean.

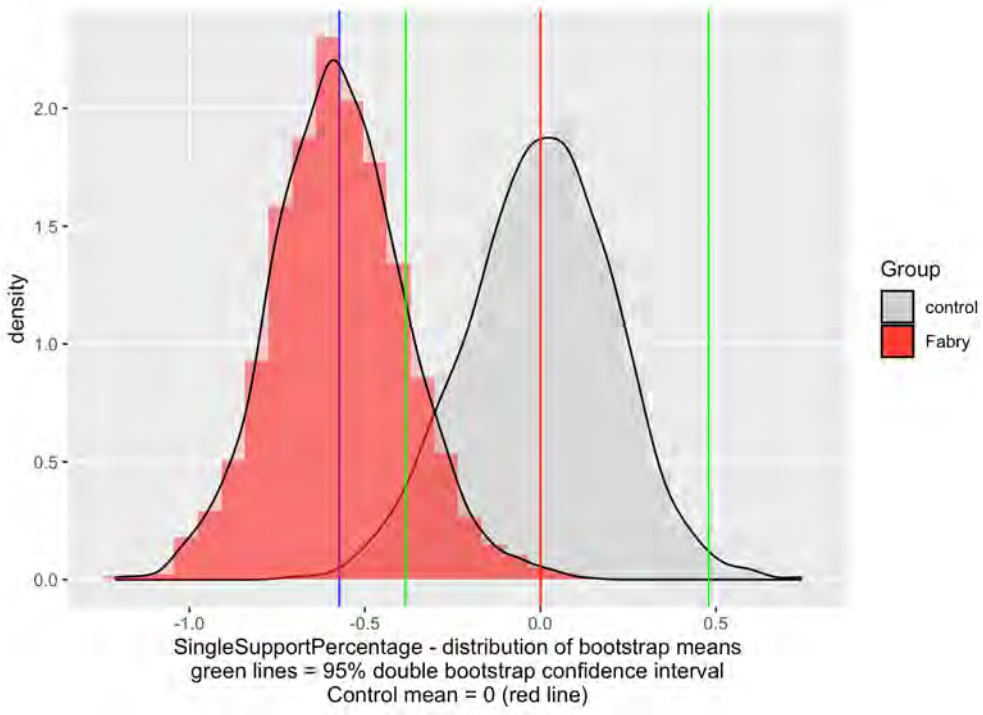


Figure 3.B6: The distribution of bootstrap means for Fabry patients and controls in single support percentage after removing the extreme patients‟ values. Green lines are the 95% confidence intervals. Red line is the control mean. Blue line is the patients mean.

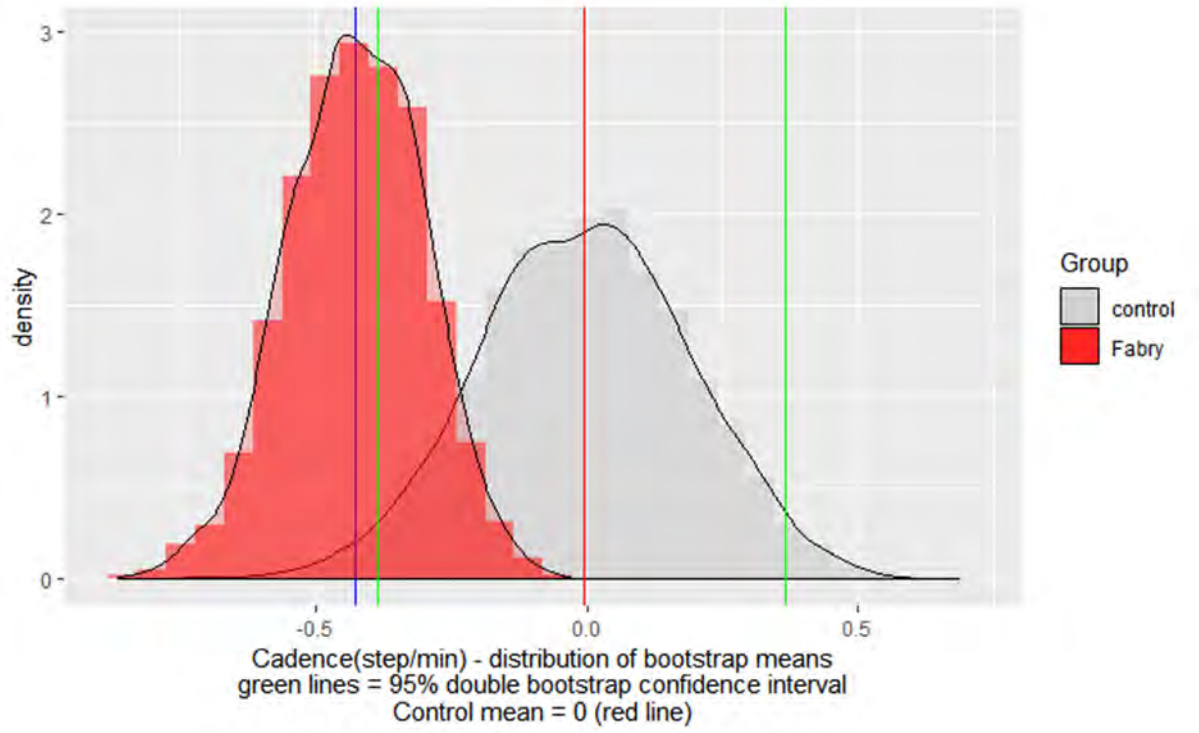


Figure 3.B7: The distribution of bootstrap means for Fabry patients and controls in cadence. Green lines are the 95% confidence intervals. Red line is the control mean. Blue line is the patients mean.

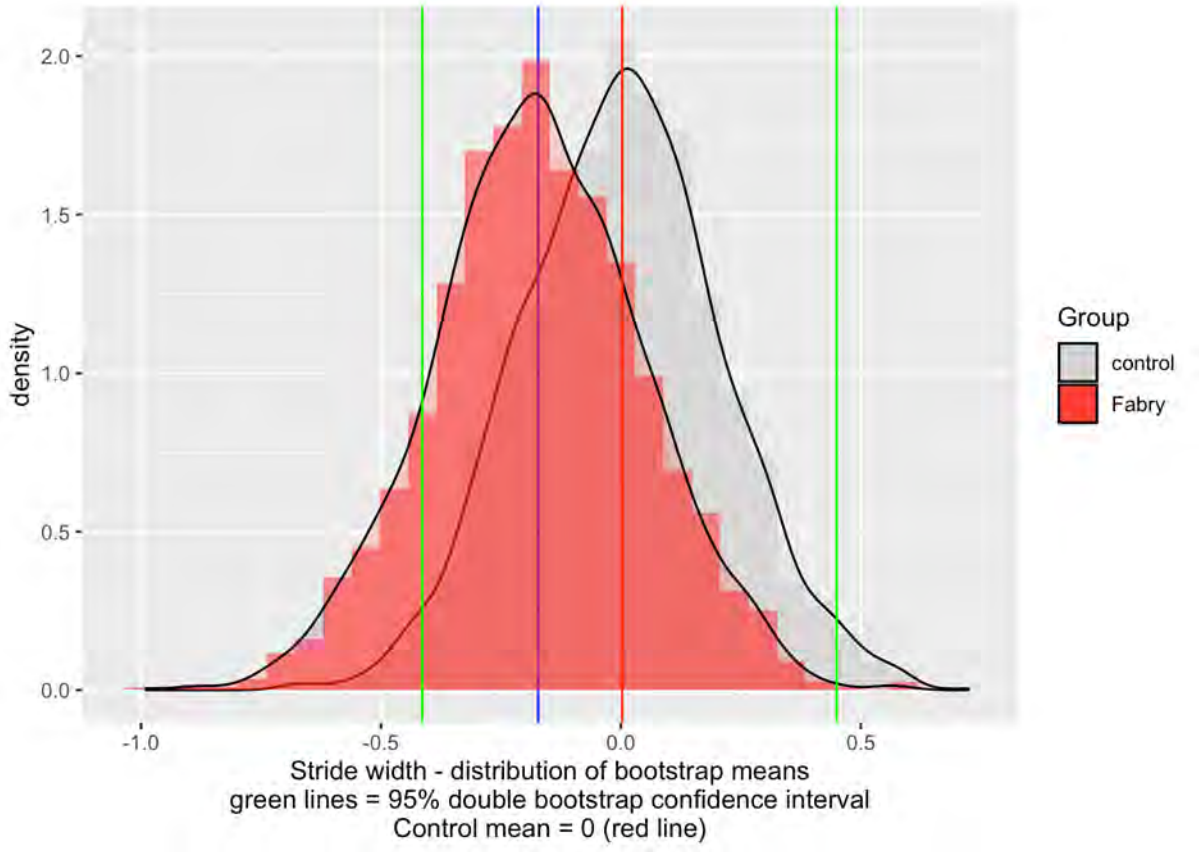


Figure 3.B8: The distribution of bootstrap means for Fabry patients and controls in stride width. Green lines are the 95% confidence intervals. Red line is the control mean. Blue line is the patients mean.

C. *Hurler patient gait figures:*

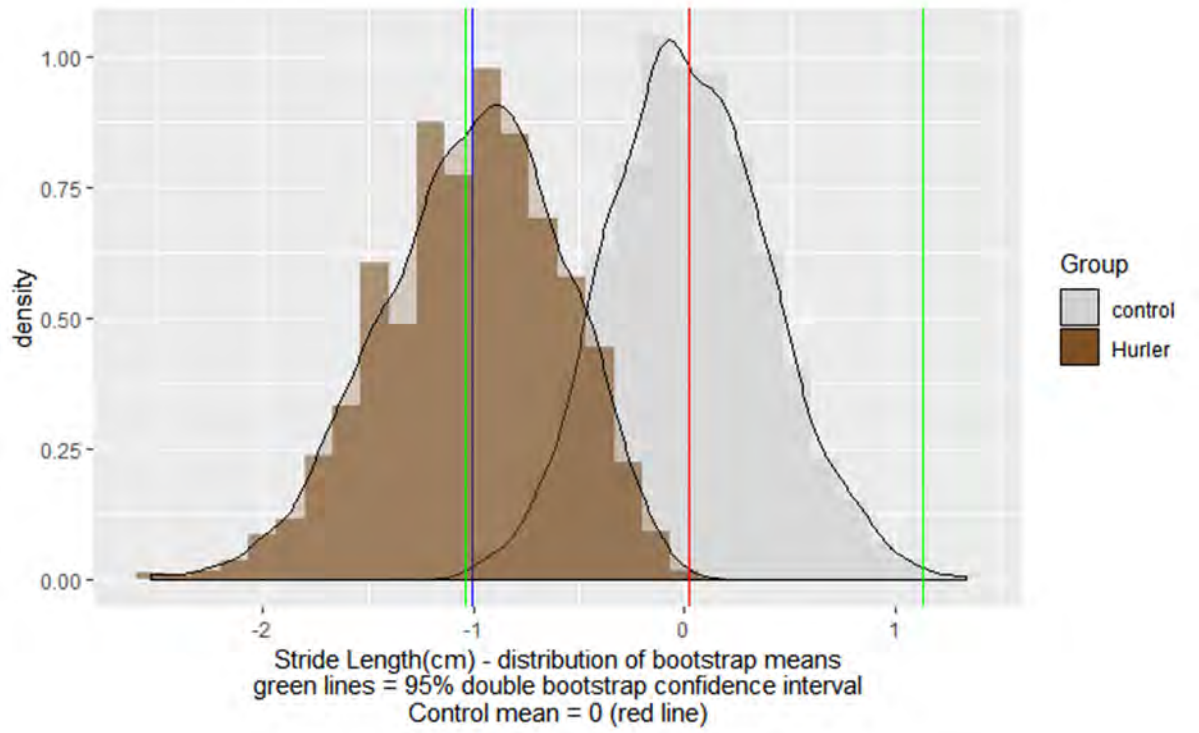


Figure 3.C1: The distribution of bootstrap means for Hurler patients and controls in stride length. Green lines are the 95% confidence intervals. Red line is the control mean. Blue line is the patients mean.

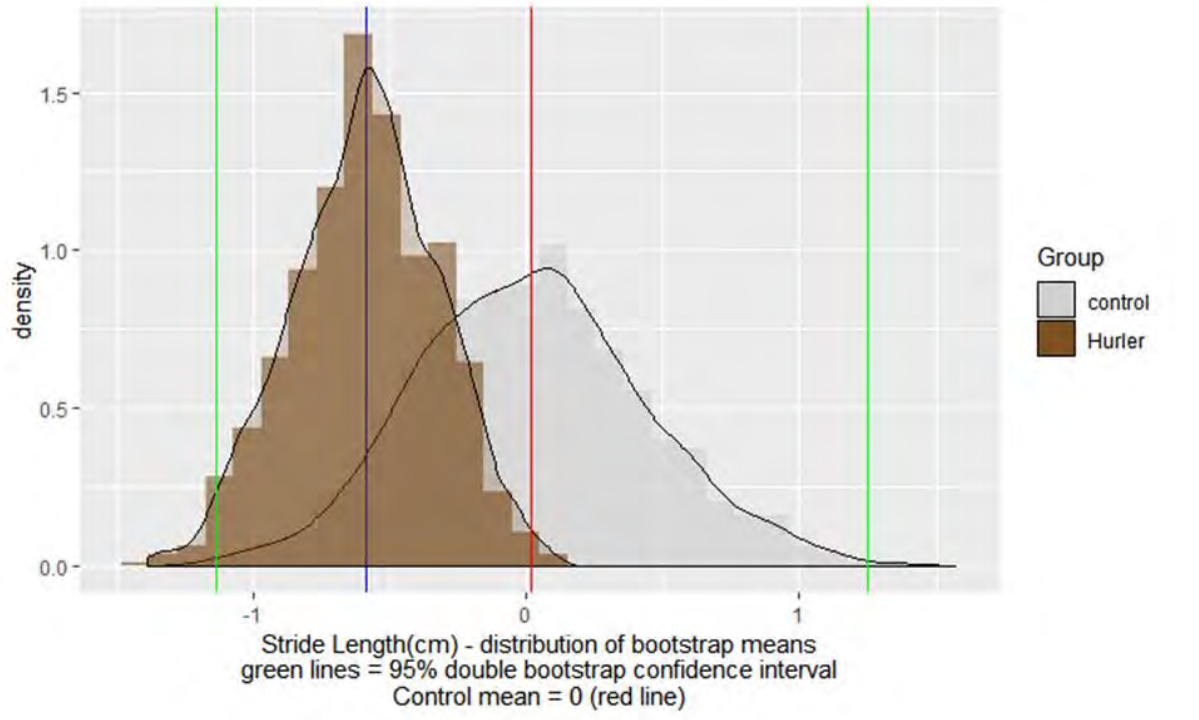


Figure 3.C2: The distribution of bootstrap means for Hurler patients and controls in stride length after removing the patient extreme value. Green lines are the 95% confidence intervals. Red line is the control mean. Blue line is the patients mean.

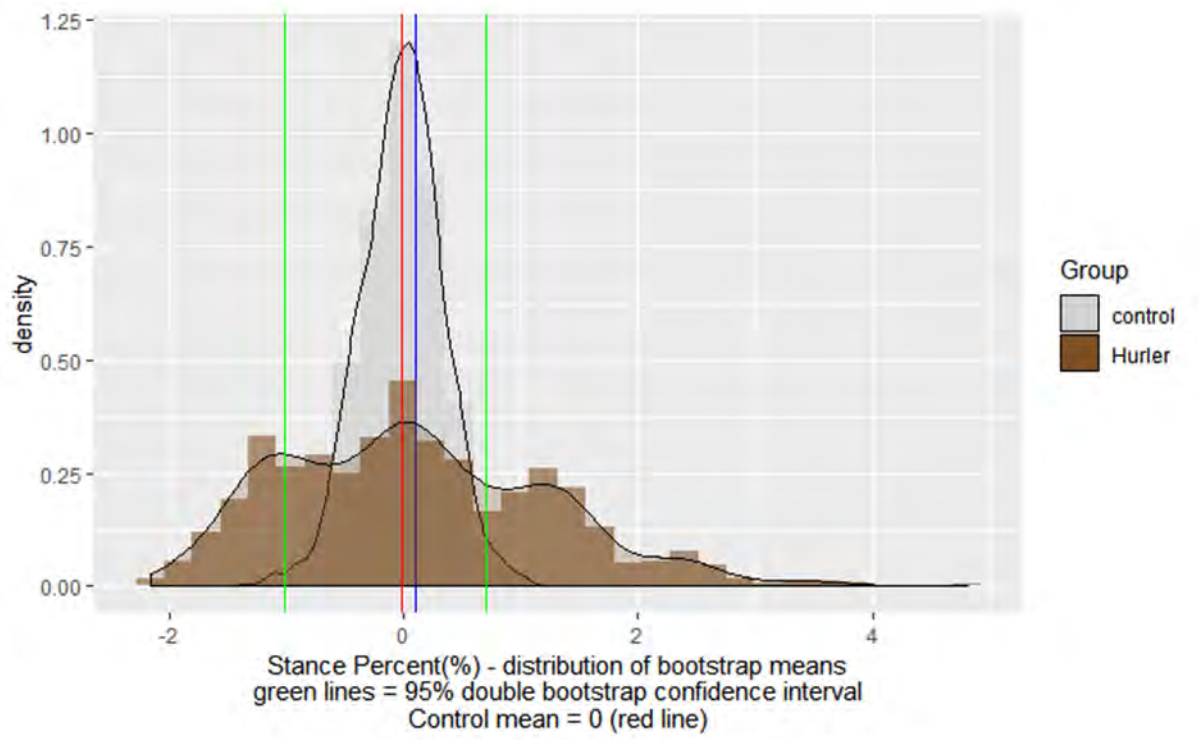


Figure 3.C3: The distribution of bootstrap means for Hurler patients and controls in stance percentage. Green lines are the 95% confidence intervals. Red line is the control mean. Blue line is the patients mean.

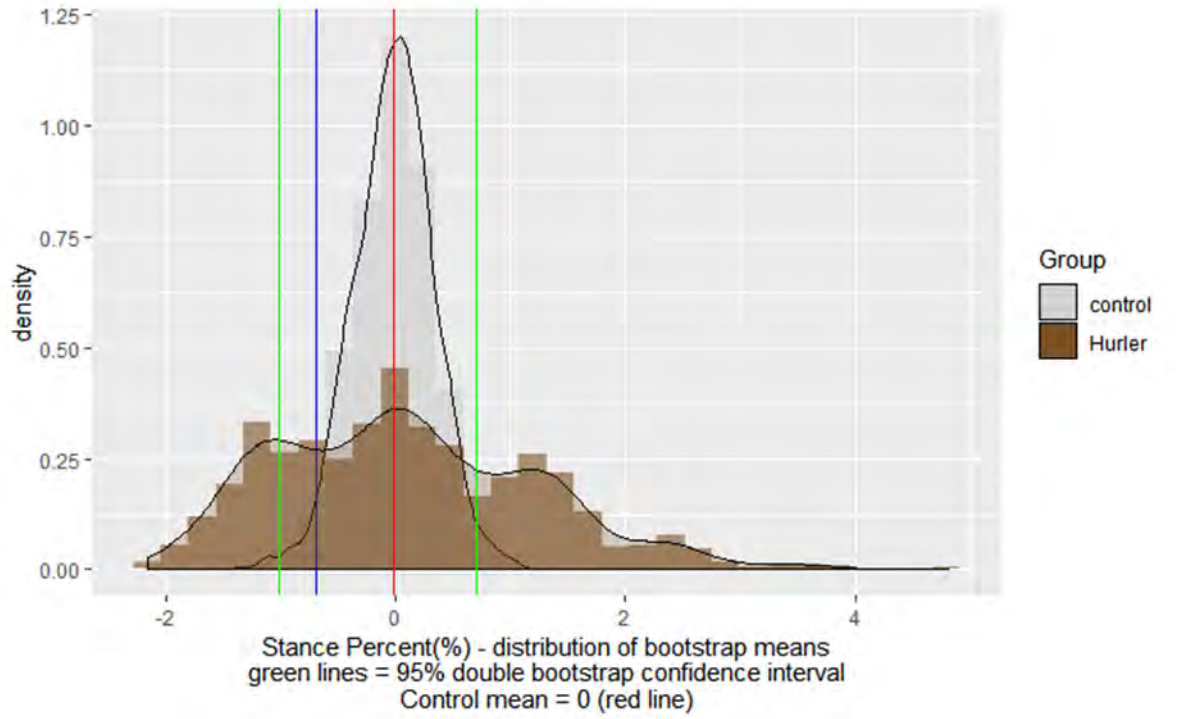


Figure 3.C4: The distribution of bootstrap means for Hurler patients and controls in stance percentage after removing the patient extreme value. Green lines are the 95% confidence intervals. Red line is the control mean. Blue line is the patients mean.

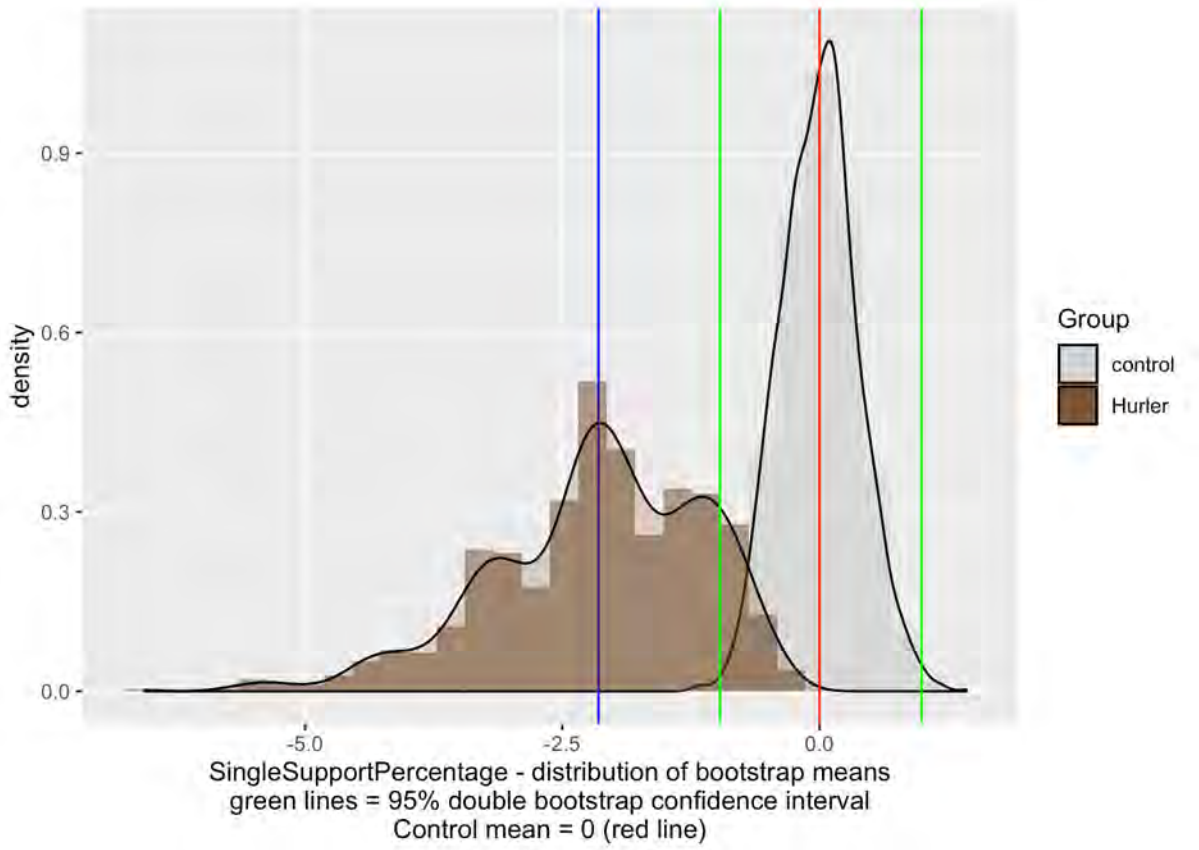


Figure 3.C5: The distribution of bootstrap means for Hurler patients and controls in single support percentage. Green lines are the 95% confidence intervals. Red line is the control mean. Blue line is the patients mean.

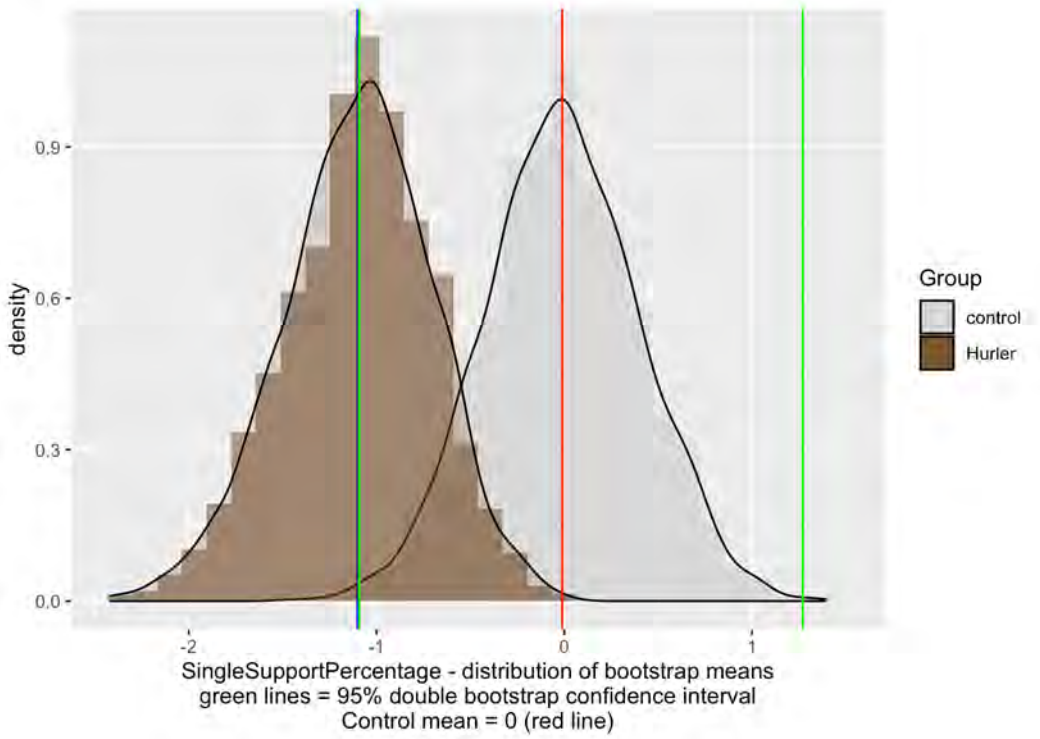


Figure 3.C6: The distribution of bootstrap means for Hurler patients and controls in single support percentage after removing the extreme value. Green lines are the 95% confidence intervals. Red line is the control mean. Blue line is the patients mean.

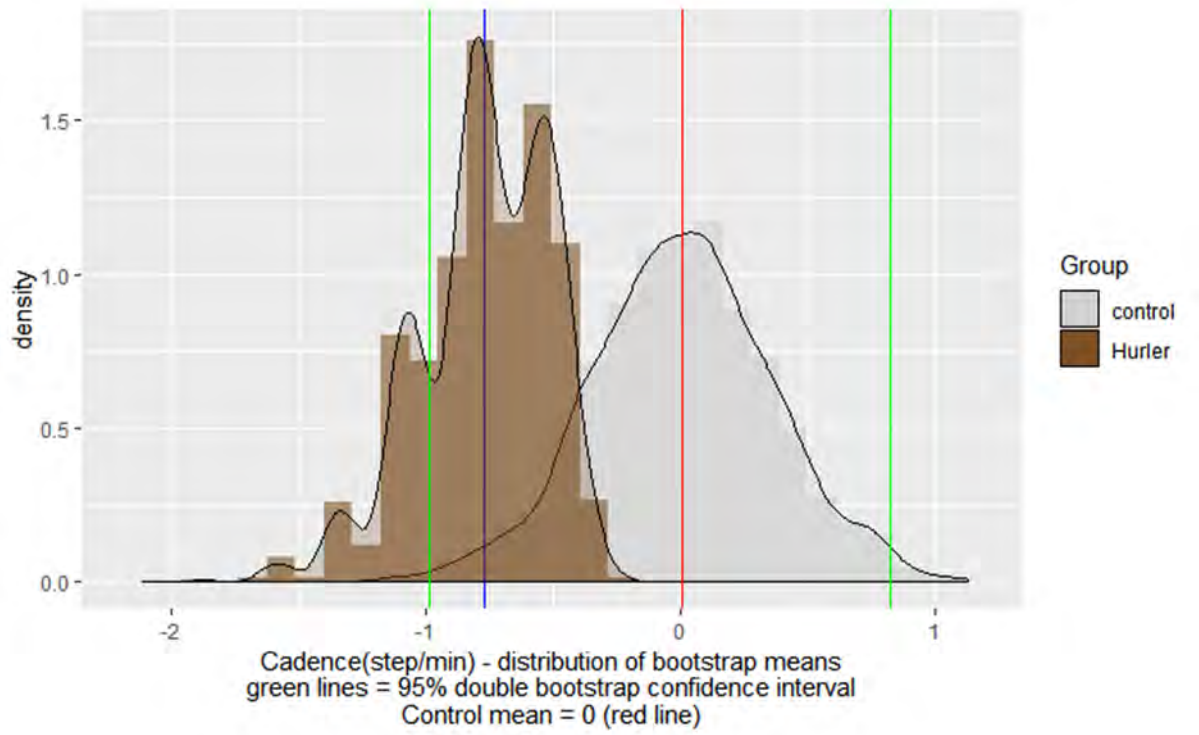


Figure 3.C7: The distribution of bootstrap means for Hurler patients and controls in cadence. Green lines are the 95% confidence intervals. Red line is the control mean. Blue line is the patients mean.

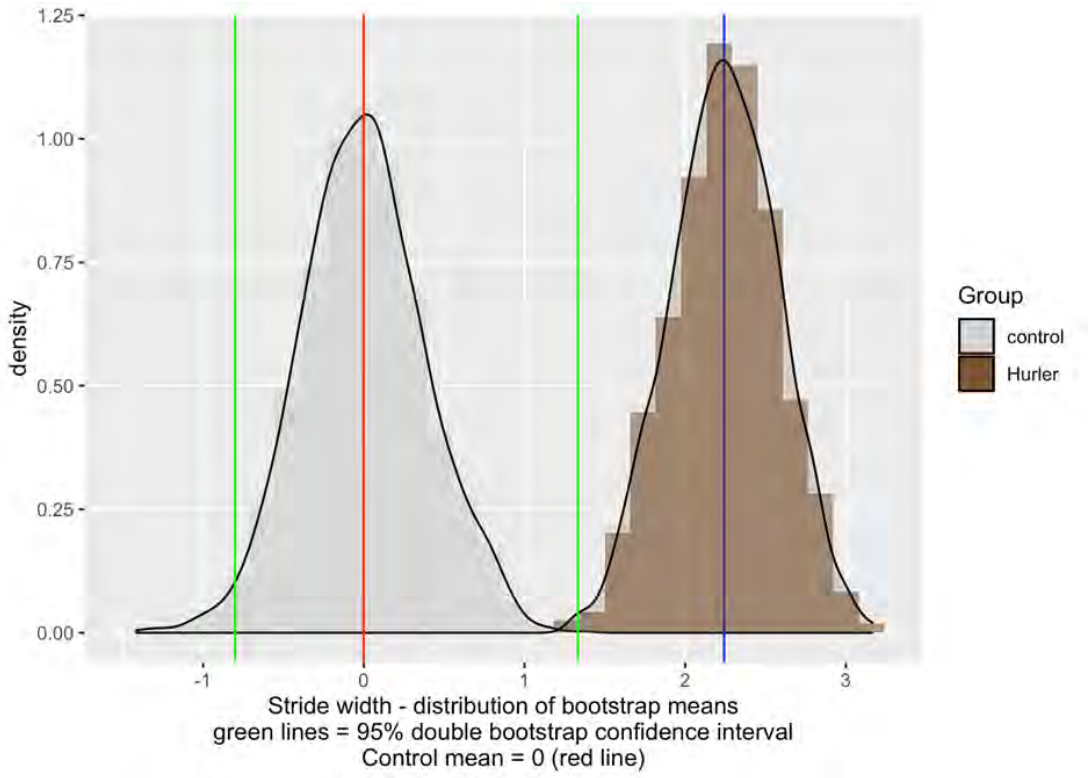


Figure 3.C8: The distribution of bootstrap means for Hurler patients and controls in stride width. Green lines are the 95% confidence intervals. Red line is the control mean. Blue line is the patients mean.

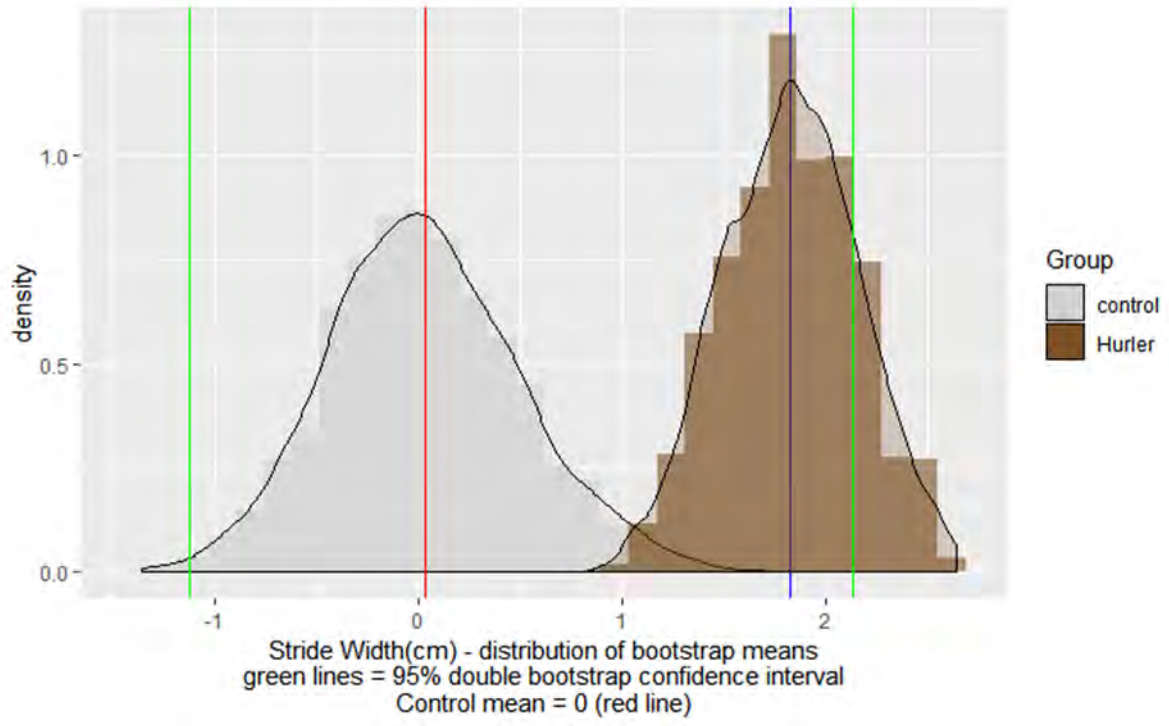


Figure 3.C9: The distribution of bootstrap means for Hurler patients and controls in stride width after removing extreme patients‟ values. Green lines are the 95% confidence intervals. Red line is the control mean. Blue line is the patients mean.

Appendix 4

A. NP-C patient balance figures:

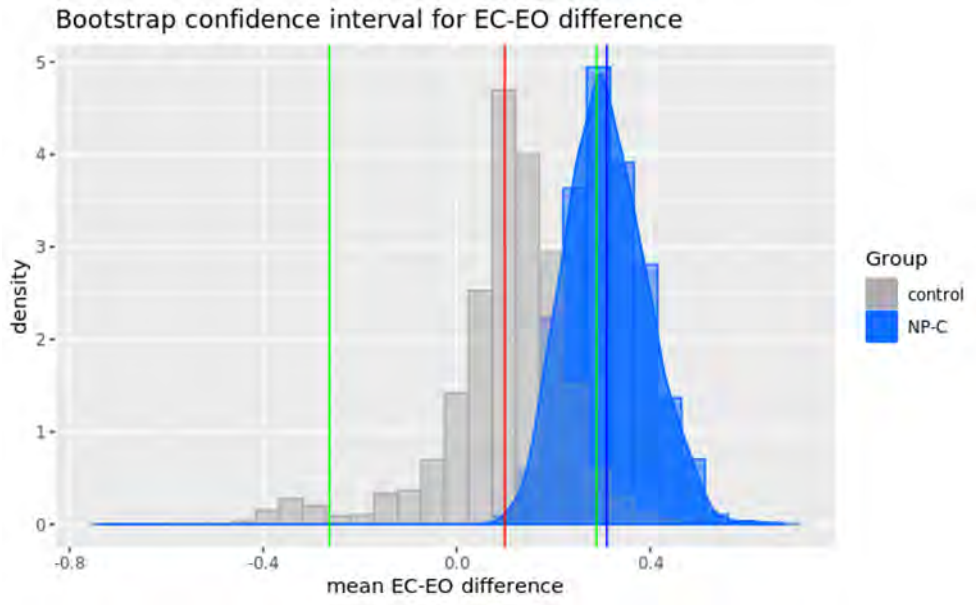


Figure 4.A1: The distribution of bootstrap means for NP-C patients and controls in jerk EC/EO difference. Green lines are the control 95% confidence intervals. Red line is the control mean. Blue line is the patients mean.

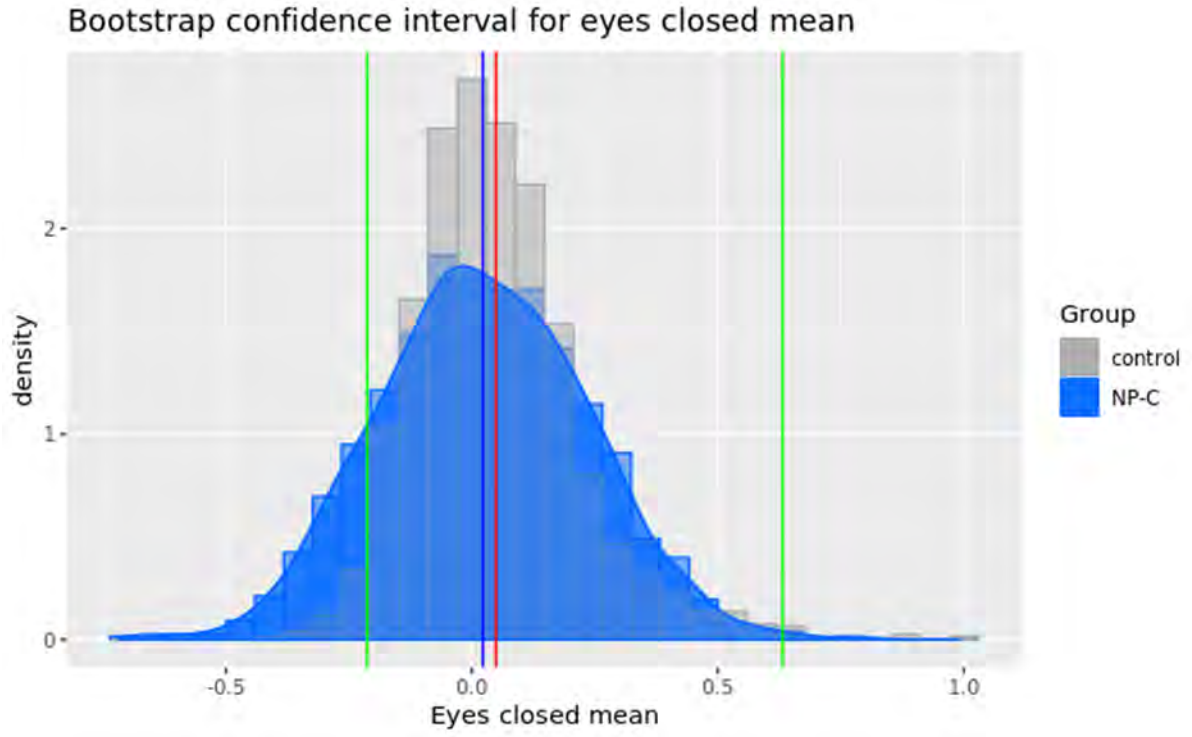


Figure 4.A2: The distribution of bootstrap means for NP-C patients and controls in jerk EC condition. Green lines are the control 95% confidence intervals. Red line is the control mean. Blue line is the patients mean.

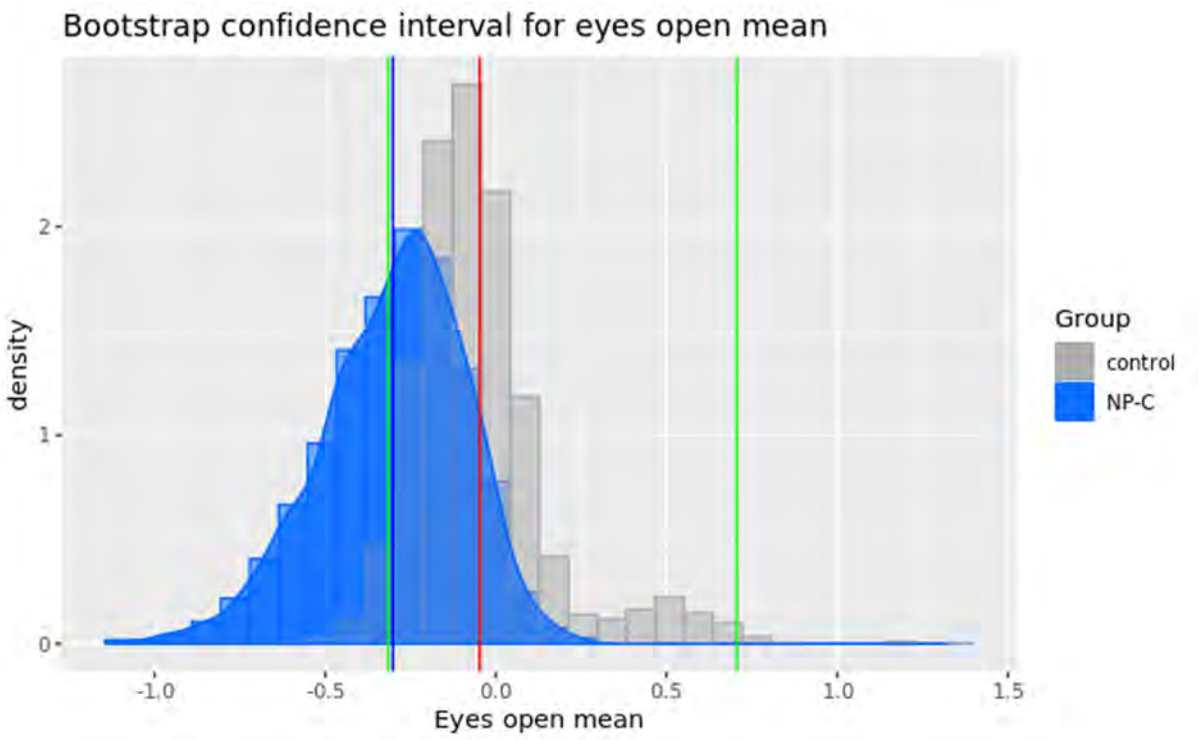


Figure 4.A3: The distribution of bootstrap means for NP-C patients and controls in jerk EO condition. Green lines are the control 95% confidence intervals. Red line is the control mean. Blue line is the patients mean.

B. Fabry patient balance figures:

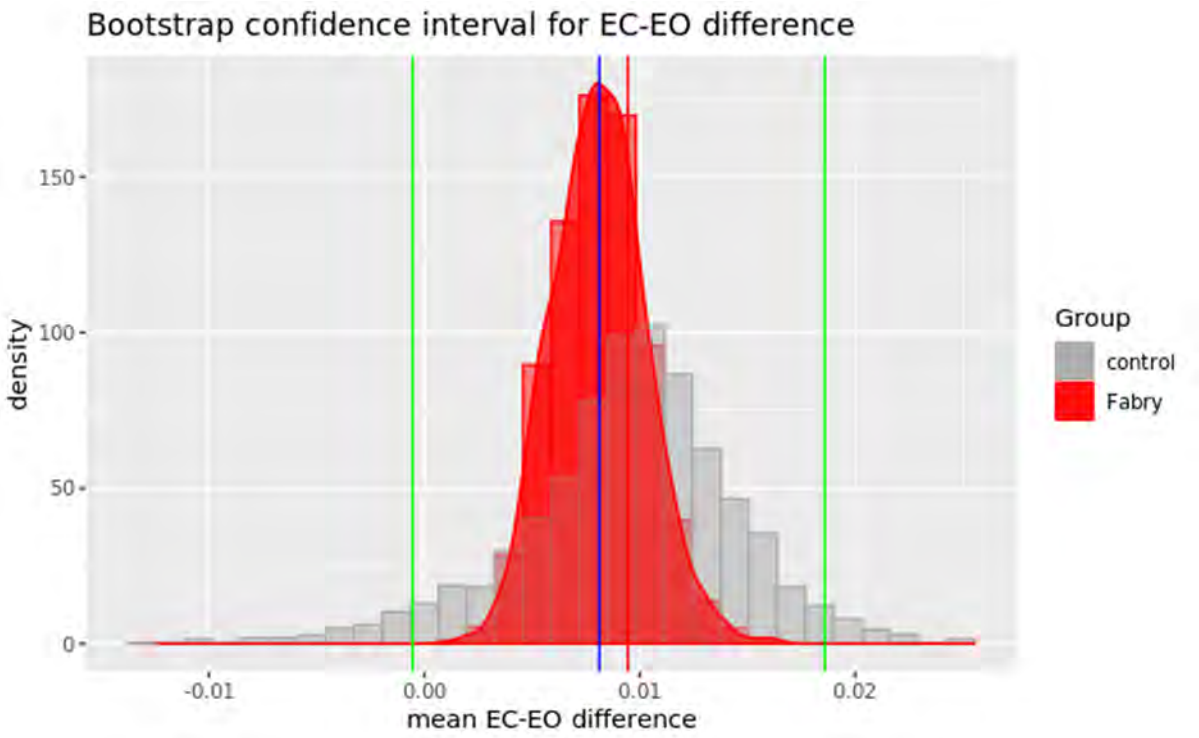


Figure 4.B1: The distribution of bootstrap means for Fabry patients and controls in RMS EC/EO difference. Green lines are the control 95% confidence intervals. Red line is the control mean. Blue line is the patients mean.

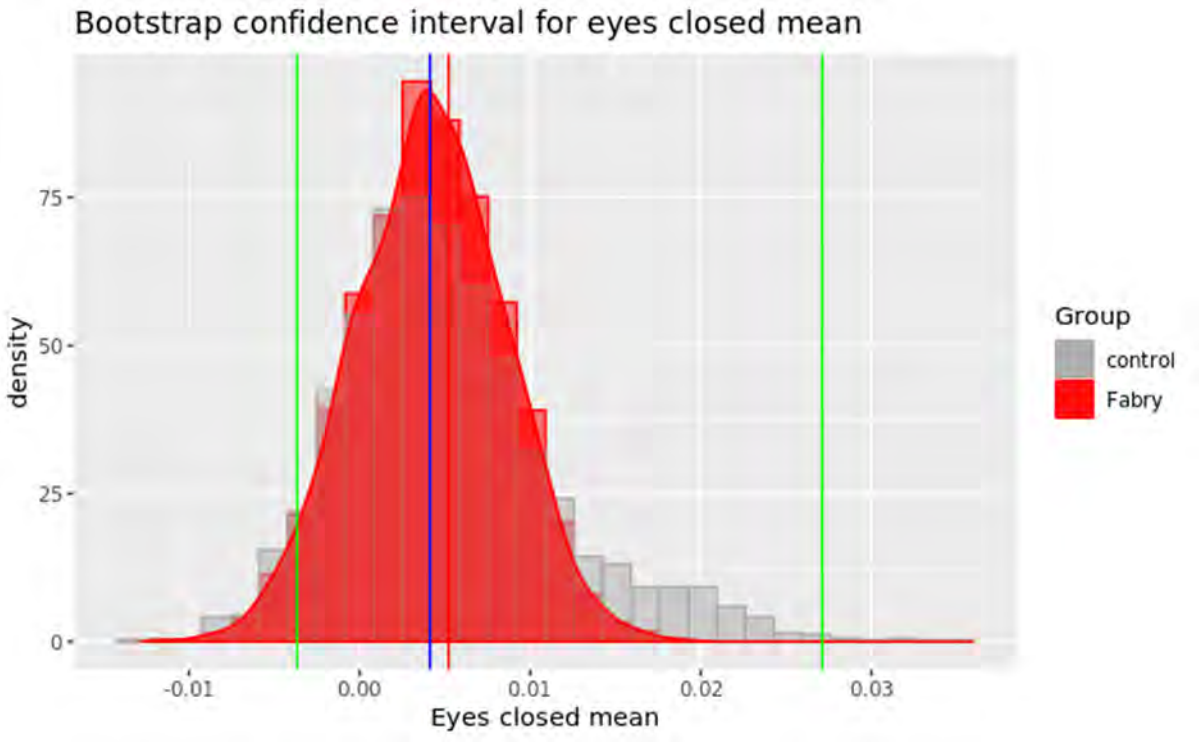


Figure 4.B2: The distribution of bootstrap means for Fabry patients and controls in RMS EC condition. Green lines are the control 95% confidence intervals. Red line is the control mean. Blue line is the patients mean.

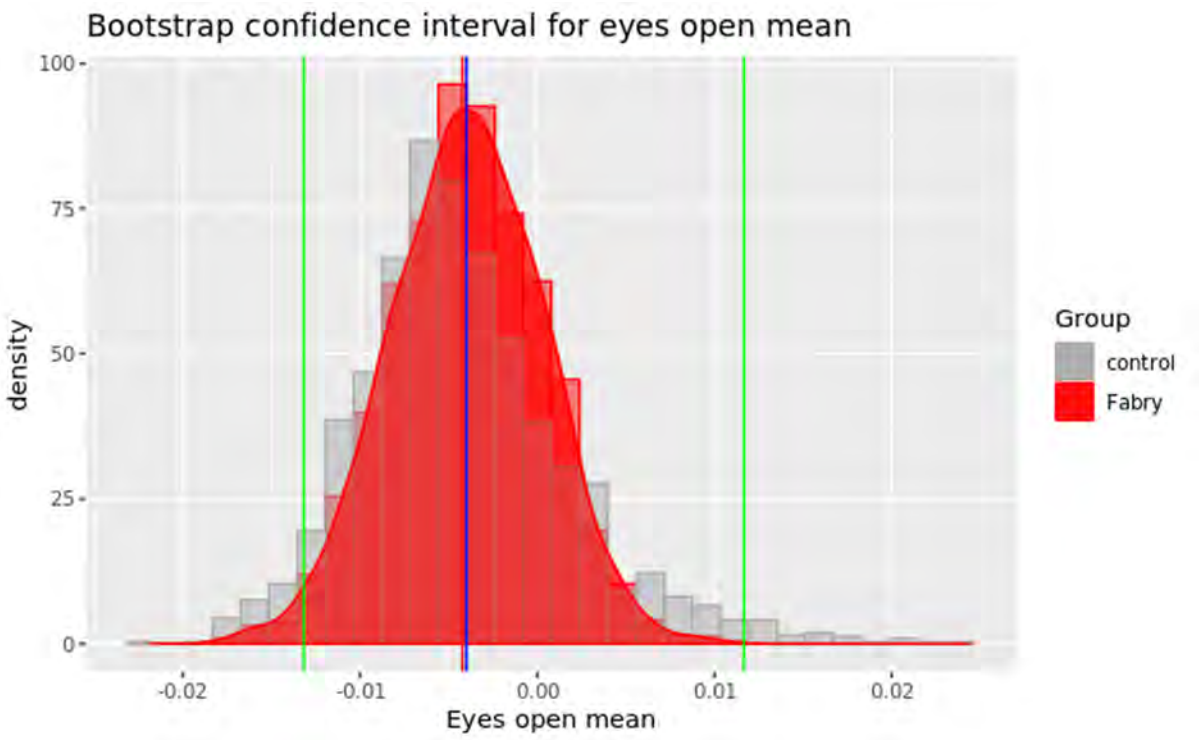


Figure 4.B3: The distribution of bootstrap means for Fabry patients and controls in RMS EO condition. Green lines are the control 95% confidence intervals. Red line is the control mean. Blue line is the patients mean.

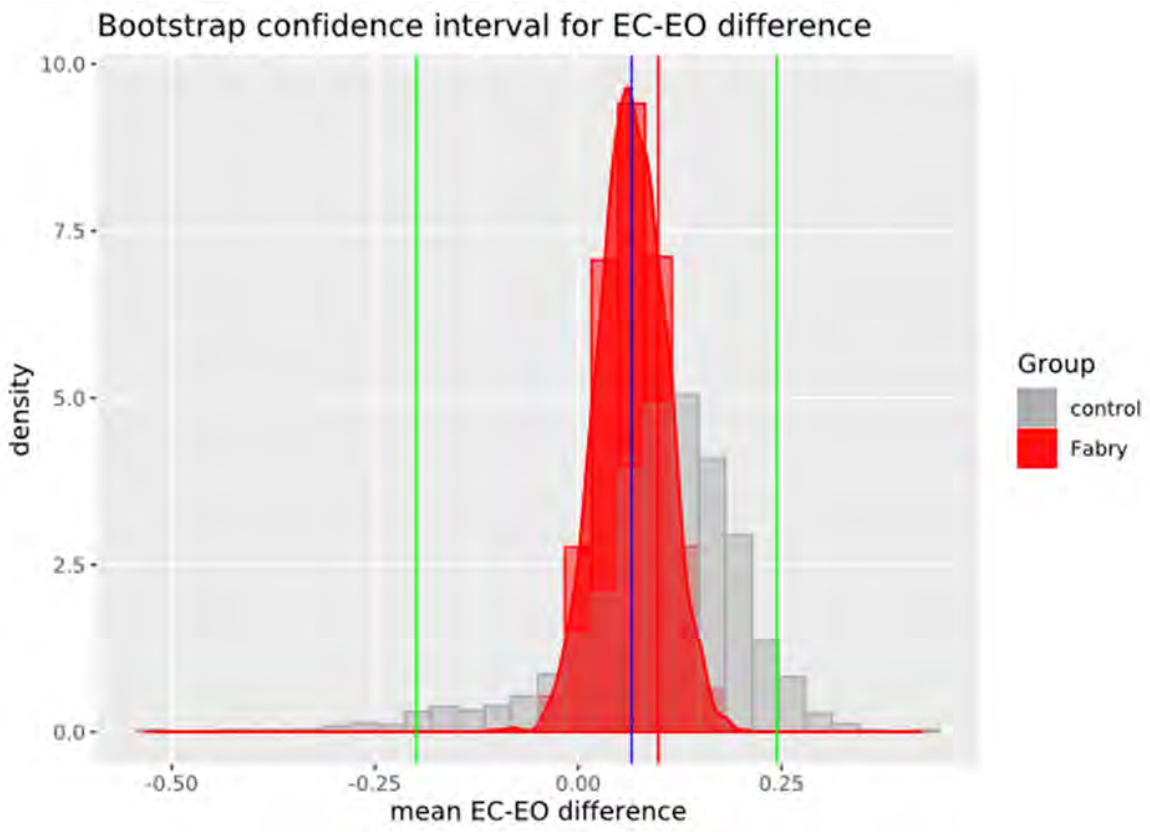


Figure 4.B4: The distribution of bootstrap means for Fabry patients and controls in jerk EC/EO difference. Green lines are the control 95% confidence intervals. Red line is the control mean. Blue line is the patients mean.

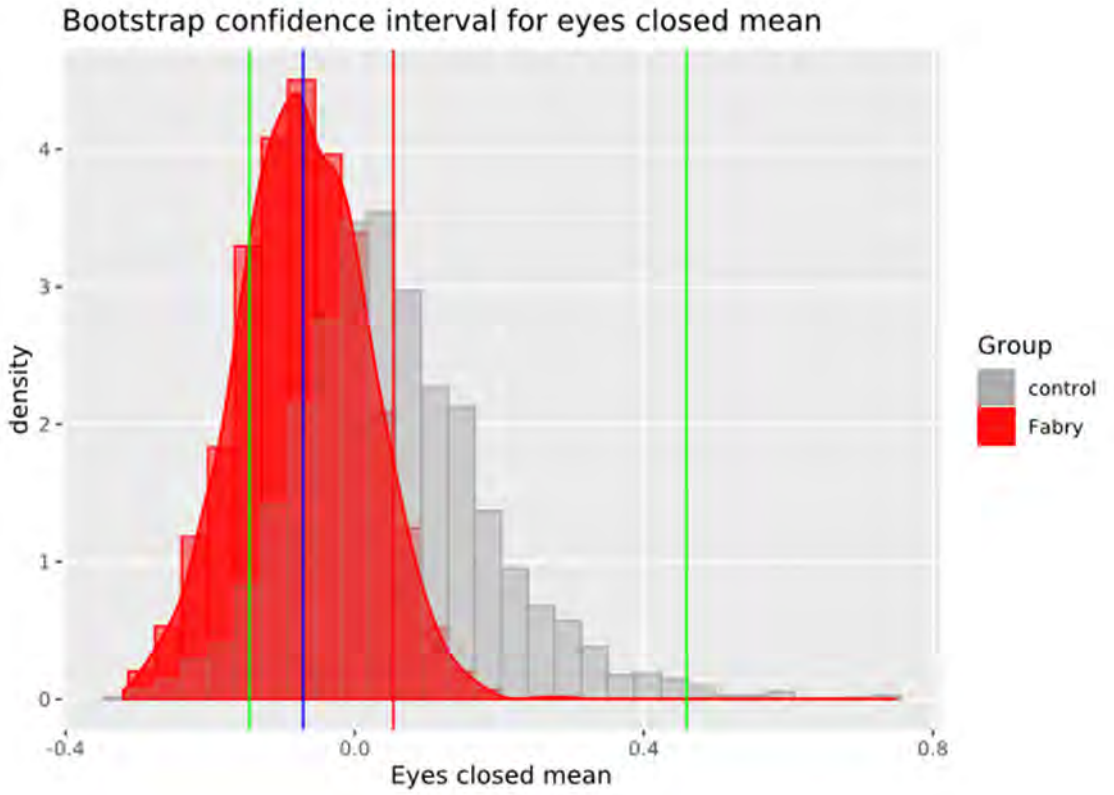


Figure 4.B5: The distribution of bootstrap means for Fabry patients and controls in jerk EC condition. Green lines are the control 95% confidence intervals. Red line is the control mean. Blue line is the patients mean.

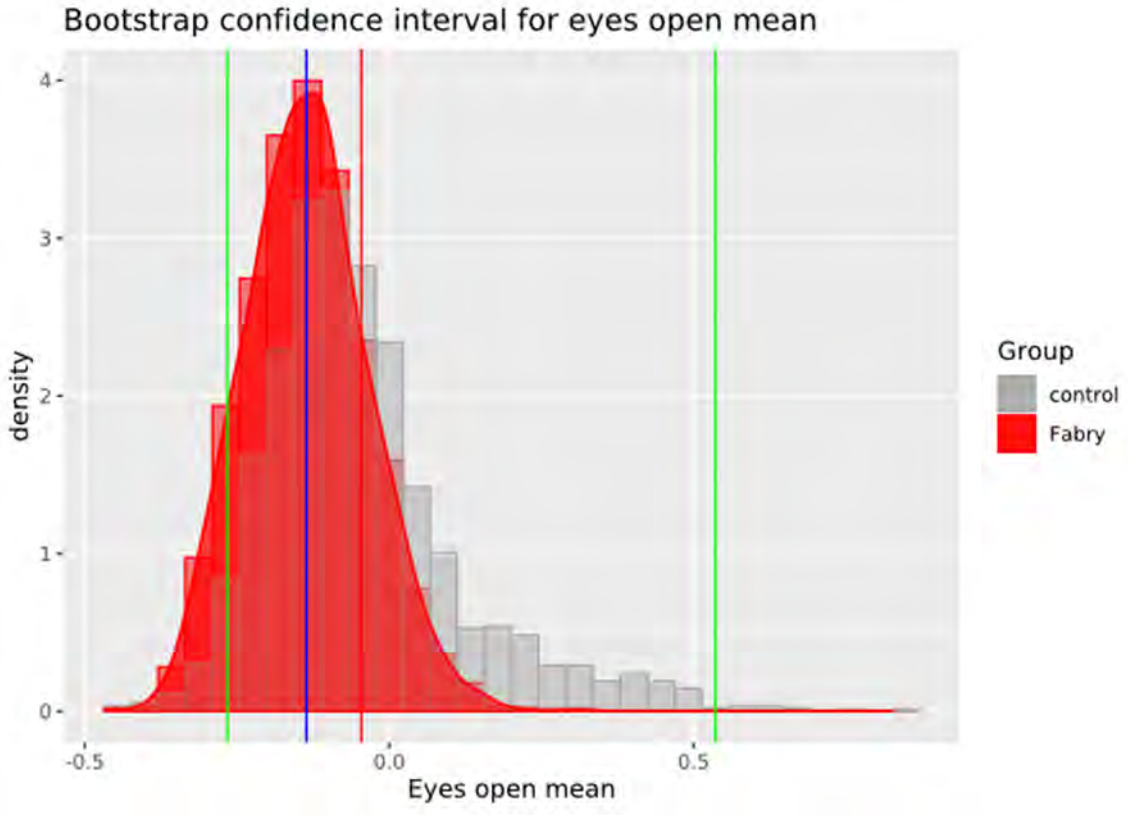


Figure 4.B6: The distribution of bootstrap means for Fabry patients and controls in jerk EO condition. Green lines are the control 95% confidence intervals. Red line is the control mean. Blue line is the patients mean.

C. *Hurler patient balance figures:*

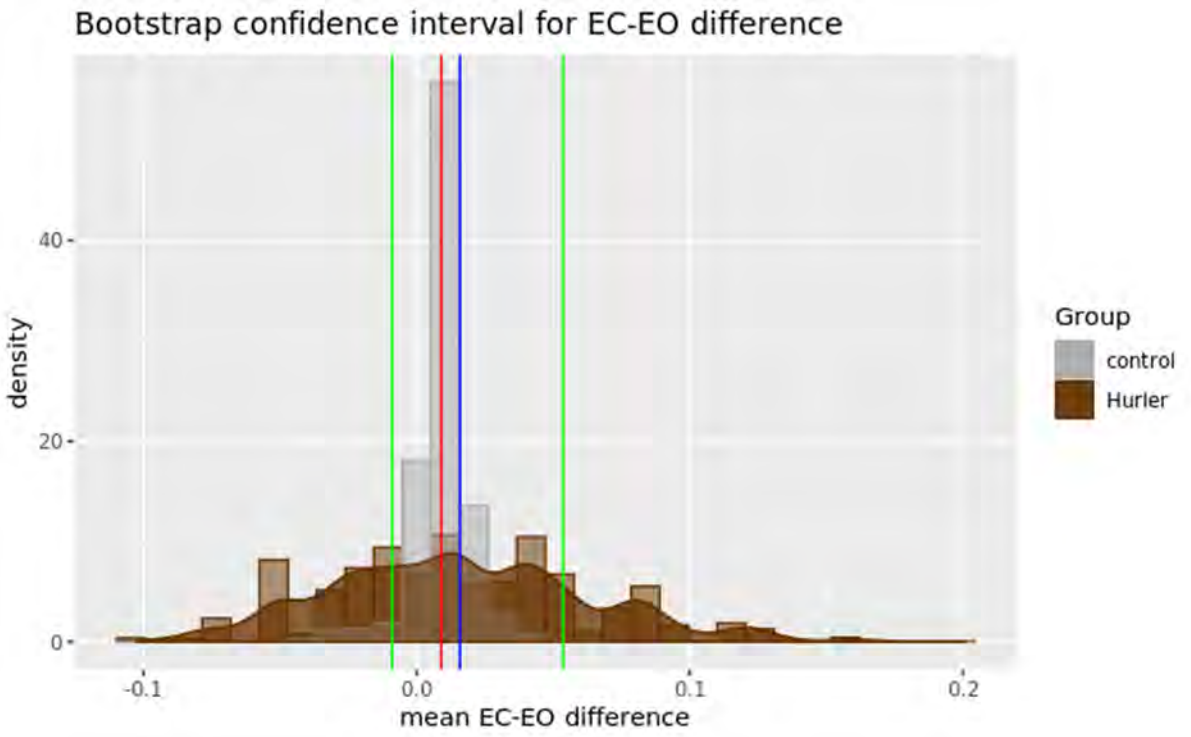


Figure 4.C1: The distribution of bootstrap means for Hurler patients and controls in RMS EC/EO difference. Green lines are the control 95% confidence intervals. Red line is the control mean. Blue line is the patients mean.

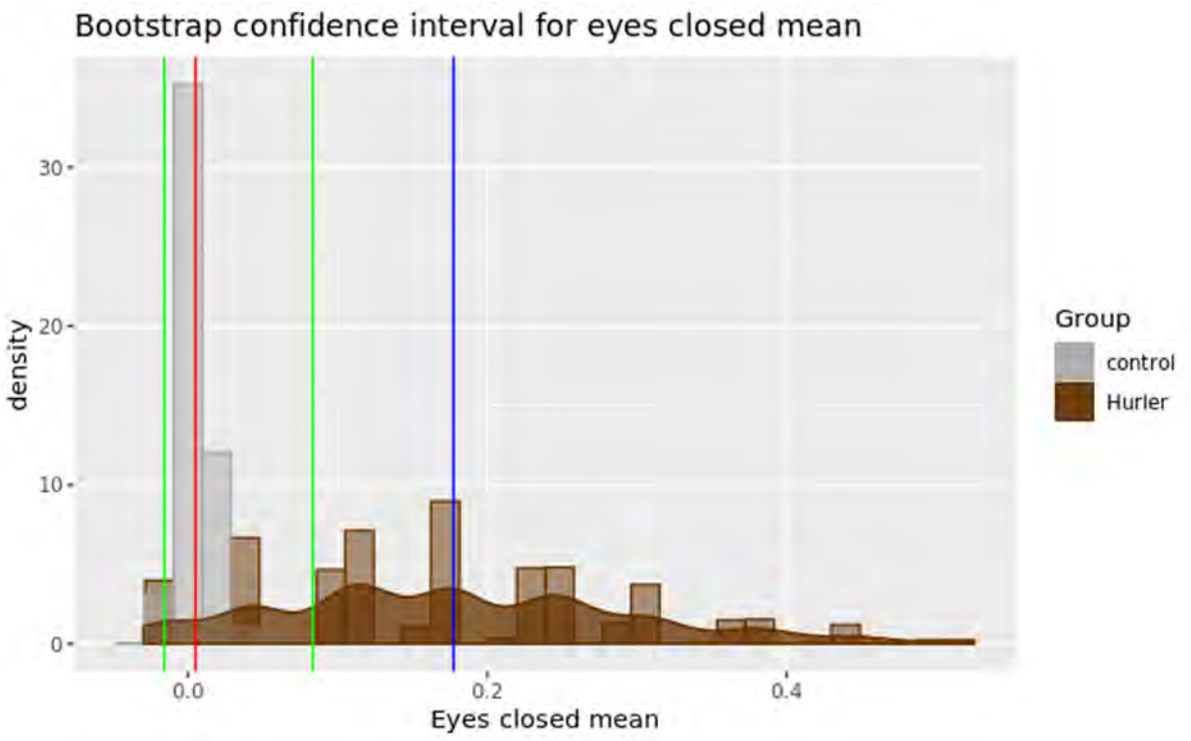


Figure 4.C2: The distribution of bootstrap means for Hurler patients and controls in RMS EC condition. Green lines are the control 95% confidence intervals. Red line is the control mean. Blue line is the patients mean.

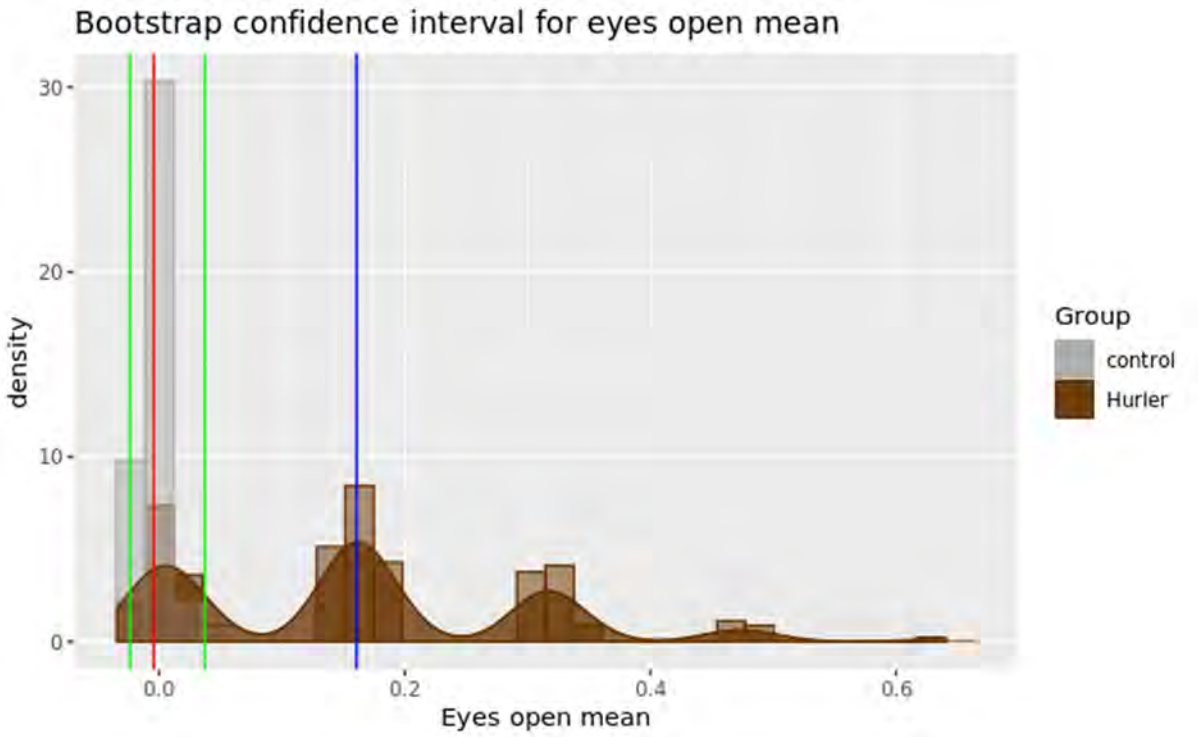


Figure 4.C3: The distribution of bootstrap means for Hurler patients and controls in RMS EO condition. Green lines are the control 95% confidence intervals. Red line is the control mean. Blue line is the patients mean.

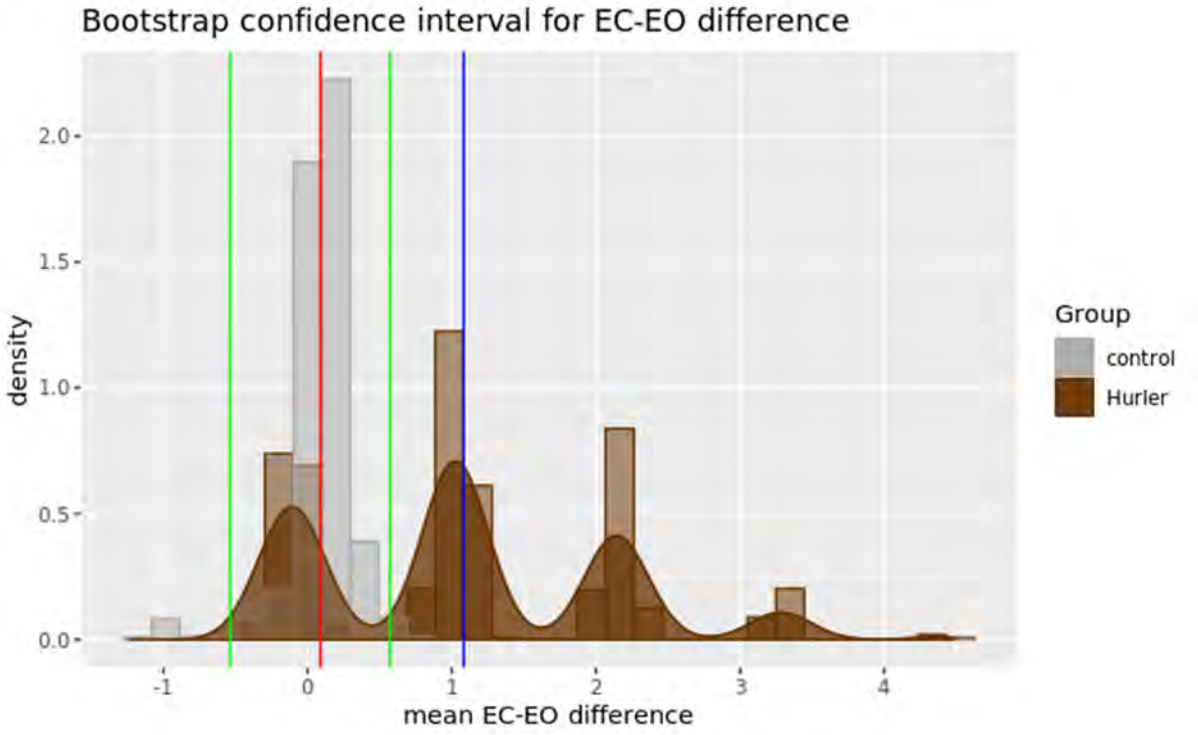


Figure 4.C4: The distribution of bootstrap means for Hurler patients and controls in jerk EC/EO difference. Green lines are the control 95% confidence intervals. Red line is the control mean. Blue line is the patients mean.

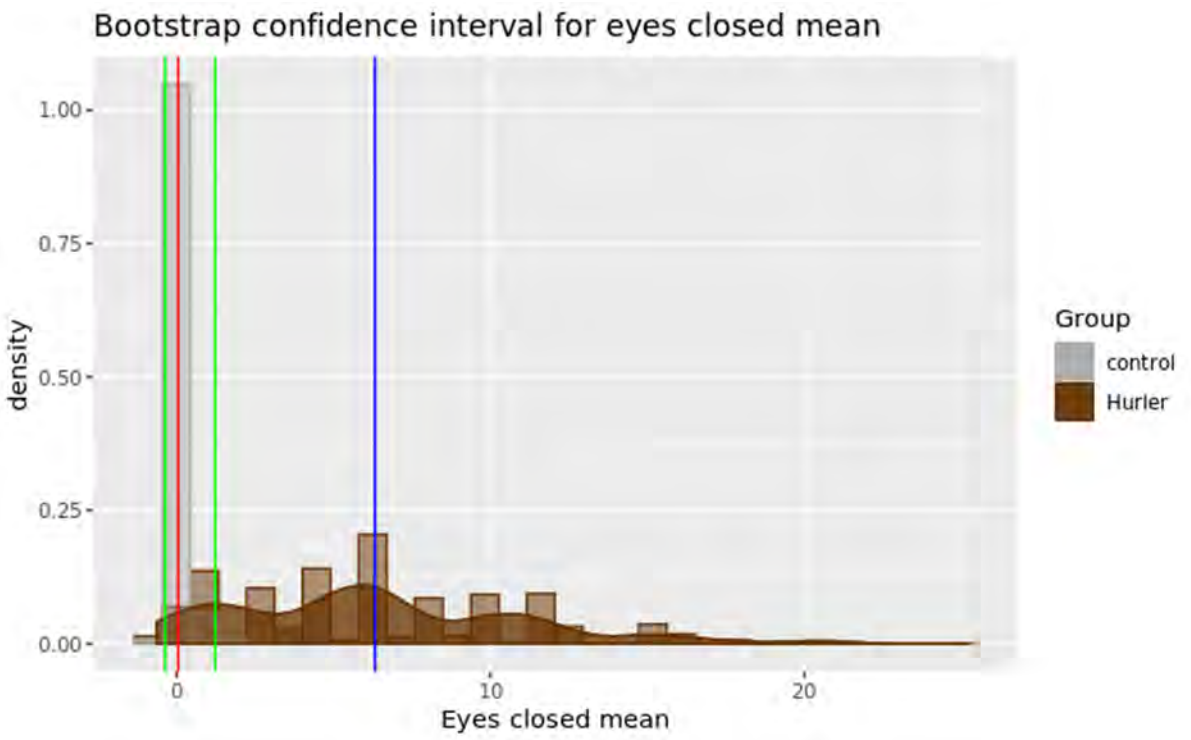


Figure 4.C5: The distribution of bootstrap means for Hurler patients and controls in jerk EC condition. Green lines are the control 95% confidence intervals. Red line is the control mean. Blue line is the patients mean.

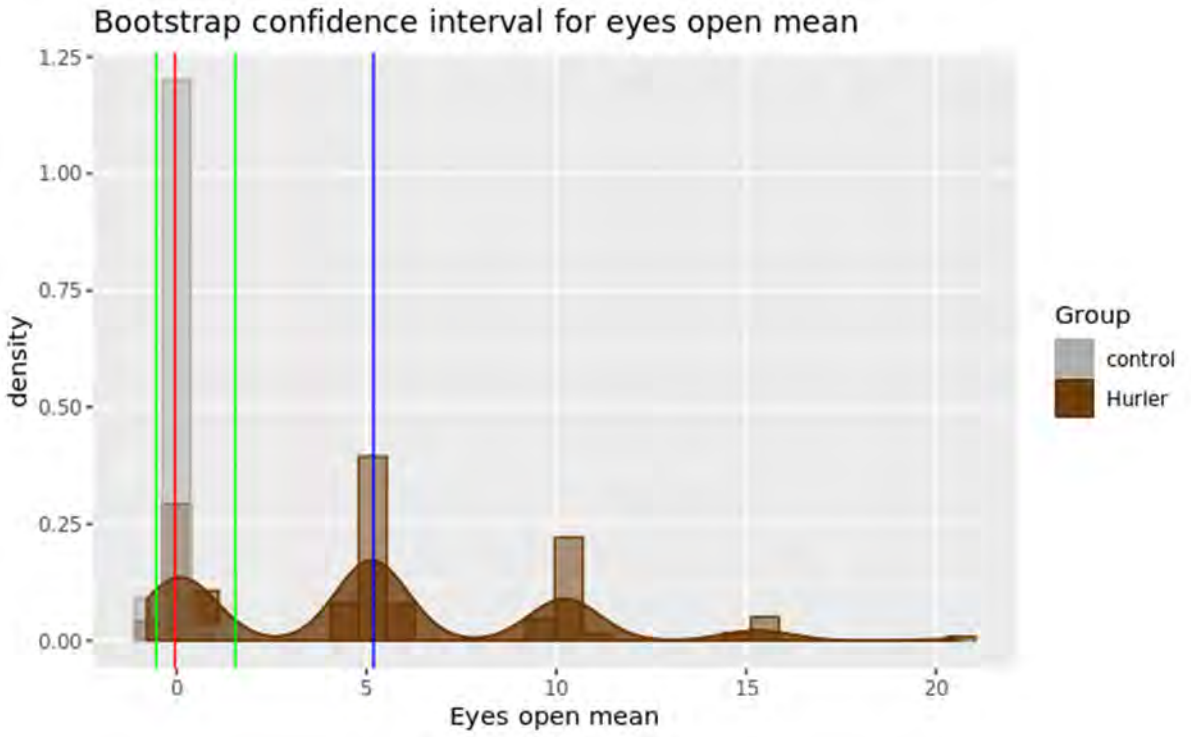


Figure 4.C6: The distribution of bootstrap means for Hurler patients and controls in jerk EO condition. Green lines are the control 95% confidence intervals. Red line is the control mean. Blue line is the patients mean.

Appendix 5

A. *NP-C patient gait correlation figures:*

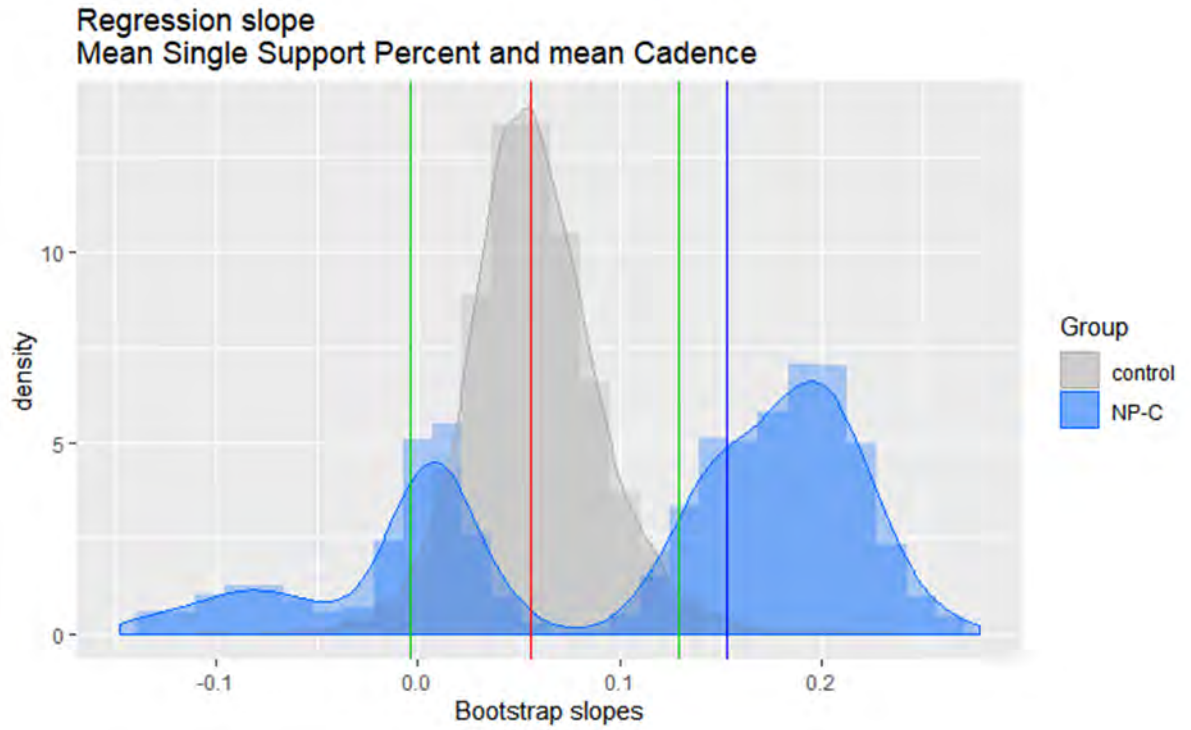


Figure 5.A1: The distribution of bootstrap slopes for the relationship between single support % and cadence in NP-C patients and controls. Green lines are the boundaries of the 95% confidence interval for controls. The red line is the control mean. The blue line is the patient mean.

B. *Fabry patient gait correlation figures:*

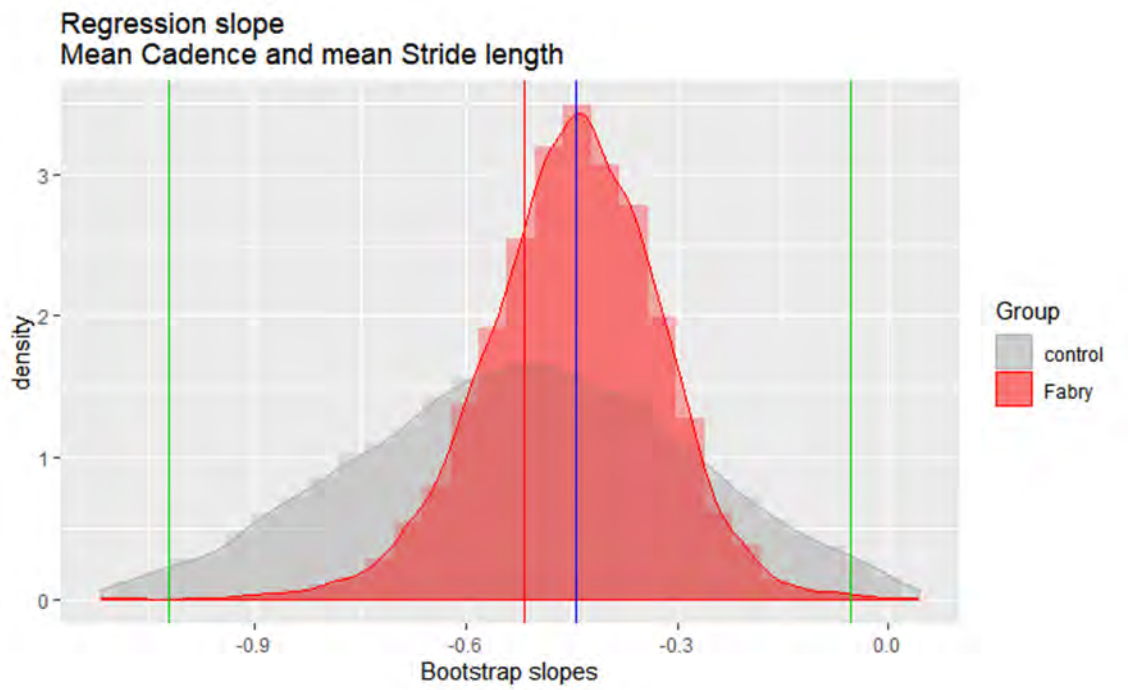


Figure 5.B1: The distribution of bootstrap slopes for the relationship between cadence and stride length in Fabry patients and controls. The green lines are the boundaries of the 95% confidence interval for controls. The red line is the control mean. The blue line is the patient mean.

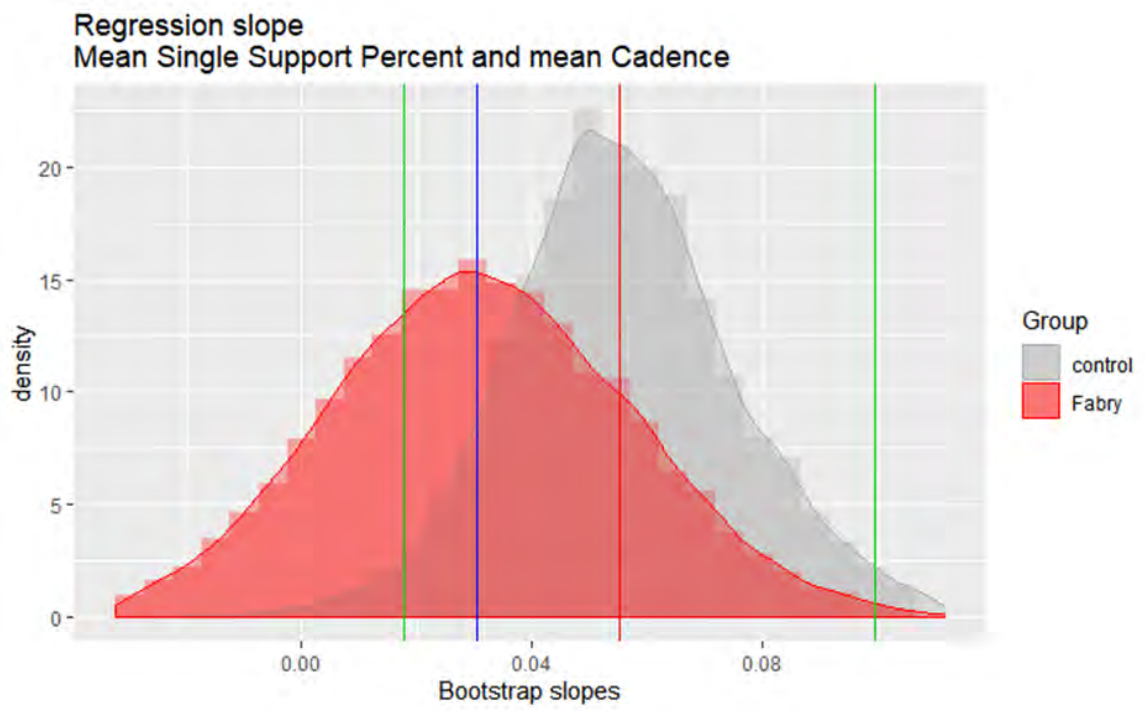


Figure 5.B2: The distribution of bootstrap slopes for the relationship between single support % and cadence in Fabry patients and controls. Green lines are the boundaries of the 95% confidence interval for controls. The red line is the control mean. The blue line is the patient mean.

C. *<u>NP-C patient sbalance correlation figures:</u>*

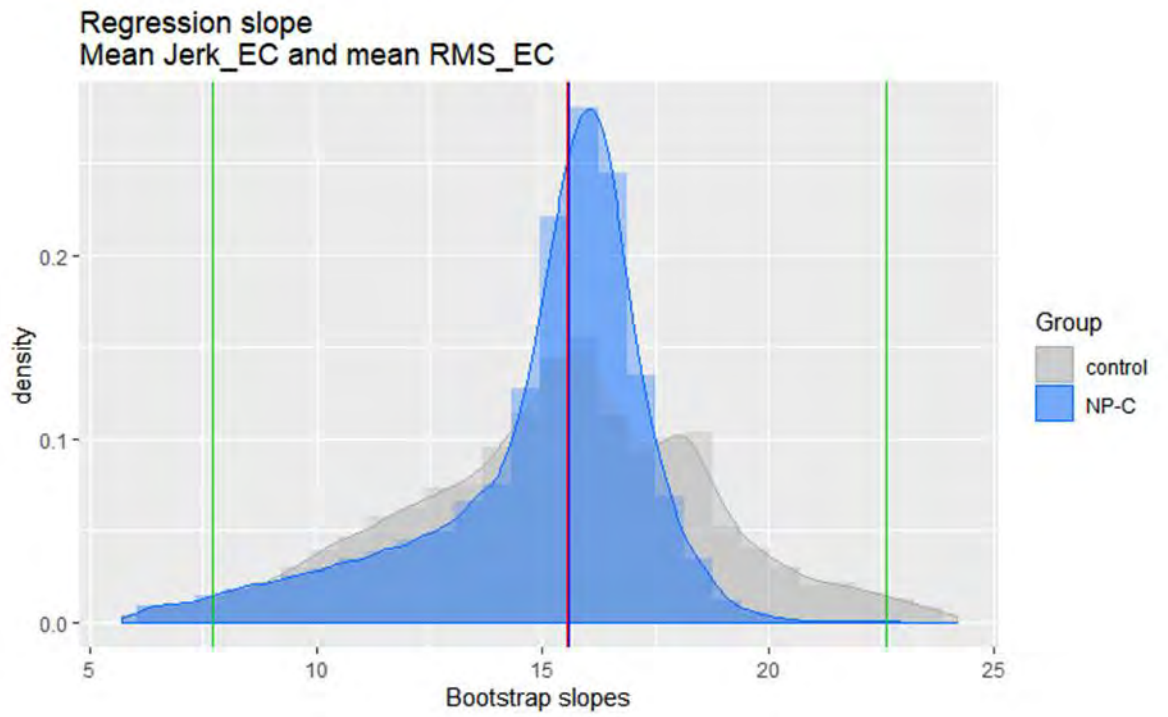


Figure 5.C1: The distribution of bootstrap means for NP-C patients and control group in RMS EC and jerk EC correlation. Green lines are the 95% confidence intervals. Red line is the control mean. Blue line is the patients mean.

D. *Fabry patient balance correlation figures:*

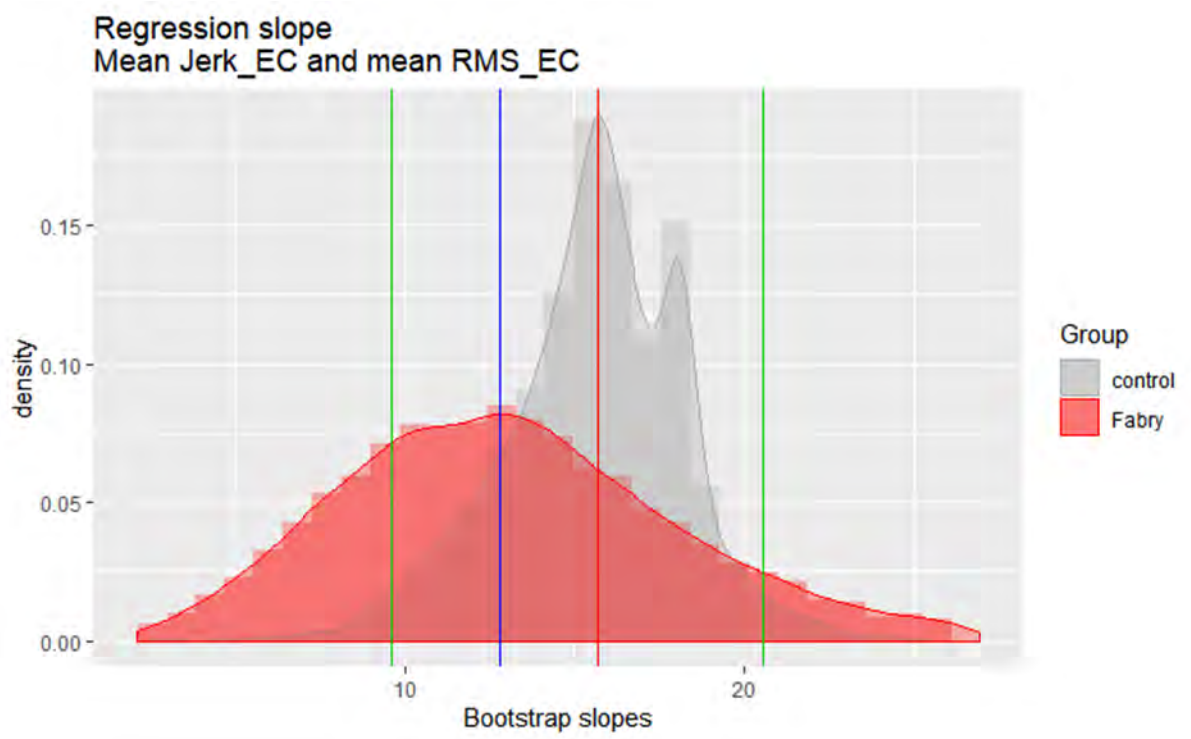


Figure 5.D1: The distribution of bootstrap means for Fabry patients and control group in RMS EC and jerk EC correlation. Green lines are the 95% confidence intervals. Red line is the control mean. Blue line is the patients mean.

E. *NP-C patient gait and balance correlation figures:*

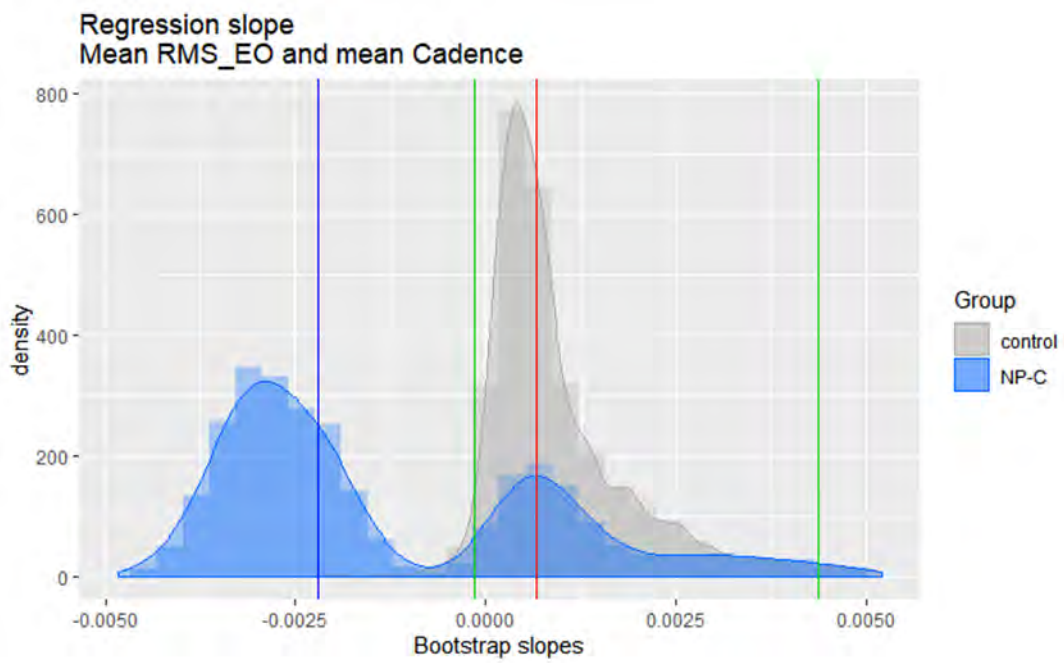


Figure 5.E1: The distribution of bootstrap means for NP-C patients and control group in RMS EO and cadence correlation. Green lines are the 95% confidence intervals. Red line is the control mean. Blue line is the patients mean.

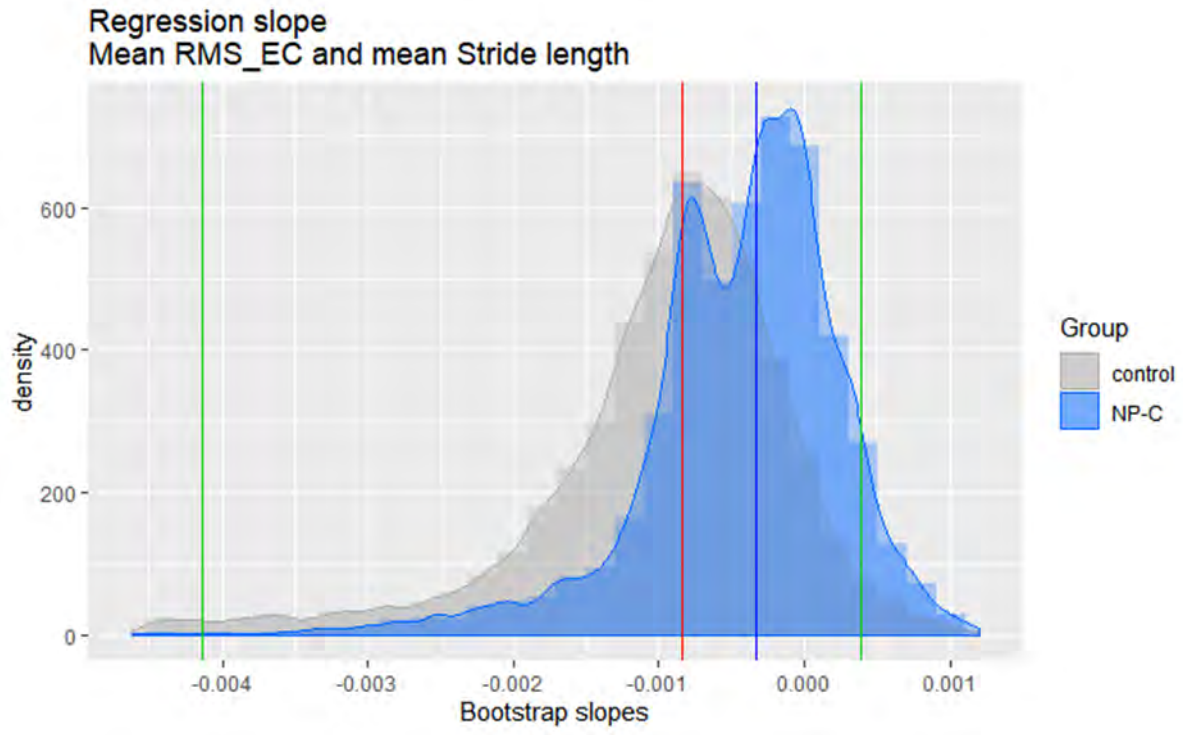


Figure 5.E2: The distribution of bootstrap means for NP-C patients and control group in RMS EC and stride length correlation. Green lines are the 95% confidence intervals. Red line is the control mean. Blue line is the patients mean.

F. *Fabry patient gait and balance correlation figures:*

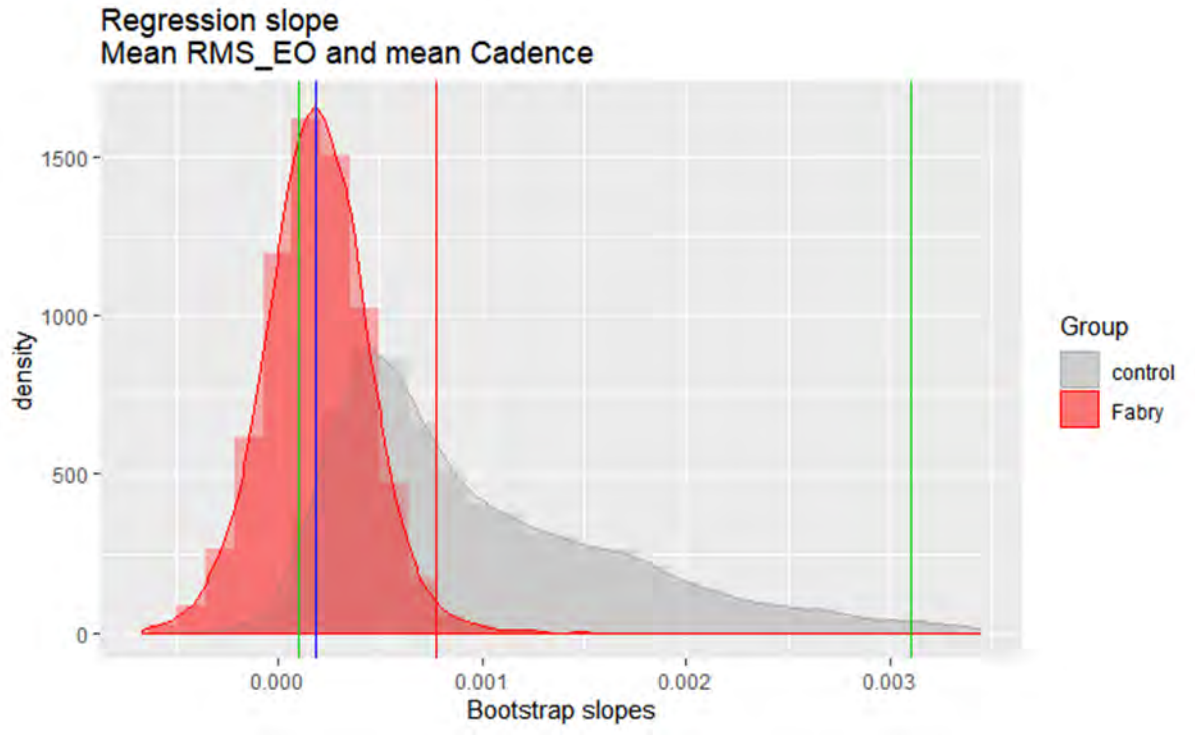


Figure 5.F1: The distribution of bootstrap means for Fabry patients and control group in RMS EO and cadence correlation. Green lines are the 95% confidence intervals. Red line is the control mean. Blue line is the patients mean.

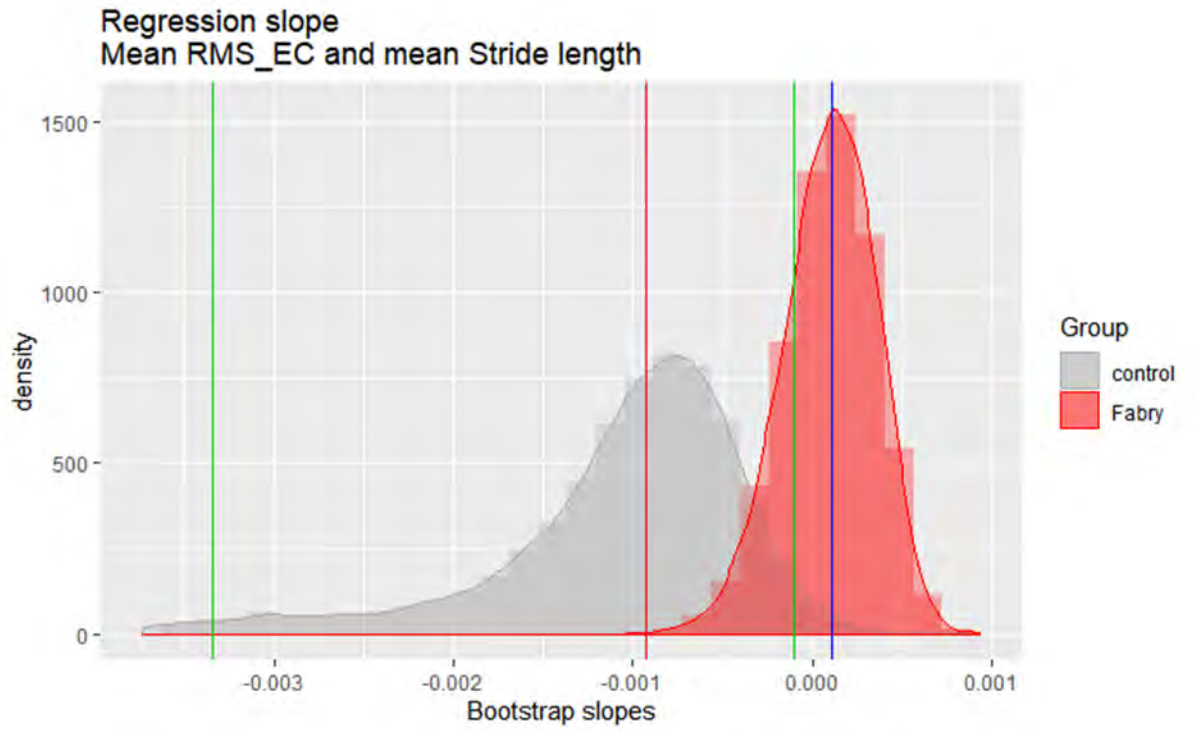


Figure 5.F2: The distribution of bootstrap means for Fabry patients and control group in RMS EC and stride length correlation. Green lines are the 95% confidence intervals. Red line is the control mean. Blue line is the patients mean.