KU LEUVEN

GROEP BIOMEDISCHE WETENSCHAPPEN

FACULTEIT BEWEGINGS- EN REVALIDATIEWETENSCHAPPEN

The follow-up of alterations in gait pattern and muscle strength in ambulant growing children with Duchenne muscular dystrophy

An integrated evaluation platform to explore the interaction between pathological gait and underlying muscle mechanisms in growing children with Duchenne muscular dystrophy

door Amber SCHEERS
en Susan SONG

masterproef aangeboden tot het behalen van de graad van Master of Science in de revalidatiewetenschappen en kinesitherapie

o.l.v.

PROF. DR. K. DESLOOVERE, PROMOTOR

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Opgesteld volgens de richtlijnen van *Gait & Posture*

Woord vooraf

Deze masterthesis is tot stand gekomen in functie van het behalen van de master in de Revalidatiewetenschappen en Kinesitherapie specialisatie pediatrie aan de KU Leuven. Graag wil ik me richten aan alle personen die ons als duo geholpen hebben bij het tot stand komen van deze thesis.

In de eerste plaats wil ik mijn dankwoord richten aan Prof. dr. Kaat Desloovere voor het aanbieden van het interessante onderwerp, de professionele begeleiding met kritische raadgevingen en adviezen en voor de lessen die dienden als een grote bron van informatie. Vervolgens wil ik mijn oprechte dank betuigen aan onze copromotor dra. Ines Vandekerckhove. Zij heeft ons doorheen het hele proces van het uitwerken en schrijven van deze thesis bijgestaan en we konden steeds met onze vele vragen bij haar terecht. Haar toegewijde begeleiding, constructieve feedback en vertrouwen waren een enorme hulp.

Verder wil ik uiteraard mijn thesis partner Amber bedanken voor de fijne samenwerking en al de leuke opleidingsherinneringen. Daarnaast wil ik ook de steun van het thuisfront vermelden voor de goede zorgen. Mijn mama, die me de kans heeft gegeven voor het volgen van deze opleiding en me een duwtje in de rug gaf wanneer dit nodig was, ben ik erg dankbaar. Ook richt ik me tot mijn vrienden voor hun aanmoediging en verzorging van tussentijdse ontspanning. Tot slot gaat een speciale vermelding uit naar mijn vriend Yolan, die van in het begin in mij heeft geloofd. Zijn steun, luisterend oor en ingeving van kennis en tips gedurende deze periode ben ik heel dankbaar.

Aalter, 22 mei 2020 S.S.

Situering

Deze masterthesis is gekaderd binnen het overkoepelende project “Een geïntegreerd evaluatie platform om de interactie tussen pathologische gang en onderliggende spiermechanismen te onderzoeken in groeiende kinderen met Duchenne musculaire dystrofie (DMD)”. Dit onderzoek heeft als doel om onze inzichten in de klinische symptomen van DMD te vergroten, met het oog op het bevorderen van klinische besluitvorming omtrent behandelingen en hulpmiddelen in deze populatie. Vooraleer dit doel bereikt kan worden, moeten de progressieve veranderingen in het afwijkend gangpatroon, spierkracht en -morfologie over de tijd gedefinieerd worden in groeiende kinderen met DMD. Daarnaast is het belangrijk om de interacties tussen de spiereigenschappen (de verminderde spierkracht en veranderde spiermorfologie), alsook het afwijkend gangpatroon beter te begrijpen. Dit project behoort tot de Neurorevalidatie onderzoeksgroep van de Faculteit Bewegings- en Revalidatiewetenschappen aan de KU Leuven.

Kinderen met DMD zijn de doelgroep van het bovengenoemde project. DMD is een X-gebonden degeneratieve neuromusculaire aandoening[1], met een prevalentie bij jongens van 1 op 3500-5000.[2] De aandoening wordt gekenmerkt door progressieve spiermassa afname[3], veroorzaakt door een mutatie in het dystrofine gen.[4,5] Bijgevolg ontstaan er al vanaf een jonge leeftijd moeilijkheden in de grove motoriek.[6] De initiële typische symptomen bij ambulante jongens met DMD zijn gesitueerd ter hoogte van de onderste ledematen[7], waarbij spierfunctie en -structuur achteruitgang, alsook een pathologisch gangpatroon, zich steeds verder ontwikkelen naarmate de jongens met DMD ouder worden.[8,9]

Het merendeel van de voorgaande studies betreffende de klinische symptomen van DMD zijn cross-sectioneel van design. Omwille van de heterogeniteit in de onderzochte groepen en de afwezigheid van conformiteit in de uitkomsten van deze studies, veroorzaakt door verschillen in meetprocedures, parameterselectie en data-analyse[10], is er een tekort aan kennis over de symptomenprogressie van DMD op lange termijn. Bovendien is het algemeen klinisch aanvaard dat spierzwakte in de onderste ledematen een beduidende rol speelt in de afwijkingen van het gangpatroon in kinderen met DMD, ook al is er nog geen bestaande literatuur die dit gegeven bevestigt. Bijgevolg is er een gebrek aan kennis over enerzijds de longitudinale veranderingen in gangafwijkingen alsook de spierkracht, en anderzijds over de onderliggende mechanismes die het pathologische gangpatroon bepalen in kinderen met DMD.

Vertrekkende uit deze tekorten, werd het meervoudig doel van deze masterthesis opgesteld. De progressieve veranderingen in het afwijkend gangpatroon en de spierkracht van de onderste ledematen werden onderzocht en vastgesteld in ambulante groeiende kinderen met DMD.

Daarnaast werd in eenzelfde cohort nagegaan of er interacties tussen spierzwakte en gangafwijkingen gevonden konden worden. Gebruik van gestandaardiseerde drie dimensionale ganganalyses en isometrische spierkrachttesten maakte het mogelijk om de gewenste objectieve gegevens te kwantificeren.

Aldus kan deze masterthesis, met een gemixt longitudinaal-cross-sectioneel design, bijdragen tot meer inzichten in zowel het natuurlijke ziekteverloop van gang- en spierkrachtafwijkingen, als in de onderliggende spiermechanismen van het pathologische gangpatroon. Zodoende willen we met deze studie bijdragen tot een ambulantie verlenging in jongens met DMD, vermits onze resultaten kunnen leiden tot betere klinische besluitvorming over therapeutische interventies en tot het accurater nagaan van de doeltreffendheid van nieuwe veelbelovende medicatie.

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Abstract

Background To explore efficacy of new medication and therapy that aim for ambulation prolongation in children with Duchenne muscular dystrophy(DMD), natural history mapping of gait and muscle strength deterioration is needed. Therefore, studies determining longitudinal changes in a standardised manner are necessary, to assemble specific and sensitive outcomes. Also, while it is generally accepted that muscle weakness affects DMD gait, no evidence has proven this yet.

Research question How do gait pattern(1) and lower limb muscle strength(2) change with age in children with DMD? Are gait deviations linked with lower limb muscle weakness(3)?

Methods 17 boys with DMD(4-17 years) were longitudinally examined every six months, resulting in 49 measurements. 27 gait and seven strength parameters were extracted, using 3D gait analysis and maximal isometric voluntary contractions. Baseline characteristics were described next to gait and strength data of 86 and 15 typically developing children, respectively. Linear mixed models were used to determine the effect of age on gait(1) and strength(2), and the effect of weakness on gait(3).

Results Cadence, walking velocity, step length, hip extension angle, dorsiflexion angle (swing), hip extension and flexion moment decreased with 0.06, 0.01, 0.01, 2.92°, 1.46°, 0.05Nm/kg and 0.03Nm/kg, per year, respectively. Step width, anterior pelvic tilt, pelvic obliquity and Gait Profile Score increased with 0.01, 1.57°,0.91° and 0.51°, per year. Plantar flexor(-0.02Nm/kg per year), hip(-0.03Nm/kg per year) and knee extensor(-0.04Nm/kg per year) strength declined. Knee extensor, hip extensor and hip abductor weakening of 1Nm/kg was linked with alterations of -0.46Nm/kg, -22.47°and 0.14 in knee extension moment, hip extension angle and step width, respectively.

Significance These results provide insight into the underlying mechanisms of DMD gait and the natural history of gait and strength alterations, essential for evaluating medication or therapy efficacy. Hence, we may contribute to improved clinical decision making and extended ambulation in DMD.

Keywords: Duchenne muscular dystrophy, Gait, Muscle weakness, Longitudinal study, Linear mixed effects models

1. Introduction

Duchenne muscular dystrophy (DMD) is a degenerative, X-linked recessive neuromuscular disorder[1], affecting approximately 1/3500-5000 male live births.[2] DMD is caused by a mutation in the dystrophin gene, which leads to a lack of dystrophin protein. The primary function of the dystrophin-associated protein complex is stabilizing the muscle cell membrane and protecting muscle fibres from contraction induced damage.[3,4] Therefore, dystrophin deficiency in DMD results in a progressive decrease in muscle mass, which is replaced by fibrofatty tissue.[5] Early symptoms in DMD, mostly presenting at the age of three to five years, are proximal lower limb and truncal muscle weakness.[6] As the disease progresses, boys with DMD have increasing walking difficulties, resulting in an altered gait pattern and eventually a complete loss of ambulation.[7,8] There is no causative treatment available for DMD. Although negative side effects are possible due to corticosteroid therapy, this treatment aims to postpone the age of becoming wheelchair bound and to prevent additional complications, such as spinal deformities and muscle contractures.[9,10]

Currently, the 6 minute walk test (6MWT), North Star Ambulatory Assessment (NSAA) and timed functional tests are used in clinical settings as standard measurements of gross motor function in ambulant boys with DMD.[11,12] The 6MWT is known as a primary outcome measure[13], reflecting clinically meaningful aspects of daily life e.g. endurance and ability to walk.[11,14] It has proven to be a validated, feasible and reproducible test.[13,14] Also, normative 6MWT data of paediatric populations is available.[11,15] The NSAA is a functional scale specifically designed for ambulant boys with DMD. It is featured by a good intra- and interobserver reliability and is applicable in several contexts.[16] Furthermore, tests such as the 10 meters timed walk/run test and timed rising from the floor are included in the NSAA. These functional timed tests have the ability to longitudinally evaluate the gross motor changes and predict loss of ambulation.[11,17] The correlation between the NSAA and the 6MWT is only moderate to good. Therefore, combining both tests is effective, since both the NSAA and 6MWT seem to include different aspects of daily used functions.[11] Although the aforementioned tests are accepted among clinicians, the sensitivity and specificity might be too low to reveal early compensation mechanisms and to detect important changes in the efficacy of clinical interventions.[18,19] These clinically accepted standard measurements only report global functional information and do not provide details about the altered gait pattern and underlying muscle weakness.[18,19] To overcome those deficits, there has been a growing need for validated, specific and sensitive outcome measures to use in clinical trials and to detect subtle longitudinal progressive deterioration changes in children with DMD.[11,18–20]

Three-dimensional gait analysis (3DGA) appears to provide more sensitive outcomes than the aforementioned standard clinical care measurements, since it can identify early and subtle progressive changes in walking performances.[19] This method objectively quantifies the altered gait pattern, as it measures joint kinematics and kinetics in detail. For that reason, 3DGA is already frequently used in the planning and assessment of treatments for other locomotor system impairments than DMD, such as cerebral palsy.[19,21] In general, gait alterations in boys with DMD are mainly caused by progressive muscle weakness, muscle fatigue and joint contractures.[17,22] Sutherland et al.[23] were the first to describe the pathological biomechanics of gait in DMD, introducing three stages of ambulation, namely: the early, transitional and late stage. Already in the *early stage,* subtle gait deviations can be observed.[23,24] Both cadence and walking speed are decreased compared to typically developing (TD) children. Commonly, weakness of the lower limb extensor muscles is compensated by increased activation of the hip flexors and plantar flexors, as well as the passive use of posterior soft tissue structures of the knee, to obtain forward progression and body support.[1,23–26] Overcompensation by the plantar flexor muscles results in a flat foot- or forefoot-strike pattern at initial contact and excessive plantar flexion during swing phase.[23,24,27] Therefore, increased hip flexion and abduction during swing phase occur to aid foot clearance.[27] In the *transitional stage*, progressive muscle hip abductor weakness[24] leads to changes in alignment, i.e. increased base of support, lateral arm swing and lateral trunk lean. Furthermore, an increased anterior pelvic tilt and lumbar lordosis are present[23,24], which can be explained by hip and knee extensor weakness, as well as hip flexor stiffness and contractures.[27] Due to more progressive muscle weakening in the *late ambulation stage* of the disease, further alignment changes arise. To maintain passive stability, children with DMD walk with an even broader base of support and a smaller step length, leading to a more reduced natural gait velocity.[1,28,29] Joint contractures cause enhanced difficulties in maintaining body alignment and stance stability, which results in more frequent falling. The anterior pelvic tilt further increases and toe walking occurs.[24] Although 3DGA is an essential method to recognize the aforementioned early and clinically meaningful changes in the altered gait pattern, Goudriaan et al.[30] found that the generalizability of the outcomes obtained from different 3DGA studies seemed to be poor, due to limited conformity of the parameter outcomes. Therefore, detailed description of the chosen material and analysis methods is a priority in forthcoming studies. In that way, gait alterations can be determined in a more standardized manner, leading to an increased understanding in the pathological DMD gait.[30,31] Furthermore, the progressiveness of the gait pathology has been nearly exclusively investigated in recent cross-sectional 3DGA studies across heterogenous samples of boys with DMD.[30] Therefore, longitudinal studies with larger datasets that clearly demonstrate the disease progression are required in research to understand DMD gait and its underlying mechanisms.[19,31]

In boys with DMD, not all muscles are affected at the same time in the disease progression.[17,32] For this reason, measuring muscle strength within a longitudinal perspective in children with DMD, is useful to represent the weakness topography and the disease progression rate.[33] In previous studies, the manual muscle test was often used to evaluate muscle strength. However, this test appeared to have restricted reliability, accuracy and sensitivity.[34–36] Therefore, recent studies measured muscle weakness by using a hand-held dynamometer on patients performing a maximal voluntary isometric contraction (MVIC). Dynamometry is more reliable to assess muscle strength and therefore, a preferred method.[37] The progressive muscle-specific decline in children with DMD is initially marked in the proximal muscle groups, with the distal muscle groups deteriorating commonly at an older age.[17,34,35] Mathur et al.[34] found that significant weakness was already seen in young boys compared with TD children and that this relative difference between both groups increased with age. According to longitudinal data, an increase of muscle strength was observed until the age of seven and a half years in boys with DMD. However, their strength profile still tended to be decreased compared to TD children. A significant decrease in muscle strength arose from the age of seven and a half years, with a more pronounced decrement after the age of nine years.[38,39] The rate of deterioration appeared to be higher in extensor muscles compared to flexor muscles.[17,40] Further, the influence of corticosteroids on muscle strength still remains unclear. Yet, it is known that boys who follow corticosteroid treatment tend to have slightly higher strength values.[39] Although quantitative muscle strength measurement methods are more frequently used for clinical assessments in boys with DMD, a delineation of changes in the weakness topography over time is still needed, to improve the understanding of the disease progression and to evaluate the effectiveness of promising novel medications.[38,39,41]

Although muscle weakness is considered the main contributor to the pathological gait pattern in children with DMD, no research has verified this relationship. So far, only Goudriaan et al.[31] examined if weakness was associated with pathological gait. However, no significant linear relationship could be found. This suggests that the interaction between muscle weakness and altered gait in children with DMD is complex and difficult to detect by cross-sectional studies, with small and heterogeneous samples. Therefore, it is possible that longitudinal studies examining the changes in the relationship between muscle weakness and gait deviations over time in growing children with DMD, are more effective in detecting significant interactions.

The main objective of this study was to describe the alterations in the pathological gait pattern and lower limb muscle strength over time as well as the contribution of muscle weakness to gait deviations, in ambulant growing children with DMD. Specifically, the first and second aim were to determine the effect of increasing age on gait deviations and muscle strength, respectively. The

third objective was to investigate the effect of increasing weakness on changes in the pathological gait pattern. We formulated three hypotheses related to these goals: Firstly, we hypothesised that gait abnormalities increase as the children with DMD grow older. Secondly, we expected a muscle-specific strength decline as the boys with DMD age. Lastly, we presumed that increased muscle weakness of the lower limbs is linked to the accumulation of gait deviations in growing children with DMD. Profound knowledge of the natural history of the gait deviations and lower limb muscle weakness in boys with DMD is useful to better quantify the efficacy of promising novel medication. Furthermore, improving our insights into the underlying mechanisms contributing to the pathological gait pattern is valuable to improve clinical decision making about treatments that aim at prolonging the ambulation in boys with DMD.

2. Materials and methods

2.1 Participants

17 boys with DMD were included in this study. Inclusion criteria of the participants were: diagnosis of DMD confirmed by mutation of the dystrophin gene, muscle biopsy and/or immunohistochemistry (1), no history of lower limb surgery (2), ability to walk independently (3) and aged between 4 and 17 years (4). Exclusion criteria were presence of behavioural and/or psychiatric disturbances. An overview of the corticosteroids intake and dose of the included children with DMD is displayed in the Appendix (Appendix 4).

The baseline patient characteristics of the children with DMD were described next to the data of TD children with a similar age range. This normal data was derived from two databases (i.e. one for gait and one for muscle strength) from the Clinical Motion Analysis Laboratory of the University Hospital of Pellenberg (CMAL-Pellenberg), collected for earlier research. The gait parameter database included 86 TD children. Data for the lower limb muscle strength contained outcomes from 15 TD children.

All measurements took place in CMAL-Pellenberg. A written informed consent was obtained from the child's parent or caretaker for approval to report the clinical assessment data anonymously. Children aged twelve years or older, also signed a consent form themselves. This study was approved by the local ethics committee *(Commissie Medische Ethiek KU Leuven, under S61324)* under the Declaration of Helsinki (Appendix 2).

2.2 Data collection

Data from the boys with DMD were longitudinally collected for this study, with a follow-up assessment every six months. This follow-up assessment included a clinical investigation, followed by 3DGA and MVIC lower limb strength measurements. However, several contextual factors, such as age, collaboration or tiredness of the child, sometimes necessitated alterations in the order of the measurements. All 17 boys with DMD underwent a baseline assessment and a six-months follow-up measurement. An additional third (twelve months) follow-up moment took place for ten of the 17 children, of which five boys even had a fourth (18 months) follow-up assessment. In that way, a total of 49 measurements was assembled.

For the 3DGA data collection, participants were requested to walk barefoot on a ten meters pathway at a comfortable and natural walking velocity, without any physical aid devices. The Full

Body Plug-In-Gait model was used to stick markers (14 mm in diameter) to the skin. Furthermore, the gait analysis laboratories were supplied with a 10-15 camera Vicon system (Vicon-UK, Oxford, UK), which was used to document the kinematic movements based on the marker trajectories, with a 100 Hz sampling rate. A built-in Woltring filter (with mode MSE and smoothing 15mm^2) was applied to filter those trajectories. Two force plates (AMTI, Watertown, MA, USA) integrated in the walkway, registered the ground reaction forces with a 1500 Hz sampling rate. The ground reaction forces combined with the kinematic data were used to calculate the kinetics of the movements. A video recording system matching the camera system was used as well.[31]

To achieve consistent data, at least three trials with kinetic and ten trials with kinematic data were assembled bilaterally. Nexus software (Nexus 2.9. Vicon-UK, Oxford, UK) was used to determine gait cycles and to estimate the kinematic as well as the kinetic data. The current study only focussed on the lower limb and pelvic kinematics and kinetics, from the Full Body Plug-in-Gait model.

To evaluate the longitudinal muscle strength progression and the association between gait deviations and muscle weakness in boys with DMD, muscle strength of the weakest leg was measured. Based on the manual muscle strength outcomes of the clinical examination, we could estimate which leg was the weakest. In case of perfect symmetry, the side to be evaluated was randomly selected by flipping a coin. MVICs were measured for the hip flexors, hip extensors, hip abductors, knee flexors, knee extensors, plantar flexors and dorsiflexors. To assess lower limb strength, the protocol of Goudriaan et al.[31] was followed. For this, a custom-made chair was used. In order to maximally restrict the compensatory movements of the child and the influence of the assessor's strength, the child and dynamometer were fixed to the chair in a standardized manner. The children were secured with a strap at the pelvis and upper leg(s) and their arms needed to be crossed in front of the chest during measurement. The foot was placed in a heel cuff for MVIC measurements of the hip flexion, hip extension, plantar flexion and dorsiflexion muscle strength. The hand-held dynamometer (MicroFet Hogan Health Industries, West Jordan, UT USA) was positioned at 75% of each segment length, with the force sensor perpendicular to the main rotation axis of the joint. In that way, the measured internal moments expressed the moment component of the perpendicular force. To compensate for gravitational benefits, the gravitational torque in rest was subtracted from the MVIC outcomes for hip extension, knee flexion and plantar flexion.

The child was instructed to perform a maximal muscle contraction, during a period of three to five seconds. A graph (with on the x-axis a representation of time in seconds and on the y-axis the executed force in Newton) was displayed on a computer screen as a way of providing visual

feedback. Three actual trials were performed, with at least ten seconds of rest in between. Before the actual trials, a test trial took place in order to make sure the child understood the task. Verbal directives and encouragement were applied in a standardized manner.

In total, 49 measurement sessions, including both 3DGA and MVIC measurements, were planned. The performed 3DGA sessions were completed on each of the 49 time points. However, the MVIC data collection was not complete on all time points. For nine assessments, measurement moments of the MVICs for the hip muscles were missing. This lack of data can be explained by insufficient motivation or fatigue of the (young) child with DMD during the measurement. For the remaining 40 MVIC measurements, all muscle groups were measured.

2.3 Data analysis

In this study, MATLAB (The MathWorks Inc., Natick, M.A., 2019a) was used for analysing the 3DGA and MVIC data. The continuous waveforms emerged from the kinematic and kinetic 3DGA processing, were time-normalized to the duration of the gait cycles. The custom-made *Multiple Joint Software* was applied to check the quality of the gait cycles (i.e. ten kinematic and three kinetic waveforms per measurement moment per subject). Gait cycles with good quality were selected to calculate an average of the spatiotemporal, kinematic and kinetic parameters. In addition, only data of the weakest side was included in further analyses. The spatiotemporal parameters included: walking speed expressed in meters per second (m/s), cadence in number of steps per second (/sec), step length in meters (m) and step width in meters (m). Step length and step width were converted into normalized non-dimensional values by the equation of Hof (equation 1 and 2, respectively), to correct for the effect of leg length. Additionally, walking velocity was converted (equation 3) into a normalized value as well, to compensate for the effect of leg length and gravitational acceleration.[42,43] Maxima, minima, range of motions and values at specific events in the gait cycle were extracted from the continuous kinematic and kinetic waveforms, to achieve the required discrete gait parameters. Beside those parameters, we also included the Gait Profile Score (GPS) as an overall gait parameter. The GPS is a global kinematic measure over the whole gait cycle, used to describe overall gait variability, and is therefore applied to detect clinically relevant changes in gait pathologies. This clinical index is computed by combining several kinematic values, from the children with DMD, and comparing this obtained value to an identical kinematic reference TD dataset.[44,45] The included gait features in this study were selected based on clinical reasoning, knowledge from local experts and previous research in which common DMD gait alterations were reported.[18,19,23,24,27,29,31,46,47] In that way, we aimed for a selection of clinically relevant parameters that properly represent DMD

gait pathology. Kinematic data was expressed in degrees (°). The joint moments and power were normalized to body weight. Consequently, the kinetic data was expressed in Newton meters per kilogram bodyweight (Nm/kg) for the internal net joint moments and in Watt per kilogram bodyweight (W/kg) for the power data.

$$SL_{norm} = \frac{SL}{l} \quad (1) \qquad SW_{norm} = \frac{SW}{l} \quad (2) \qquad v_{norm} = \frac{v}{\sqrt{g * l}} \quad (3)$$

Equations of Hof with SL, SW, v, norm, l and g representing step length, step width, walking velocity, normalized value, leg length and gravitational acceleration respectively.

For calculating parameters from the MVIC strength data (from the weakest leg), another custom-made software (MATLAB) was utilized. The force data - expressed in Newton (N) - was resampled to 100 Hz. The average of the maximal force (N) over three MVIC trials was computed. We multiplied the averaged maximal force (N) with the moment arm (m) to determine the net joint moment (Nm). In addition, moments normalized to bodyweight (Nm/kg) were calculated to ensure the ability to compare our outcomes with other literature.[48] The Total Composite Score (TCS) was determined as a measure of general muscle weakness, by calculating the average muscle weakness of all included seven muscle groups.

2.4 Statistical analysis

In order to delineate the baseline gait deviations and strength outcomes of the children with DMD, means and standard deviations or medians and interquartile ranges - depending on the distribution of the parameters - were reported next to data of the TD databases. Normality of the parameters was evaluated by the Shapiro-Wilk test (Appendix 5: table 1-3; Appendix 6: figure 1-4 for the Quantile-Quantile plots).[49] As DMD is a progressive disorder, a difference at baseline between the younger and older boys with DMD could be expected. Therefore, we divided the children with DMD into two groups (a group aged under and above ten years old).

Linear mixed effects models were used to investigate the effect of increasing age on gait alterations (hypothesis one), the effect of increasing age on muscle strength changes (hypothesis two) and the effect of muscle weakness on gait deviations (hypothesis three). In contrast to simple linear regression analysis, both fixed and random effects are included in Linear mixed effects models.[50–54] In our first hypothesis, age represented the fixed predictor and the evolution in the gait parameters (n=27) - containing four spatiotemporal, twelve kinematic, and eleven kinetic parameters - represented the expected responses. In the second hypothesis, the fixed predictor

was age, while the expected responses were represented by alterations in the muscle strength outcomes (n=7), i.e. hip flexion, hip extension, hip abduction, knee extension, knee flexion, dorsiflexion and plantar flexion strength. For the third hypothesis, multiple regression analyses with multiple fixed effects were performed. A combination of maximally three fixed predictors out of the muscle strength outcomes (n=6) were selected to predict changes in the gait parameters (n=25). If a gait parameter was expected to be influenced by general muscle weakness, such as for example the GPS and gait velocity, the TCS was used as the fixed predictor. To evaluate the risk of multicollinearity in case of multiple regression analysis, the variation inflation factor (VIF), i.e. an index that expresses how much the variance of a regression coefficient is increased because of multicollinearity[55], was calculated. In contrast to fixed parameters, random effects are parameters that vary at the level of each child with DMD.[51,54] Both random intercepts and random slopes are integrated in random effects and are considered to have a normal distribution.[50,51,54] Therefore, the standard deviations of the random effects were reported. By adding random intercepts into the linear predictor, the dependence of the clustered data was taken into account.[50,52,53] In that way, we were able to estimate the position of each child relative to the average regression line. Adding random slopes into the predictor on the other hand, took the variation in progression rates between the children with DMD into consideration.[54]

As a result, three different statistical models could be applied: a standard linear regression model (1), a linear regression model with random intercepts (2) and a linear regression model with random intercepts and slopes (3). For each parameter, the three different models were compared with the theoretical Likelihood-ratio test and the model with the best statistical fit was selected based on Akaike Information Criterion, Bayesian Information Criterion and Log-Likelihood values (Appendix 7: table 1-3).[56,57] In case of random intercept models, intraclass correlation coefficients were calculated to demonstrate the additional variance, explained by the model with added random intercepts, compared to a standard linear regression model. To compare the three models, the alpha level ($\alpha = 0.05$) was set to a corrected alpha of 0.0167, defined by the Bonferroni correction. After selection of the best fitted model, the normal distribution of the residuals was verified for all three hypotheses by the Shapiro-Wilk test (Appendix 8: table 1-3).

To determine the effect of age on gait (hypothesis one) and on muscle strength (hypothesis two), as well as the effect of muscle weakness on gait deviations (hypothesis three), the significance of the regression coefficients was evaluated. The baseline alpha ($\alpha = 0.05$) was corrected by the Benjamini-Hochberg procedure for each hypothesis, to correct for multiple testing. In addition, outcomes of the Shapiro-Wilk test were also interpreted with the same corrected alpha level. The Benjamini-Hochberg procedure controls the False Discovery Rate at the chosen significance level and is characterised with more power compared to single step procedures.[49]

All statistical analyses were executed in MATLAB (The MathWorks Inc., Natick, M.A., 2019a).

3. Results

Table 1 and 2 show the baseline characteristics of the children with DMD (divided into a group of < and ≥ 10 years old) for the muscle strength and gait analysis measurements, respectively, next to data of TD children of a similar age range**.** Figure 1A displays the ages of the children with DMD at the time of enrolment, to provide an overview of the age distribution in our study sample. Figure 1B represents the ascending ages of the children with DMD at the different follow-up assessments.

Table 1.
Baseline values for the muscle strength parameters

	DMD				TD	
	< 10 years		**≥ 10 years**			
Age range in years [minimum-maximum]	[4,58-9,61]		[10,06-15,90]		[5,71-15,44]	
Measure (units)	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age (years)	7.15	1.78	12.57	2.14	8.78	2.45
BMI (kg/m²)	17.96	4.05	22.41	3.16	15.74	1.55
Hip flexor strength (Nm/kg)	0.81	0.39	0.77	0.39	/	/
Hip extensor strength (Nm/kg)	0.41	0.24	0.34	0.20	/	/
Hip abductor strength (Nm/kg)	0.47	0.25	0.46	0.20	/	/
Knee flexor strength (Nm/kg)	0.41	0.10	0.34	0.16	1.01	0.29
Knee extensor strength (Nm/kg)	0.72	0.22	0.44	0.27	1.29	0.48
Plantar flexor strength (Nm/kg)	0.32	0.09	0.23	0.06	0.61	0.23
Measure (units)	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**
Weight (kg)	20.80	18.17, 23.85	36.00	34.50, 44.40	23.70	20.05, 33.10
Height (m)	1.08	1.08, 1.17	1.31	1.30, 1.32	1.16	1.10, 1.29
Dorsiflexor strength (Nm/kg)	0.15	0.13, 0.19	0.13	0.10, 0,14	0.27	0.23, 0.30

Abbreviations; in alphabetic order: DMD = Duchenne Muscular Dystrophy; IQR = interquartile range of 25th and 75th percentile; kg = kilograms; kg/m^2 = kilograms per square meters; m = meters; Nm/Kg = Newton meters per kilogram bodyweight; SD = standard deviation; TD = typically developed.

Table 2.
Baseline values for the gait analysis parameters

	DMD				TD	
	< 10 years		≥ 10 years			
Age range in years [minimum-maximum]	[4,58-9,61]		[10,06-15,90]		[4,59-17,12]	
Measure (unit)	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age (years)	7.15	1.78	12.57	2.14	8.62	3.01
BMI (kg/m²)	17.96	4.05	22.41	3.16	17.00	3.24
Cadence (/sec)	2.40	0.21	1.98	0.16	2.15	0.36
Step length, Hof	0.74	0.04	0.36	0.33	0.78	0.12
Walking velocity, Hof	0.42	0.04	0.35	0.04	0.46	0.08
Step width, Hof	0.28	0.04	0.29	0.05	0.15	0.05
Max anterior pelvic tilt (°)	15.23	3.55	22.16	6.80	13.24	5.13
ROM pelvic obliquity (°)	7.98	2.21	12.42	3.85	9.34	3.21
ROM pelvic rotation (°)	12.12	5.96	17.08	7.82	12.70	5.71
Max hip extension angle in stance (°)	-8.25	6.01	4.16	11.66	-9.44	5.84
Max hip abduction angle in stance (°)	-4.54	4.08	-6.61	2.79	-4.28	2.88
Max hip abduction angle in swing (°)	-8.26	3.24	-10.68	3.77	-6.15	2.47
Max knee extension angle in swing (°)	28.70	3.57	27.04	5.95	29.32	5.80
Ankle angle at initial contact (°)[a]	2.67	6.49	-2.76	5.94	-0.36	5.20
Max dorsiflexion angle in stance (°)	15.76	3.82	12.56	7.47	13.38	4.61
Max dorsiflexion angle in swing (°)	6.39	5.38	0.55	6.99	4.68	3.72
Gait Profile Score (°)	5.84	2.26	8.30	2.36	5.57	1.46
Max hip abduction M in stance (Nm/kg)	0.59	0.12	0.63	0.07	0.71	0.15
Max hip extension M in stance (Nm/kg)	0.58	0.22	0.40	0.20	1.06	0.38
Max hip flexion M in stance (Nm/kg)	-0.72	0.10	-0.68	0.31	-0.91	0.25
Max knee extension M in stance (Nm/kg)	0.38	-0.13	0.28	0.18	0.48	0.23
Max knee flexion M in stance (Nm/kg)	-0.11	0.07	-0.05	0.14	-0.30	0.15
Max plantar flexion M in preswing (Nm/kg)	0.93	0.13	1.14	0.09	1.37	0.26
Measure (unit)	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**
Weight (kg)	20.80	18.17, 23.85	36.00	34.50, 44.40	52.25	26.60, 46.40
Height (m)	1.08	1.08, 1.17	1.31	1.30, 1.32	1.64	1.30, 1.58
Leg length (m)	0.51	0.50, 0.57	0.66	0.64, 0.68	0.85	0.65, 0.83
%GC when the sagittal hip M equals 0 (%)	5.94	5.94, 11.63	4.95	4.95, 16,83	21.15	17.26, 26.80
Max hip power generation in stance (Nm/kg)	1.65	0.32, 2.61	1.06	0.40, 2.29	0.61	0.36, 0.92
Max knee flexion angle in swing (°)	64.26	62.55, 67.50	66.48	62.11, 72.55	62.54	58.91, 67.65
Max dorsiflexion M in LR (Nm/kg)	0.00	-0.06, 0.00	-0.01	-0.02, -0.01	-0.13	-0.18, -0.09
Max ankle power generation in preswing (W/kg)	1.69	0.30, 2.23	2.16	0.74, 3.02	4.06	3.46, 4.71
Max ankle power absorption in LR (W/kg)	-0.38	-0.72, -0.29	-0.58	-0.71, -0.49	-0.37	-0.57, -0.33

Abbreviations; in alphabetic order: BMI = Body Mass Index; DMD = Duchenne Muscular Dystrophy; %GC = percentage of gait cycle; IQR = interquartile range of 25th and 75th percentile; kg = kilograms; kg/m^2 = kilograms per square meters; LR = loading response; m = meters; M = moment; Max = maximal; Nm/Kg = Newton meters per kilogram bodyweight; ROM = range of motion; SD = standard deviation; sec = seconds; TD = typically developed; W/kg = Watts per kilogram bodyweight; ° = degrees.

[a] ankle angle with dorsiflexion as a positive and plantar flexion as a negative value.

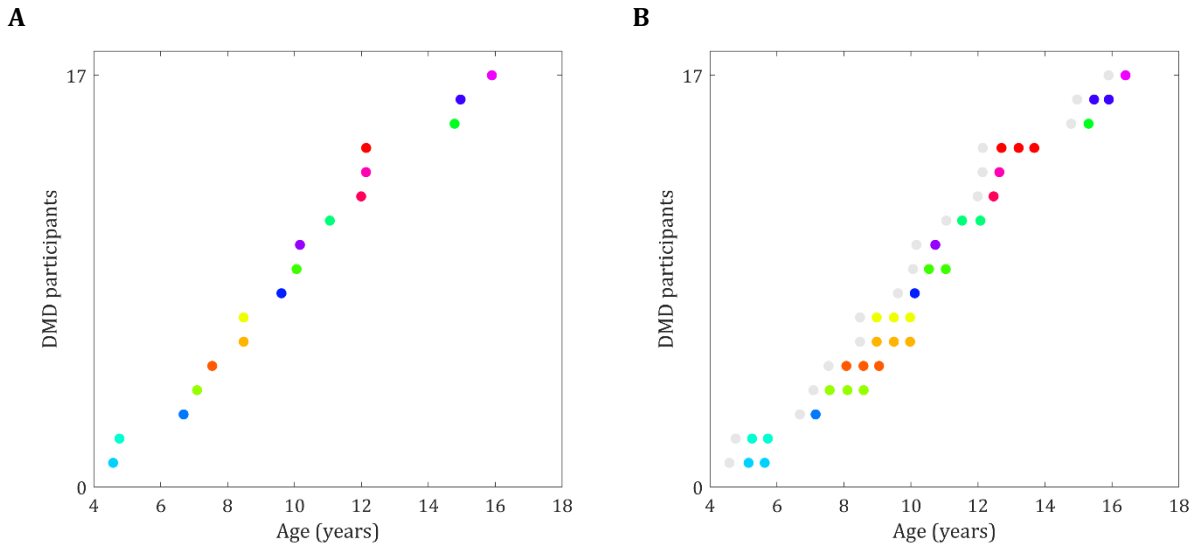

Figure 1.
Age distribution of the children with DMD included in this study. Each colour corresponds with one DMD participant. Panel **A** shows an overview of the age distribution at baseline. Panel **B** shows an overview of the ascending ages at the follow-up assessments. The grey dots represent the baseline assessments of each DMD participant.
Abbreviations; DMD = Duchenne Muscular Dystrophy.

3.1. Alterations in the gait pattern

Outcomes of the first hypothesis indicate that eleven of the 27 included gait parameters have a significant regression coefficient and thus, show a significant interaction with increasing age (table 3). Considering the spatiotemporal gait measures, all parameters achieve statistical significance. The cadence (figure 2B) decreases with 0.06 steps/sec ($p < 0.001$), the normalized step length (figure 2D) with 0.01 ($p < 0.01$) and the normalized walking velocity (figure 2C) with 0.01 ($p < 0.001$), as the boys with DMD age one year. On the contrary, the normalized step width (figure 2A) has a positive regression coefficient, indicating that the distance between both feet in the frontal plane augments with 0.01 per year ($p < 0.001$). Additionally, five kinematic parameters appear to have significant regression coefficients ($p < 0.001$). The maximal hip extension (figure 3A) and dorsiflexion angle (figure 3D) in swing decrease with 2.92° and 1.46°, over a period of one year respectively. The maximal pelvic tilt (figure 3C) enhances in relation to increasing age. Concretely, this means that over a period of one year, the maximal anterior pelvic tilt significantly increases with 1.57°. Significant longitudinal positive regressions are also detected in the following kinematic parameters: the range of motion of the pelvic obliquity (figure 3E) and the Gait Profile Score (GPS) (figure 3B). The pelvic obliquity range of motion increases with 0.91° over a one-year period. Since the regression coefficient of the GPS amounts 0.51, we can state that the children with DMD deviate 0.51° from TD children per year in their overall gait pattern. Finally,

significant relationships were found for two kinetic parameters. The maximal hip extension (figure 4A) and hip flexion moment in stance (figure 4B) decrease with 0.05 Nm/kg ($p < 0.001$) and 0.03 Nm/kg ($p < 0.01$) over one year, respectively.

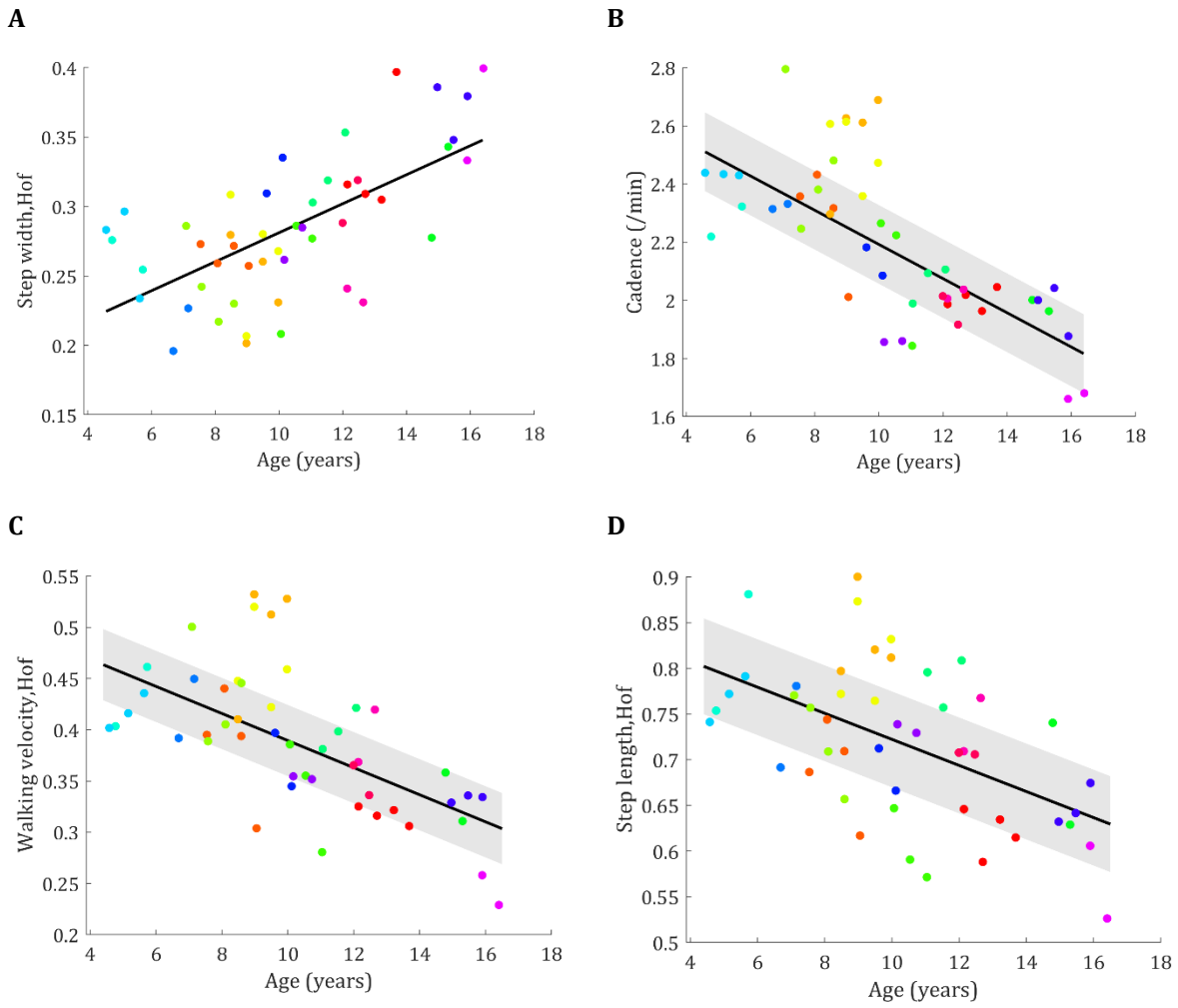

Figure 2.
Relationship between increasing age and alterations in the spatiotemporal gait parameters (hypothesis one). Each colour corresponds with the values of one participant with DMD. Age (years) is the fixed predictor. (A) Normalized step width, (B) cadence (/min), (C) normalized walking velocity and (D) normalized step length represent the expected responses, with a significant regression coefficient of 0.01 ($p < 0.001$), -0.06 ($p < 0.001$), -0.01 ($p < 0.001$) and -0.01 ($p < 0.01$), respectively. Figure 2A shows the mean regression line computed by the simple linear regression model. Figures 2B, C and D show the mean regression line and grey band, computed by the random intercepts model. The grey band represents one standard deviation of the added random intercepts. Abbreviations: DMD = Duchenne Muscular Dystrophy; Max = maximal; min = minutes. p-value from regression analysis in Linear mixed effects models.

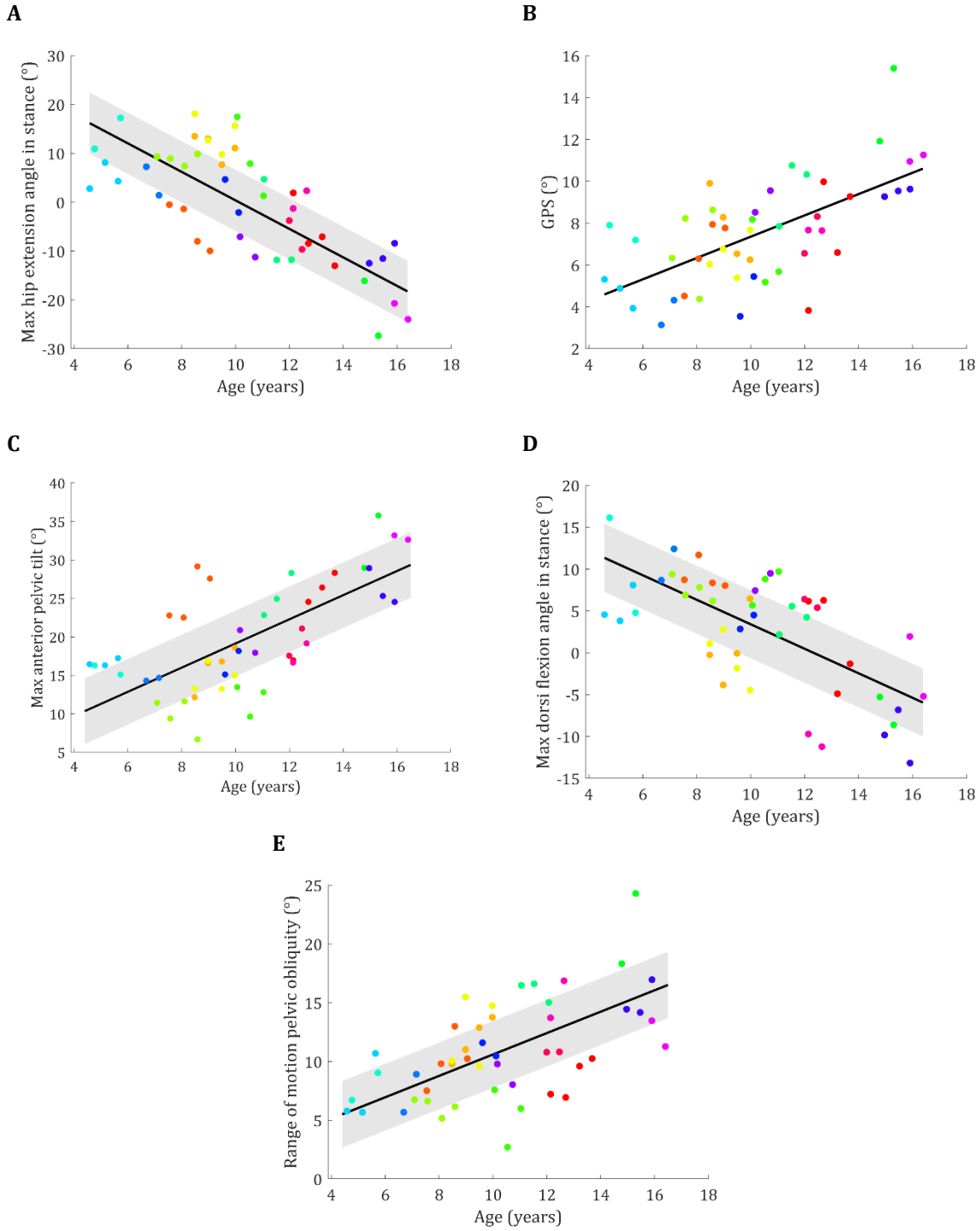

Figure 3.

Relationship between increasing age and alterations in the kinematic gait parameters (hypothesis one). Each colour corresponds with the values of one participant with DMD. Age (years) is the fixed predictor. (A) Maximal hip extension angle in stance (°), (B) GPS (°), (C) maximal anterior pelvic tilt (°), (D) maximal dorsiflexion angle in stance (°) and (E) range of motion of the pelvic obliquity (°) represent the expected responses, with a significant regression coefficient of -2.92 ($p < 0.001$), 0,51 ($p < 0.001$), -1.46 ($p < 0.001$), 1.57 ($p < 0.001$) and 0.91 ($p < 0.001$), respectively. Figure 3B shows the mean regression line computed by the simple linear regression model. Figures3A, C, D and E show the mean regression line and grey band, computed by the random intercepts model. The grey band represents one standard deviation of the added random intercepts.

Abbreviations: DMD = Duchenne Muscular Dystrophy; GPS = Gait Profile Score; Max = maximal; ° = degrees. p-value from regression analysis in Linear mixed effects models.

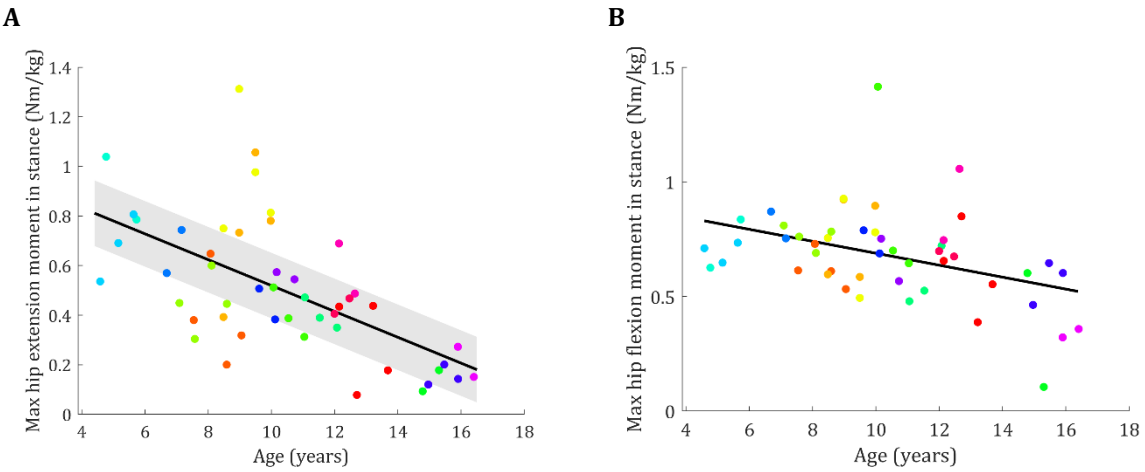

Figure 4.

Relationship between increasing age and alterations in the kinetic gait parameters (hypothesis one). Each colour corresponds with the values of one participant with DMD. Age (years) is the fixed predictor. (A) Maximal hip extension moment in stance (Nm/kg) and (B) maximal hip flexion moment in stance (Nm/kg) represent the expected responses, with a significant regression coefficient of -0.05 ($p < 0.001$) and -0.03 ($p < 0.01$), respectively. Figure 4B shows the mean regression line computed by the simple linear regression model. Figure 4A shows the mean regression line and grey band, computed by the random intercepts model. The grey band represents one standard deviation of the added random intercepts.

Abbreviations: DMD = Duchenne Muscular Dystrophy; Max = maximal; Nm/kg = Newton meters per kilogram bodyweight. p-value from regression analysis in Linear mixed effects models.

Table 3.
Significance of the regression coefficients of the gait parameters in relation to increasing age, listed by ascending p-value (hypothesis one)

Gait measure (unit)	Regression coefficient	p-value[1]	Corrected BH α-level
Max hip extension angle in stance (°)	-2.92*	<0.001	0.002
Step width, Hof	0.01*	<0.001	0.004
Gait Profile Score (°)	0.51*	<0.001	0.006
Cadence (/sec)	-0.06*	<0.001	0.007
Max anterior pelvic tilt (°)	1.57*	<0.001	0.009
Max dorsiflexion angle in swing (°)	-1.46*	<0.001	0.011
Max hip extension M in stance (Nm/kg)	-0.05*	<0.001	0.013
Walking velocity, Hof	-0.01*	<0.001	0.015
ROM pelvic obliquity (°)	0.91*	<0.001	0.017
Step length, Hof	-0.01*	0.002	0.019
Max hip flexion M in stance (Nm/kg)	-0.03*	0.004	0.020
Max hip abduction angle in stance (°)	0.43	0.028	0.022
Max ankle power absorption in LR (W/kg)	0.04	0.024	0.024
Ankle angle at initial contact (°)[a]	-1.25	0.033	0.026
Max dorsiflexion angle in stance (°)	-0.74	0.033	0.028
ROM pelvic rotation (°)	0.92	0.033	0.030
Max plantar flexion M in preswing (Nm/kg)	0.02	0.038	0.032
Max knee flexion M in stance (Nm/kg)	0.01	0.058	0.033
Max knee extension M in stance (Nm/kg)	-0.02	0.121	0.035
Max hip abduction M in stance (Nm/kg)	0.01	0.146	0.037
Max hip power generation in stance (W/kg)	-0.10	0.181	0.039
Max hip abduction angle in swing (°)	0.32	0.195	0.041
Max knee extension angle in swing (°)	0.35	0.273	0.043
%GC when the sagittal hip M equals 0 (%)	-0.35	0.393	0.044
Max dorsiflexion M in LR (Nm/kg)	-0.00	0.430	0.046
Max ankle power generation in preswing (Nm/kg)	0.04	0.601	0.048
Max knee extension angle in swing (°)	0.07	0.869	0.050

Abbreviations; in alphabetic order: BH = Benjamini-Hochberg procedure; %GC = percentage of gait cycle; LR = loading response; M = moment; Max = maximal; Nm/kg = Newton meters per kilogram bodyweight; sec = seconds; W/kg = Watts per kilogram bodyweight; ° = degrees.

[a] ankle angle with dorsiflexion as a positive and plantar flexion as a negative value.

***** statistically significant correlation between the gait parameter and increasing age.

[1] p-value from regression analysis in Linear mixed effects models.

3.2. Alterations in the lower limb muscle strength

Three of the seven muscle strength outcomes, collected to test the second hypothesis, have a statistically significant interaction with increasing age (table 4). In all three parameters, a negative regression coefficient is obtained, which indicates progressive muscle strength decline as the children grow older. The plantar flexor strength (figure 5A) decreases with 0.02 Nm/kg ($p < 0.01$), the hip extensor strength (figure 5B) with 0.03 Nm/kg ($p < 0.01$) and the knee extensor strength (figure 5C) with 0.04 Nm/kg ($p < 0.05$), as the boys with DMD age one year.

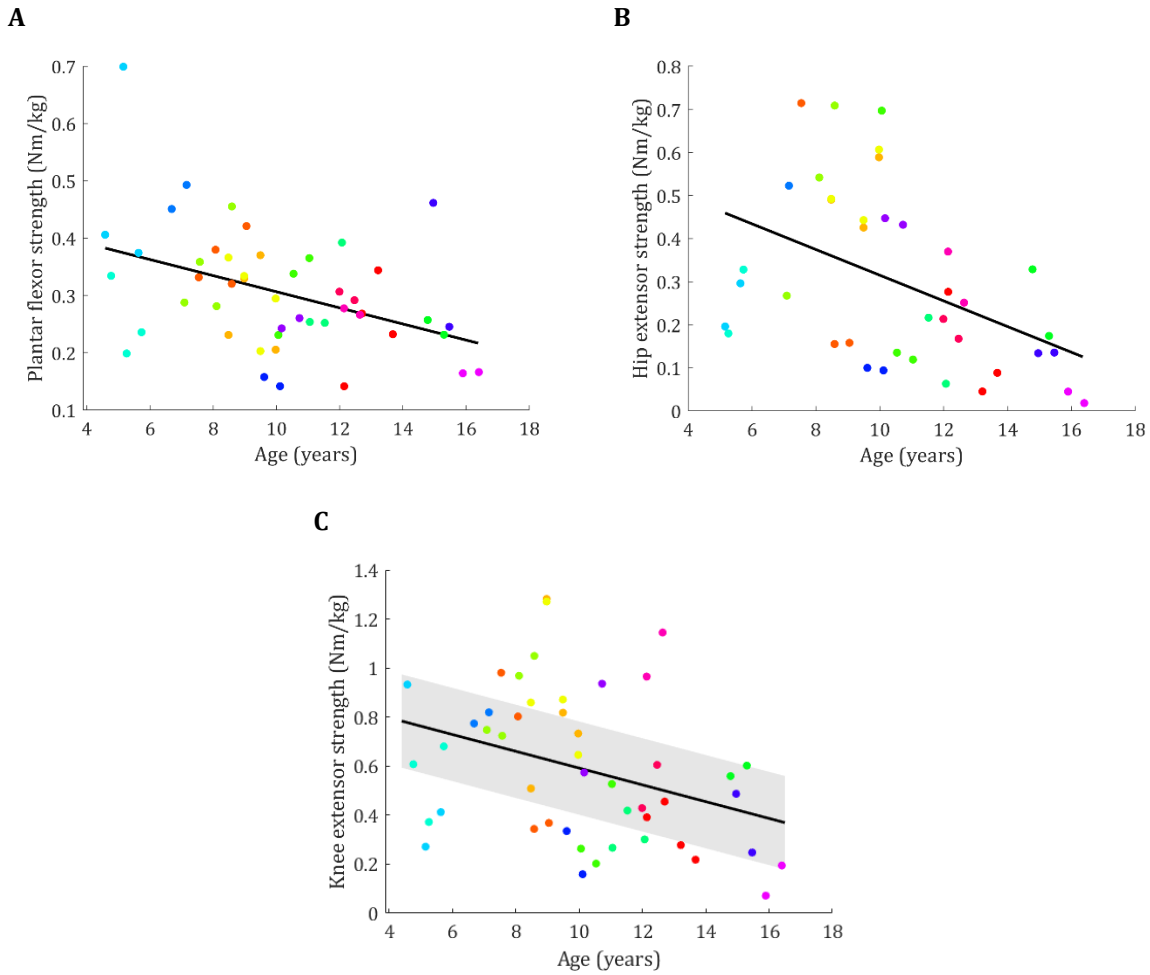

Figure 5.
Relationship between increasing age and alterations in the muscle strength parameters (hypothesis two). Each colour corresponds with the values of one participant with DMD. The values (Nm/kg) on the y-axis decrease as muscle strength decreases. Age (years) is the fixed predictor. (A) Plantar flexor (Nm/kg), (B) hip extensor (Nm/kg) and (C) knee extensor (Nm/kg) strength represent the expected responses, with a significant regression coefficient of 0.02 ($p < 0.01$), 0.03 ($p < 0.01$) and 0.04 ($p < 0.05$), respectively. Figures 5A and B show the mean regression line computed by the simple linear regression model. Figure 5C shows the mean regression line and grey band, computed by the random intercepts model. The grey band represents one standard deviation of the added random intercepts.
Abbreviations: DMD = Duchenne Muscular Dystrophy; Nm/kg = Newton meters per kilogram bodyweight. p-value from regression analysis in Linear mixed effects models.

Table 4.
Significance of the regression coefficients of the muscle strength parameters in relation to increasing age, listed by ascending p-value (hypothesis two)

Muscle strength measure (Nm/kg)	Regression coefficient	p-value[1]	Corrected BH α-level
Plantar flexors	-0.02*	0.003	0.007
Hip extensors	-0.03*	0.004	0.014
Knee extensors	-0.04*	0.013	0.021
Knee flexors	-0.01	0.066	0.029
Dorsiflexors	-0.01	0.089	0.036
Hip abductors	-0.01	0.239	0.043
Hip flexors	-0.02	0.284	0.050

Abbreviations; in alphabetic order: BH = Benjamini-Hochberg procedure; Nm/kg = Newton meters per kilogram bodyweight.
***** statistically significant correlation between the muscle strength parameter and increasing age.
[1] p-value from regression analysis in Linear mixed effects models.

3.3. Alterations in the gait pattern in relation to lower limb muscle weakness

For our third hypothesis, in reference to the VIF outcomes (Appendix 9: table 3b), multicollinearity seemed to be non-existent in all the examined interactions. Four of the 33 examined interactions between a gait and a lower limb muscle weakness parameter had statistically significant ($p < 0.001$) regression coefficients (table 5). Firstly, a significant interaction between the maximal hip extension angle and hip extensor weakness is found (figure 6B). The regression coefficient for this interaction amounts -22.47, which indicates that for a hip extensor weakness increase of 1 Nm/kg, the maximal hip extension angle during stance phase decreases with 22.47°. Subsequently, an increased normalized step width of 0.14 and an increased maximal hip abduction moment in stance of 0.41 Nm/kg, are both linked with hip abductor weakening of 1 Nm/kg (figure 6D and 6C, respectively). Finally, we can state that the maximal knee extension moment is reduced with 0.46 Nm/kg, as the knee extensors weaken with 1 Nm/kg in the children with DMD (figure 6A).

A complete overview of the outcomes obtained from testing our hypotheses with linear mixed effects models can be found in the Appendix (Appendix 9: table 1-3b).

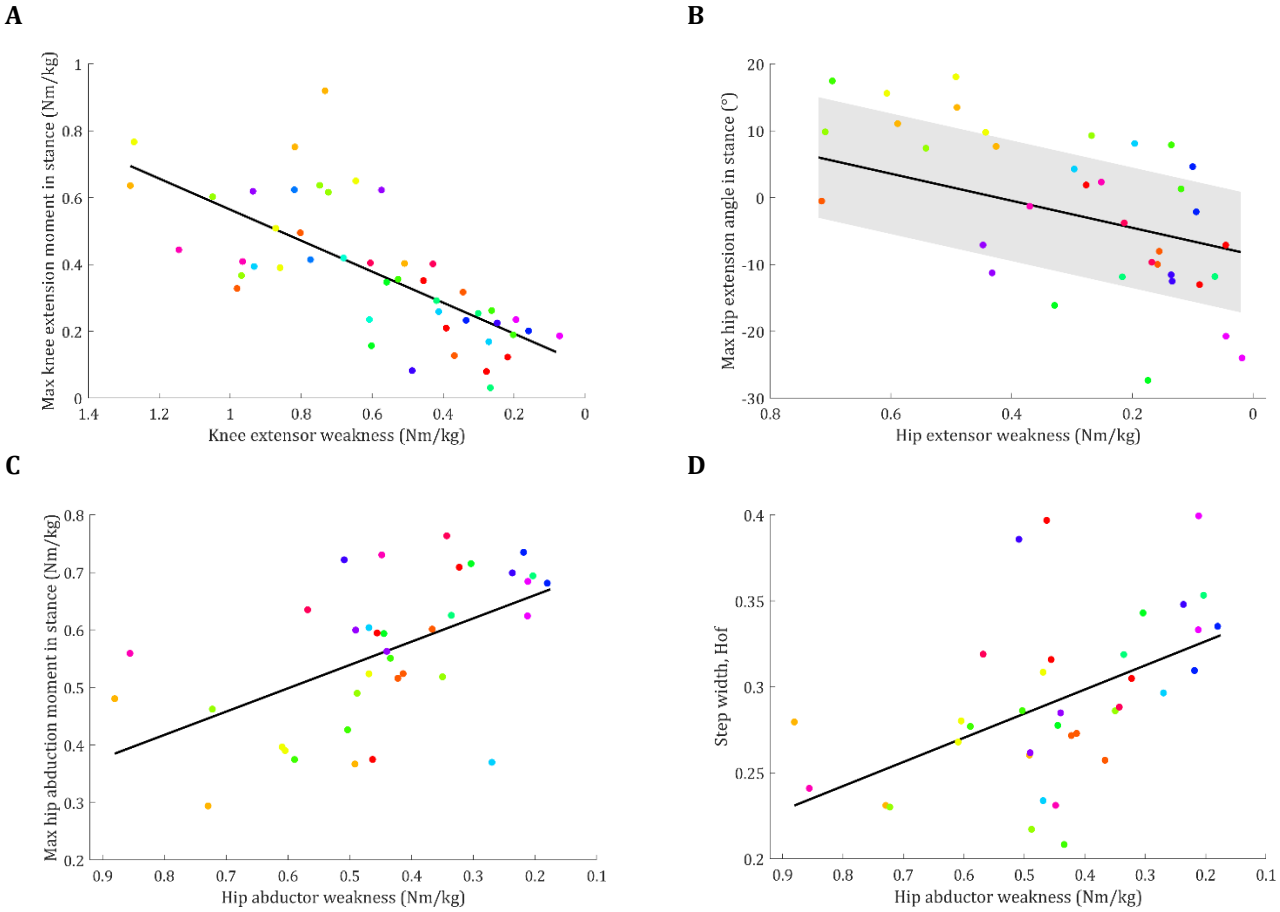

Figure 6.

Relationship between increasing muscle weakness and alterations in the gait parameters (hypothesis three). Each colour corresponds with the values of one participant with DMD. Because muscle strength declines with increasing age, the muscle strength values (Nm/kg) on the x-axis are displayed in descending order. Hereby, the x-axis represents increasing muscle weakness. (A) Knee extensor, (B) hip extensor, (C) hip abductor and (D) hip abductor weakness (Nm/kg) are the fixed predictors. (A) Maximal knee extension moment in stance (Nm/kg), (B) maximal hip extension moment in stance (Nm/kg), (C) maximal hip abduction moment in stance (Nm/kg) and (D) normalized step width represent the expected responses, with a significant regression coefficient of -0.46 ($p < 0.001$), -22.47 ($p < 0.001$), 0.41 ($p < 0.001$) and 0.14 ($p < 0.01$), respectively. Figures 6A, C and D show the mean regression line computed by the simple linear regression model. Figure 6B shows the mean regression line and grey band, computed by the random intercepts model. The grey band represents one standard deviation of the added random intercepts.

Abbreviations: DMD = Duchenne Muscular Dystrophy; Max = maximal; Nm/kg = Newton meters per kilogram bodyweight. p-value from multiple regression analysis in Linear mixed effects models.

Table 5.

Significance of the regression coefficients of the gait parameters in relation to muscle weakness, listed by ascending p-values (hypothesis three)

Gait measure (units)	Muscle weakness measure (Nm/kg)	Regression coefficient	p-value[1]	BH α-level
Max knee extension M in stance (Nm/kg)	Knee extensors	-0.46*	<0.001	0.002
Max hip extension angle in stance (°)	Hip extensors	-22.47*	<0.001	0.003
Max hip abduction M in stance (Nm/kg)	Hip abductors	0.41*	<0.001	0.005
Step width, Hof	Hip abductors	0.14*	<0.001	0.006
Max hip extension M in stance (Nm/kg)	Hip extensors	-0.36	0.022	0.008
Max knee extension angle in swing (°)	Knee extensors	-4.89	0.023	0.009
Max anterior pelvic tilt (°)	Hip extensors	7.59	0.056	0.011
Walking velocity, Hof	TCS	-0.12	0.099	0.012
Gait Profile Score (°)	TCS	4.91	0.152	0.014
Max hip abduction angle in stance (°)	Hip abductors	-3.11	0.218	0.015
Max ankle power absorption in LR (W/kg)	Dorsiflexors	-0.60	0.224	0.017
Max hip extension angle in stance (°)	Knee extensors	5.40	0.239	0.018
Max knee flexion angle in swing (°)	Dorsiflexors	27.94	0.292	0.020
Max hip abduction angle in swing (°)	Plantar flexors	-4.58	0.318	0.021
Max ankle power absorption in LR (W/kg)	Plantar flexors	-0.36	0.324	0.023
Ankle angle at initial contact (°)[a]	Dorsiflexors	10.49	0.350	0.024
Max anterior pelvic tilt (°)	Knee extensors	3.26	0.353	0.026
ROM pelvic obliquity (°)	Hip abductors	2.80	0.384	0.027
%GC when the sagittal hip M equals 0 (%)	Hip extensors	-5.40	0.477	0.029
Max hip abduction angle in swing (°)	Hip flexors	-1.23	0.515	0.030
Max dorsiflexion M in LR (Nm/kg)	Dorsiflexors	0.06	0.525	0.032
Max hip power generation in stance (Nm/kg)	Hip extensors	-0.32	0.525	0.033
Cadence	TCS	-0.17	0.569	0.035
Ankle angle at initial contact (°)[a]	Knee extensors	-1.36	0.575	0.036
Max plantar flexion M in preswing (Nm/kg)	Plantar flexors	0.09	0.578	0.038
Max dorsiflexion angle in stance (°)	Plantar flexors	4.18	0.619	0.039
Step length, Hof	TCS	-0.03	0.706	0.041
Max hip abduction angle in swing (°)	Dorsiflexors	-3.25	0.731	0.042
Max ankle power absorption in LR (W/kg)	Knee extensors	-0.05	0.774	0.044
Max dorsiflexion angle in swing (°)	Dorsiflexors	1.42	0.904	0.046
Max ankle power generation in preswing (W/kg)	Plantar flexors	0.08	0.940	0.047
ROM pelvic rotation (°)	TCS	-0.36	0.950	0.049
Max dorsiflexion angle in stance (°)	Knee extensors	0.13	0.957	0.050

Because muscle strength declines with increasing age, this insinuates an increase in muscle weakness. This is represented by the muscle weakness measures in the second column.

Abbreviations; in alphabetic order: BH = Benjamini-Hochberg procedure; %GC = percentage of gait cycle; LR = loading response; M = moment; Max = maximal; Nm/kg = Newton meters per kilogram bodyweight; ROM = range of motion; TCS = total composite score; W/kg = Watts per kilogram bodyweight; ° = degrees.

[a] ankle angle with dorsiflexion as a positive and plantar flexion as a negative.

***** statistically significant correlation between the gait and muscle weakness parameter.

[1] p-value from multiple regression analysis in Linear mixed effects models.

4. Discussion

This study investigated the alterations of the pathological gait pattern and the lower limb muscle strength over time, as well as the contribution of muscle weakness to gait deviations, in growing ambulant children with DMD. Three hypotheses were formulated. Firstly, we hypothesized that gait deviations increase as children with DMD age. Subsequently, a specific lower limb muscle strength decline was presumed in the growing boys. Finally, we hypothesized that enhanced lower extremity muscle weakness was linked to an increase in gait deviations.

4.1. Alterations in the gait pattern

Significant alterations in the gait pattern with increasing age were detected in the children with DMD, confirming our first hypothesis. Specifically, four spatiotemporal, five kinematic and two kinetic gait parameters showed significant changes over time.

Considering the spatiotemporal outcomes from this study, a decrease in cadence, walking velocity and step length, as well as an increased step width, showed meaningful relationships with increasing age. Decline in cadence and walking velocity were similarly described findings over the progressive ambulation stages, introduced by Sutherland et al.[23] As a broader step width leads to a larger base of support, this could be an adaptation mechanism in children with DMD to improve balance, as previously suggested by D'Angelo et al.[27] Even though it was previously reported that the GPS cannot distinguish any gait deviation differences between children with DMD with different motor abilities[45], the current results obtained a significant GPS outcome. This may be explained by the longitudinal study design with multiple follow-up measurements, increasing the power of this study, compared to previous cross-sectional research. Consequently, this study proposed that the GPS is a valid outcome parameter for longitudinal DMD research. Since the GPS is an overall gait index, estimated by combining several kinematic parameters[44], this finding can presumably be explained by significant alterations in the other four kinematic outcomes, i.e. pelvic obliquity range of motion, ankle dorsiflexion angle in swing, maximal hip extension angle and maximal anterior pelvic tilt. The pelvic obliquity range of motion increase, was an earlier reported finding in studies comparing children with DMD to TD children.[18,29] The other three findings are also consistent with the three progressive stages described by Sutherland et al.[23] Progressive loss of dorsiflexion in swing was reported over all ambulation stages, with the least impairment in the early and the most in the late group. Decreased hip extension angle and exaggerated anterior pelvic tilt, were described as features to move the ground reaction force in front of the knee-joint to minimize stress on the quadriceps and avoid

knee buckling during single-limb support. Both features were present in the transitional group and increased further in the late stage of the disease.[23] D'Angelo et al.[27] suggested that enhanced hip abduction and knee flexion in swing may occur as compensation strategies for decreased ankle dorsiflexion in swing. Those alterations were observed trends with increasing age in the current study, however, these did not reach a significant level. As described by Gaudreault et al.[29], a decreased hip extension angle could potentially cause a shorter step length and therefore a diminished walking velocity, both significant progressive declines in our study. Further, previous studies indicated that reduced hip extension could be a possible consequence of the more distinct anterior pelvic tilt.[23,28,29] Lastly, considering the results from the kinetic parameters, a diminished maximal hip flexion moment and hip extension moment in stance with age, were obtained results from the current study. It has been suggested that children with DMD tend to compensate for weak hip extensors, by quickly positioning the ground reaction force behind the hip joint, thereby creating a decreased hip extension moment.[18,30] Consequently, we assume that the hip flexion moment might be higher, compared to TD children at a young age. This reduced hip extension moment in stance, in children with DMD compared with TD children, was also previously described by Heberer et al.[19] But, as children with DMD get older, the anterior pelvic tilt increases, possibly caused by psoas muscle contractures[27–29]. Hereby, the ground reaction force gets closer to the hip joint, resulting in a reduced hip flexion moment.

According to the systematic review of Goudriaan et al.[30], previous research investigated gait pattern alterations in an exploratory and cross-sectional way, mainly comparing 3DGA outcomes from TD children to boys with DMD. Due to the heterogeneity of the DMD-samples in those studies, but also the disconformity in measurement methods, parameter selection and data analysis, the diverse results could not be easily compared. Also, not all children with DMD display an identical disease progression. To that end, longitudinal evaluations of the same cohort, with larger sample sizes, were recommended for future research to provide more valuable information about the natural history of pathological DMD gait, compared to cross-sectional studies. As a result, the longitudinal aspect of this study could add novel insights into the current knowledge on DMD gait, as well as into the evaluation of the efficacy of medical interventions and clinical decision making. In that way, the current study aims to contribute to ambulation prolongation in boys with DMD.

4.2. Alterations in the lower limb muscle strength

The results in the current study demonstrated progressive muscle-specific strength decline in the lower limbs. Specifically, the plantar flexor, hip extensor and knee extensor muscles showed a

statistically significant deterioration in the aging children with DMD. Therefore, our second hypothesis was confirmed.

Previous cross-sectional studies described similar findings of decreased muscle strength in boys with DMD.[31,34,39,58,59] In addition to the outcomes from this study, previous literature also reported reduced muscle strength of the hip flexors, hip abductors, knee flexors and dorsiflexors compared to TD children.[31,34,58] However, we need to be aware that comparing the current longitudinal results with outcomes from those cross-sectional studies is complex, and therefore perhaps not accurate, due to disconformity in units expressing muscle strength (e.g. discrepancy in corrections applied for the effect of bodyweight), different applied measurement methods and study designs. Previous longitudinal findings reported cut-off ages for apparent muscle strength decline in boys with DMD.[38] Lerario et al.[38] reported knee extensor and flexor weakening only above the age of seven and a half years, with a more advanced decline in boys older than nine years old. Buckon et al.[39] also found that age has a significant influence on the hip flexor, knee extensor and ankle dorsiflexor muscle strength deterioration, at the baseline of their natural history study, with more profound weakness in older boys (≥ 8 years) compared to younger boys (4-7 years) with DMD. In this study, baseline muscle strength differences between the older (≥ 10 years) and younger (< 10 years) children with DMD were not statistically explored. Only a tendency of reduced strength in the older group at baseline could be found.

Nevertheless, we were the first to demonstrate significant muscle strength decline within a longitudinal perspective for the plantar flexors, as well as for the hip and knee extensors in growing boys with DMD of various ages, using Linear mixed effects models. As previous research reported cut-off ages of distinctly present muscle weakening in boys with DMD, future longitudinal studies probably need more complex models to indicate potential non-linear trends in the long term. In that way, significant longitudinal changes for other muscle groups might appear. Results from the current research show what muscle groups are deteriorating significantly in a growing DMD cohort, which can contribute to further insight into the natural history of lower limb muscle weakening.[38,39,41,48] In that way, this study could provide more insight in accurate clinical decision making and in the effects of novel medication or other therapy forms on muscle weakness in children with DMD.

4.3. Alterations in the gait pattern in relation to lower limb muscle weakness

Based on the current dataset, four gait parameters showed a significant interaction with weakness in a muscle group. Thus, weakness of only four muscle groups could be linked to the corresponding gait alterations. Therefore, the third hypothesis was only partially confirmed.

Firstly, decrease in maximal hip extension angle during stance is linked to increased hip extensor weakness. As already mentioned before, previous research suggested that hip extensor weakness in combination with hip flexor tightness can lead to an increased anterior pelvic tilt.[27–29] It was assumed that this resulted in a reduced hip extension (in stance)[23,28,29], which could be confirmed by our results. Although hip abductor weakening in relation to increasing age was not a current (borderline) significant outcome, hip abductor weakness still showed an interaction with increased step width. A larger base of support is described as a compensation strategy for gluteus medius weakness, and may possibly be adopted with the aim of maintaining stability during gait.[23,27] It is worthwhile to highlight that in other pathologies, such as cerebral palsy and spina bifida, increased hip abductor weakness is commonly accompanied by a decrease in the maximal hip abduction moment during stance.[60,61] Yet, the current results indicate the opposite pattern (increased weakness is associated with increased hip abduction moment). This is a contradiction, and therefore an unexpected discovery in our results. As the ground reaction force is more laterally positioned relative to the hip joint with a larger step width in boys with DMD, we expect a reduced hip abduction moment. Thus, we assume that the preserved hip abduction moment, despite the hip abduction weakness, can be explained by the passive component contribution of the stiff and shortened hip abductor muscles. Moreover, due to trunk weakness, the compensatory lateral trunk leaning for hip abductor weakness, which is commonly observed in children with cerebral palsy and spina bifida[60,61], cannot be adopted to the same extent by boys with DMD.[23,62,63] Further, earlier research assumed that executing shock absorption with a reduced knee extensor moment was a compensation mechanism for quadriceps weakness in boys with DMD.[27] To our knowledge, we were the first to confirm this presumption with the found interaction between knee extensor weakening and a decreased maximal knee extension moment. This finding indicates that children with DMD compensate for quadriceps weakness by positioning the ground reaction force closer to or in front of the knee joint, as this leads to a reduced knee extension moment.[18,23,27] It has been suggested in previous studies that gait with an increased anterior pelvic tilt and toe walking, may be a compensation strategy for acquiring the aforementioned ground reaction force modifications.[23,27] However, the

interaction of knee extensor weakness with maximal anterior pelvic tilt, as well as with the ankle position in stance, did not reach statistical significance in our results.

Although it is generally excepted that progressive muscle weakness has a prominent effect on the gait pattern and functional abilities in boys with DMD[7,8,17,22–24,31,34,64,65], significant associations between gait deviations and muscle-specific weakening, have not yet been reported to our knowledge. Recent cross-sectional research of Goudriaan et al.[31] did not find significant linear associations between analogous relationships on a similar group of boys with DMD, compared to the current study. Investigating interactions between lower limb muscle weakness and gait deviations is challenging due to several reasons. Firstly, beside muscle weakness, muscle contractures and stiffness, may also have an influence on the gait pattern. It is likely that primarily those factors cause the difficulties in determining interactions between muscle weakness and gait deviations. As an example, forward tibia rotation could be controlled at the end of stance phase by the passive strength contribution of the ankle plantar flexion contractures in boys with DMD and therefore contribute to the net plantar flexion moment, despite their plantar flexor weakness.[46] In contrast, contractures and stiffness of the plantar flexors can reinforce a forefoot pattern at initial contact, thereby inducing a negative effect on the gait pattern.[23] Consequently, it remains unclear if muscle contractures and stiffness have beneficial or harmful effects on the DMD gait pattern. Therefore, future studies should investigate the influence of muscle strength, combined with muscle contractures and stiffness, on the gait pattern, to improve clinical decision making towards therapy interventions in boys with DMD. Lastly, it is presumable that the contribution of diversified weakened muscle groups in the alterations and eventual loss of ambulation has a higher variability than estimated, due to variation in disease progression in this population.[39,41,65,66] However, this was partly corrected in the current study by the use of linear mixed effects models. Since we are the first to find significant interactions between lower limb weakness and specific gait alterations in children with DMD, the testing of our third hypothesis may have contributed to a better understanding of the underlying muscle mechanisms in the altered gait pattern.[39,41,65,66]

4.4. Strengths and limitations of this study with further recommendations for future research

Considering the statistical analyses carried out in the current study, some important aspects should be emphasized. Both the longitudinal aspect of the investigation in the first two hypotheses, and the mixed longitudinal-cross-sectional aspect in exploring the third hypothesis, can be considered unique in DMD research. By executing repeated measurements within the same

DMD cohort, combined with models with added random effects, more information about the variation in parameter onset as well as evolution, and thus the data distribution, can be obtained compared to cross-sectional studies. The data distribution was represented by standard deviations from the random effects (Appendix 9: table 1, 2 and 3B), computed by the random intercepts model, or, random intercepts and slope model. The mixed longitudinal-cross-sectional design applied in the current study, is characterized by more power, and therefore more generalizability. Especially in comparison to previous cross-sectional studies investigating the disease progression, with wide age ranges and small sample sizes, as described in the systematic review by Goudriaan et al.[30] The current study showed promising results for forthcoming research. Therefore, it is recommended for future studies to apply similar (mixed) longitudinal study designs and models with added random effects, to further investigate gait and strength parameters in a long-term perspective in children with DMD.

Although this study provides valuable and clinically meaningful outcomes, its limitations must be acknowledged, on which further recommendations for future research can be formulated. First, mostly boys in the early and transitional ambulation stage of the disease[23] were included in this study. It is expected that more progressive and significant changes in the gait pattern and muscle weakness at the end of ambulation, can be detected in older boys with DMD.[23,24,58] Moreover, a follow-up period of 18 months or less, might be too short for detecting subtle alterations in the observed outcomes. Yet, since this dataset is further growing, the longitudinal aspect of this study design with repeated measurements in the same cohort, is expected to sufficiently compensate for the limited follow-up period. The lack of older boys and the possibly too short follow-up period, combined with the perhaps too heterogenous DMD-sample at baseline, may have led to the seldomly applied random slopes model in testing the hypotheses (Appendix 7: table 1, 2 and 3). Because examining the discrepancy in the disease progression between younger and older children with DMD could be relevant, use of the random slopes as an expression of the deterioration rate could be a useful tool in forthcoming studies, combined with a larger number of older children, followed-up over an extended period. In addition, it can be expected for future studies with more data, and therefore more power, that in case of variation in parameter onset and evolution between the included participants, models with added random factors would increasingly appear to be the best fit. Even though possibly more significant outcomes could have been obtained by using more complex analyses, only linear regression analyses were performed in the current study. Nevertheless, the significant outcomes resulting from simple linear regression analysis show what parameters can be relatively simply predicted, because of their rather similar evolution in children with DMD. When the random intercepts regression analysis is applied, this indicates a parameter variation in onset. Therefore, those parameters are

suggested as useful variables for using in clinical trials. An additional limitation of the current study is the exclusion of trunk motion evaluation. Further analysing those gait parameters, alongside lower limb and pelvic features, could provide valuable information, e.g. about several compensation strategies. Lastly, a total of 34 parameters was included in this study. As a result, we had to correct the alpha level quite strictly for multiple testing. Therefore, it was challenging to demonstrate significance. However, knowledge of the obtained significant parameters from this study can be useful, as future research could focus on further investigating these specific outcomes in boys with DMD.

Considering the testing of our second hypothesis, three limitations can be recognized. Firstly, during muscle strength assessment, we had to consider the risk for muscle fatigue of the child and therefore avoid an overload of measurements.[66] For that reason, although muscle weakness is equally bilaterally presented in DMD[17,38,67], only unilateral MVICs were assessed. Another study reported the exclusion of ankle dorsiflexors measurements to overcome muscle exhaustion in boys with DMD.[58] Hence, there seems to be no consensus yet in research about the prevention of muscle fatigue during muscle strength testing. In case of demotivation of the (young) child during measurement, the hip muscle assessments were excluded in this study. Consequently, fewer lower limb muscle strength outcomes were achieved. Secondly, a recent study showed that young TD children (3-7 years) are capable of executing muscle strength tests, but more encouragements and physical efforts at maximal load may be needed to achieve the most accurate results.[68] Even though encouragements were applied in a standardized manner during measurement in this study, a lack of motivation could still have influenced the MVIC outcomes in the (younger) children with DMD. Finally, we acknowledge that a small learning effect due to repetitive measurements is possible. Yet, there was a six-monthly period between every follow-up assessment, which probably provided sufficient wash-out.[69]

As our sample includes growing ambulant children with DMD, it is important to recognize longitudinal strength and gait changes that occur as a part of normal growth, to prevent mislabelling those alterations as evidence of gait pathology.[23] In growing TD children, a correlation can be found between muscle strengthening and increased muscle volumes, as well as between enhanced internal moments and increasing bodyweight.[70,71] In terms of kinetics, gait is commonly considered to reach adult-like patterns only between the ages of five and seven years or older.[72,73] Also, spatiotemporal parameters values, such as an increased step length and walking velocity, are evidently influenced by the growing body of the child. With the objective to take those underlying grow effects into consideration, the muscle strength and kinetic gait outcomes were divided by the child's bodyweight. The spatiotemporal parameters were converted into non-dimensional values by the equation of Hof.[43] Because of the progressive

major weight gain in boys with DMD, particularly in relation to corticosteroids treatment[74], it is possible that correcting for bodyweight is not the most appropriate method to compensate for growth effects.[74] This could have contributed to the significant decreased internal moments and muscle strength outcomes in our study. Therefore, only correcting for bodyweight might be insufficient. Accordingly, it is recommended for future studies investigating longitudinal muscle strength and gait changes in DMD, to take underlying grow effects into consideration by implementing adequate corrections for anthropometric characteristics. Similarly to the grow effects on the kinetic, muscle strength and spatiotemporal data, maturation processes can affect kinematic parameter outcomes, which causes larger inter- and intrasubject variability in children compared to adults, as reported by other authors. This variability seemed more pronounced with decreasing age.[75,76] It has been reported that kinematic parameters mature in growing TD children in the ages up to 3,5-4 years.[76] Since a delay in the gross motor development is a typical characteristic in DMD[9], it is likely that some of the youngest boys in this study (with an age range starting from four and a half years old), did not have much walking experiences at the time of measurement.[75,76] This may have resulted in a still immature gait pattern. No correction for the underlying maturation effects on the kinematic parameters was applied. Comparing longitudinal kinematic data from DMD children with longitudinal outcomes from TD children in future studies, could make it possible to distinguish the kinematic alterations caused by the gait pathology and by the normal underlying maturation processes.

Previous studies have already described the effects of long-term treatment with corticosteroids on the ambulation, with a prolongation up to two to five years.[10] In addition, maintenance of muscle strength and muscle function in boys with DMD result from corticosteroids intake.[77–79] However, limited research has discussed those outcomes longitudinally or examined the effect of the pharmacological treatment on alterations in specific spatiotemporal, kinematic or kinetic parameters. For that reason, further research about this topic in boys with DMD is recommended.

5. Conclusion

In summary, the current study detected significant longitudinal alterations in four spatiotemporal, five kinematic and two kinetic gait parameters, as well as in three muscle-specific strength parameters, in ambulant growing children with DMD. Further only four, but remarkably meaningful, significant interactions between increased lower limb weakness and gait deviations were found. More insight into the natural history of the DMD progression on the one hand and the underlying causes of the pathological gait on the other hand, could be gained by using statistical models with added random effects in future longitudinal studies with longer follow-up periods, as well as by including larger study samples with a higher number of older children, in both longitudinal and cross-sectional future DMD research.

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Appendix 1.
Populaire Samenvatting

Duchenne Musculaire Dystrofie (DMD) is een erfelijke, degeneratieve spieraandoening. 1 op 3500-5000 jongens wordt geboren met deze spierziekte, veroorzaakt door een mutatie in het dystrofine gen op het X-chromosoom. Dit resulteert in een tekort aan het eiwit dystrofine, dat een belangrijke rol speelt in het stabiliseren en beschermen van onze spieren. Door spierstructuurveranderingen met bijhorend spierkrachtverlies, ontwikkelen de groeiende jongens een afwijkend gangpatroon en verliezen ze alreeds tijdens de tienerjaren hun ambulantie. DMD is een frequent voorkomende spierziekte die al vanaf de kleuterleeftijd tot uiting komt, voornamelijk in de onderste ledematen. Tot op heden blijft de aandoening ongeneeslijk, waardoor uiteindelijk lethale complicaties ontstaan.

Om de invloed van veelbelovende medicatie en andere therapeutische interventies op het ziekteverloop te bepalen, is er nood aan longitudinaal onderzoek dat specifieke en subtiele veranderingen van het afwijkend gangpatroon en de spierkracht van de onderste ledematen in ambulante jongens met DMD in kaart brengt. Om die reden werden in deze masterthesis groeiende jongens met DMD (4-17 jaar) om de 6 maanden opgevolgd, over een totaalperiode van maximaal 18 maanden. Om de gang- en spierkrachtafwijkingen gestandaardiseerd te kunnen kwantificeren, werden respectievelijk ganganalysemetingen en spierkrachttesten uitgevoerd tijdens de zesmaandelijkse opvolgmomenten. Op basis van eerdere studies zijn dit objectieve en betrouwbare meetmethoden gebleken. De ganganalyses vonden plaats in een gespecialiseerd ganglabo, waarbij gegevens over de bewegende gewrichten tijdens het stappen werden verzameld. De kracht werd getest door de maximaal vrijwillig geleverde kracht gedurende vijf tellen te meten, in verschillende spieren van het onderste lidmaat. Dankzij de longitudinale analyse in deze studie, konden significante gang- en spiersterktekenmerken worden aangetoond, die duidelijk en progressief achteruitgingen over de tijd in jongens met DMD.

Het is algemeen klinisch aanvaard dat spierzwakte in de onderste ledematen een beduidende rol speelt in het afwijkende gangpatroon bij kinderen met DMD. Dit is nochtans niet bewezen in eerder onderzoek. De oorsprong van de gangafwijkingen aantonen is waardevol om klinische besluitvorming over therapie, met het oog op de verlenging van de ambulante periode, te verbeteren. Bijgevolg werd in deze masterthesis ook bestudeerd of interacties tussen bepaalde gangafwijkingen en spierzwakte van het onderste lidmaat konden gevonden worden. Enkele opmerkelijke en betekenisvolle interacties konden worden aangetoond, hoewel het er weinig in aantal waren. Het onderzoek naar de onderliggende oorzaken van het afwijkende gangpatroon blijft zeker een belangrijke piste in toekomstige studies.

Dankzij de bekomen resultaten van deze masterthesis kunnen we bijdragen aan nieuwe inzichten in de huidige kennis over het progressief afwijkende gangpatroon en de toenemende spierzwakte, alsook over de onderliggende spiermechanismes van de gangproblematiek in kinderen met DMD. De verworven resultaten kunnen eveneens dienen als uitkomstmaten voor toekomstig onderzoek, om dusdanig nog meer inzicht te verwerven in de ziekteprogressie van DMD.

Appendix 2.
Screenshot Approval by the local ethics committee *(Commissie Medische Ethiek KU Leuven, under S61324)* under the Declaration of Helsinki

De follow-up van veranderingen in spierstructuur en -functie met behulp van een geïntegreerd evaluatie platform bij ambulante kinderen met Duchenne Musculaire Dystrofie.

Communicatie geschiedenis

De verstrekte informatie toont aan dat het onderzoek in het kader van de masterproef integraal deel uitmaakt van een studie die reeds werd goedgekeurd door een erkend ethisch comité.

U hoeft bijgevolg geen nieuw dossier in te dienen in het kader van uw masterproef. Wel dient u het UZ/KU Leuven toe te voegen als nieuw deelnemend centrum aan het huidige dossier indien dit nog niet het geval was. Gelieve u bij het betreffende comité te informeren en u te conformeren aan de daar geldende procedures en hun adviezen te volgen.

Onder voorbehoud van de volledigheid en correctheid van de door u verstrekte gegevens, krijgt u hierbij de goedkeuring om het onderzoek in het kader van de masterproef te starten.

Wij willen u erop attent maken dat u zelf verantwoordelijk blijft voor uw onderzoek. Bovendien doet elke wijziging aan de door u verstrekte gegevens omtrent de onderzoeksopzet elke eerdere goedkeuring vervallen. U dient in dat geval een amendement te maken aan uw huidig dossier bij het comité dat eerder uw dossier goedkeurde.

Details met de antwoorden van de vragenlijst zijn hier raadpleegbaar.

Dossiernr.	MP007963
Stage	Masterproef FaBeR
Faculteit/opleiding	Faculteit Bewegings- en Revalidatiewetenschappen - LOBW-REVAKI-REHAB-IMAPA-SGK-EMA
Studiefase	eerste fase
Academiejaar	2018-2019
Korte omschrijving / abstract	DMD is een degeneratieve neuromusculaire aandoening met een prevalentie van 1 op 3500-5000 mannelijke geboortes. De klinische symptomen bij ambulante kinderen met DMD zijn gesitueerd thv de onderste ledematen, waarbij er een afwijkend gangpatroon wordt ontwikkeld, als ook veranderingen in de spierfunctie en -structuur, zoals een verminderende spierkracht en spierintegriteit (bijvoorbeeld toename van intramusculair vet). Deze masterthesis onderzoekt het afwijkend gangpatroon, de spierzwakte en veranderingen in spierstructuur van het onderste lidmaat inambulante, groeiende kinderen met DMD. We zullen, naast de standaard klinische metingen, een geïntegreerd evaluatie platform (ganganalyse in combinatie met isometrische krachttesten en ultrasonografie) gebruiken om deze problemen te beschrijven en de relaties tussen de verschillende symptomen te onderzoeken. Het gaat om kinderen met DMD tussen 5 en 14 jaar en ze worden om de 6 maanden opgevolgd over een periode van 1 jaar. Binnen je masterproef zal je de kans krijgen om de verschillende metingen te volgen, te ondersteunen en te analyseren, bijgestaan door je co-promotoren en de kinesitherapeut van het UZ Leuven. Je komt met dit onderzoek in contact met een bijzondere populatie van kinderen en je krijgt de mogelijk om ze gedurende het onderzoek mee op te volgen. Verder zal je verantwoordelijk zijn voor de rekrutering van typische ontwikkelende kinderen die zullen dienen als controlegroep.

Toegepaste technieken	3D gait analysis, dynamometry, ultrasound
Key publication	Goudriaan et al. (2018) Gait deviations in Duchenne muscular dystrophy-Part 2. Statistical non-parametric mapping to analyze gait deviations in children with Duchennemuscular dystrophy.
Trefwoorden	isometric strength, ultrasound, gross motor function, 3D gait analysis, follow-up, Duchenne muscular dystrophy
Gewenste taal van communicatie	nl
Promotor	Prof Kaat Desloovere (u0011470)
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Appendix 3.
Guideline for authors

Richtlijnen voor auteurs voor publicaties van de GUIDELINES FOR AUTHORS in *Gait and Posture*:

https://www.elsevier.com/journals/gait-and-posture/0966-6362/guide-for-authors

Appendix 4.
Overview of the corticosteroid dose intake in the included children with DMD at the different follow-up assessments

DMD-child	Follow-up assessment	Age (years)	CS dose (mg)	DMD-child	Follow-up assessment	Age (years)	GCs dose (mg)
Child 1	1	12.14	21	Child 8	1	11.06	18
	2	12.70	21		2	11.53	18
	3	13.21	21		3	12.07	18
	4	13.68	21	Child 9	1	4.77	0
Child 2	1	7.54	15		2	5.26	12
	2	8.07	15		3	5.73	12
	3	8.58	15	Child 10	1	4.58	0
	4	9.05	15		2	5.16	15
Child 3	1	8.48	12		3	5.64	15
	2	8.98	12	Child 11	1	6.69	18
	3	9.49	15		2	7.16	18
	4	9.98	15	Child 12	1	9.61	21
Child 4	1	8.48	12		2	10.11	21
	2	8.98	12	Child 13	1	14.96	12
	3	9.49	15		2	15.47	12
	4	9.98	15		3	15.91	12
Child 5	1	7.09	12	Child 14	1	10.16	18
	2	7.58	12		2	10.73	18
	3	8.11	12	Child 15	1	15.90	18
	4	8.59	15		2	16.40	18
Child 6	1	10.06	24	Child 16	1	12.14	18
	2	10.54	24		2	12.64	18
	3	11.04	24	Child 17	1	11.99	21
Child 7	1	14.78	21		2	12.47	21
	2	15.30	18				

Abbreviations; in alphabetic order: CS = corticosteroids; DMD = Duchenne Muscular Dystrophy; mg = milligrams.

Appendix 5.
Overview of the data distribution of the parameters, outcomes from the Shapiro-Wilk test

Table 1.
Overview of the data distribution of the patient characteristic parameters, listed by ascending p-value

Patient characteristic measure (unit)	p-value[1]	Corrected BH α-level
Leg length (m)	0.002	0.010
Weight (kg)	0.003	0.020
Height (m)	0.004	0.030
BMI (kg/m²)	0.056	0.040
Age (years)	0.363	0.050

Abbreviations; in alphabetic order: BH = Benjamini-Hochberg procedure; BMI = Body Mass Index; kg = kilograms; kg/m^2 = kilograms per squared meters; m = meters.
[1] p-value from the Shapiro-Wilk test

Table 2.
Overview of the data distribution of the muscle strength parameters, listed by ascending p-value

Muscle strength measure (Nm/kg)	p-value[1]	Corrected BH α-level
Dorsiflexion	0.003	0.007
Plantar flexion	0.012	0.014
Hip abduction	0.074	0.021
Hip extension	0.111	0.029
Knee extension	0.115	0.036
Knee flexion	0.145	0.043
Hip flexion	0.795	0.050

Abbreviations; in alphabetic order: BH = Benjamini-Hochberg procedure; Nm/kg = Newton meters per kilogram bodyweight.
[1] p-value from the Shapiro-Wilk test.

Table 3.
Overview of the data distribution of the gait parameters, listed by ascending p-value

Gait measure (unit)	p-value[1]	Corrected BH α-level	Gait measure (unit)	p-value[1]	Corrected BH α-level
%GC when the sagittal hip M equals 0 (%)	< 0.001	0.002	Max dorsiflexion angle in stance (°)	0.112	0.028
Max dorsiflexion M in LR (Nm/kg)	< 0.001	0.004	Max hip extension angle in stance (°)	0.135	0.030
Max hip power generation in stance (Nm/kg)	< 0.001	0.006	Max hip abduction angle in stance (°)	0.168	0.032
Max knee flexion angle in swing (°)	< 0.001	0.007	Step width, Hof	0.268	0.033
Max ankle power absorption in LR (W/kg)	< 0.001	0.009	Gait Profile Score (°)	0.310	0.035

Max ankle power generation in preswing (W/kg)	0.005	0.011	Cadence (/sec)	0.316	0.037
Max hip flexion M in stance (Nm/kg)	0.014	0.013	Max hip abduction angle in swing (°)	0.455	0.039
Max dorsiflexion angle in swing (°)	0.018	0.015	Max plantar flexion M in preswing (Nm/kg)	0.473	0.041
Max knee extension M in stance (Nm/kg)	0.076	0.017	Max hip abduction M in stance (Nm/kg)	0.513	0.043
Max hip extension M in stance (Nm/kg)	0.082	0.019	Max knee flexion M in stance (Nm/kg)	0.584	0.044
Max anterior pelvic tilt (°)	0.097	0.020	Walking velocity, Hof	0.758	0.046
Max knee extension angle in swing (°)	0.103	0.022	Ankle angle at initial contact (°)[a]	0.841	0.048
ROM pelvic rotation (°)	0.105	0.024	Step length, Hof	0.905	0.050
ROM pelvic obliquity (°)	0.105	0.026			

Abbreviations; in alphabetic order: BH = Benjamini-Hochberg procedure; %GC = percentage of gait cycle; LR = loading response; M = moment; Max = maximal; Nm/kg = Newton meters per kilogram bodyweight; ROM = range of motion; sec = seconds; W/kg = Watts per kilogram bodyweight; ° = degrees.

[a] ankle angle with dorsiflexion as a positive and plantar flexion as a negative value.

[1] p-value from the Shapiro-Wilk test.

Appendix 6.
Quantile-Quantile plots of the extremily non-normally distributed parameters

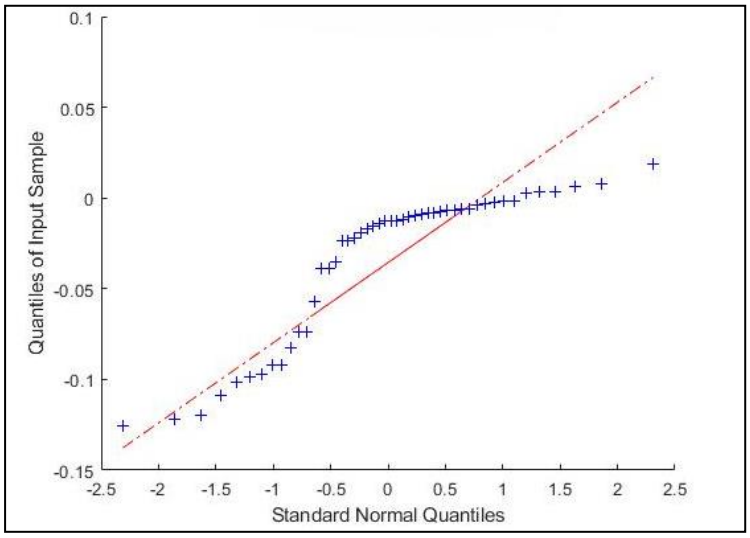

Figure 1.
Maximal dorsiflexion moment in loading response (Newton meters per kilogram bodyweight)

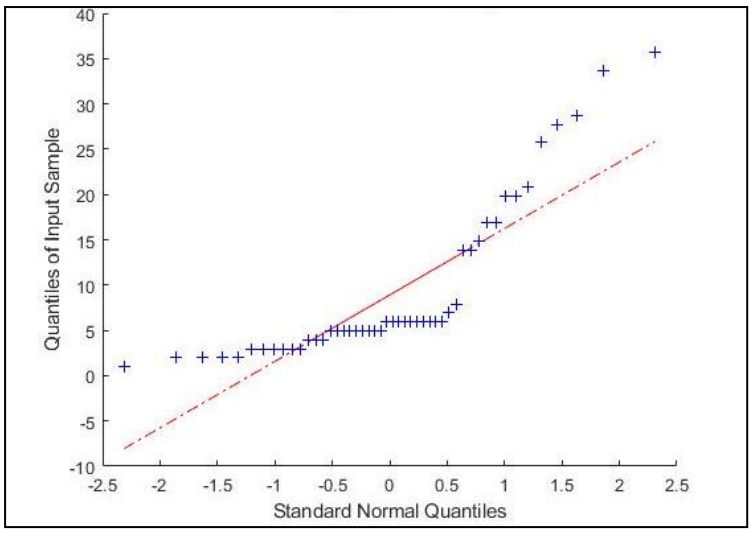

Figure 2.
Percentage of the gait cycle when the sagittal hip moment equals zero (%)

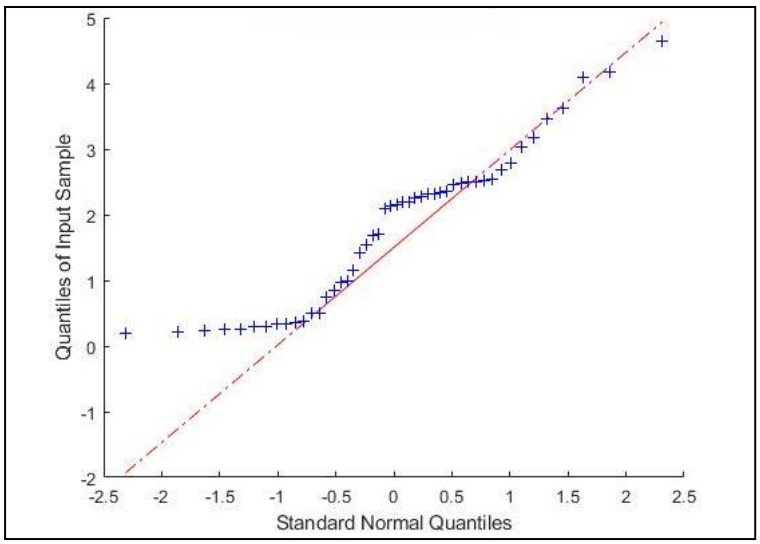

Figure 3.
Maximal ankle power generation in preswing (Watts per kilogram bodyweight)

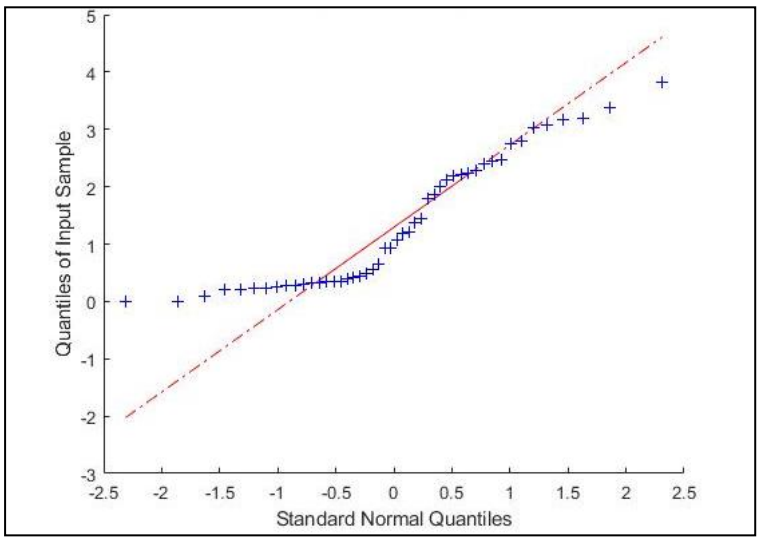

Figure 4.
Maximal hip power generation in stance (Newton meters per kilogram bodyweight)

Appendix 7.
Comparison between the three models for the best statistical fit from Linear mixed effects models

Table 1.
Comparison between the three models for the best statistical fit: gait parameters in relation to increasing age (first hypothesis)

Gait measure (unit)	model 1			model 2			model 3			model 1 vs. 2	model 2 vs. 3	model 1 vs. 3
	AIC	*BIC*	*LogLik*	*AIC*	*BIC*	*LogLik*	*AIC*	*BIC*	*LogLik*	*p-value*[1]	*p-value*[1]	*p-value*[1]
Cadence (/sec)	-17.51	-11.90	11.76	-28.58	-21.10	18.29	-25.05	-13.82	18.52	< 0.001	0.794	0.004
Step length, Hof	-111.70	-106.08	58.85	-127.83	-120.35	67.92	-125.10	-113.87	68.55	< 0.001	0.531	< 0.001
Walking velocity, Hof	-139.14	-133.52	72.57	-148.08	-140.60	78.04	-144.92	-133.69	78.46	< 0.001	0.659	0.008
Step width, Hof	-169.81	-164.20	87.91	-171.15	-163.67	89.58	-168.62	-157.39	90.31	0.068	0.480	0.187
Max anterior pelvic tilt (°)	298.36	303.98	-146.18	269.03	276.51	-130.52	273.02	284.25	-130.51	< 0.001	0.995	< 0.001
ROM pelvic obliquity (°)	259.77	265.38	-126.88	239.31	246.79	-115.65	236.98	248.21	-112.49	< 0.001	0.042	< 0.001
ROM pelvic rotation (°)	324.51	330.12	-159.25	287.86	295.35	-139.93	290.29	301.51	-139.14	< 0.001	0.454	< 0.001
Max hip extension angle in stance (°)	339.02	344.63	-166.51	316.20	323.68	-154.10	319.45	330.67	-153.72	< 0.001	0.687	< 0.001
Max hip abduction angle in stance (°)	244.74	250.35	-119.37	228.03	235.51	-110.01	231.99	243.22	-110.00	< 0.001	0.982	< 0.001
Max hip abduction angle in swing (°)	267.69	273.31	-130.85	248.92	256.40	-120.46	246.60	257.82	-117.30	< 0.001	0.042	< 0.001
Max knee extension angle in swing (°)	289.45	295.06	-141.72	277.10	284.59	-134.55	272.11	283.34	-130.06	< 0.001	0.011	< 0.001
Max knee flexion angle in swing (°)	324.00	329.61	-159.00	325.93	333.41	-158.96	329.90	341.13	-158.95	0.788	0.987	0.992
Ankle angle at initial contact (°)[a]	289.67	295.28	-141.83	280.73	288.21	-136.36	284.04	295.27	-136.02	< 0.001	0.709	0.009
Max dorsiflexion angle in stance (°)	299.81	305.43	-146.91	288.31	295.80	-140.16	288.74	299.96	-138.37	< 0.001	0.167	< 0.001
Max dorsiflexion angle in swing (°)	298.59	304.21	-146.30	285.26	292.75	-138.63	288.34	299.57	-138.17	< 0.001	0.630	0.001
Gait Profile Score (°)	203.77	209.39	-98.89	202.50	209.99	-97.25	205.26	216.49	-96.63	0.070	0.539	0.211
Max hip abduction M in stance (Nm/kg)	-64.33	-58.71	35.16	-66.60	-59.11	37.30	-63.74	-52.51	37.87	0.039	0.566	0.144
Max hip extension M in stance (Nm/kg)	-5.15	0.46	5.58	-13.09	-5.60	10.54	-11.08	0.15	11.54	0.002	0.370	0.008
Max hip flexion M in stance (Nm/kg)	-20.96	-15.35	13.48	-18.97	-11.48	13.48	-15.58	-4.35	13.79	0.937	0.738	0.893
Max knee extension M in stance (Nm/kg)	350.20	355.81	-172.10	351.97	359.45	-171.98	355.63	366.86	-171.82	0.629	0.848	0.905
Max knee flexion M in stance (Nm/kg)	-17.89	-12.27	11.94	-28.21	-20.72	18.10	-24.86	-13.63	18.43	< 0.001	0.721	0.005

Max plantar flexion M in preswing (Nm/kg)	-68.81	-63.19	37.40	-72.51	-65.03	40.26	-68.51	-57.29	40.26	0.017	0.999	0.127
Max ankle power absorption in LR (W/kg)	-167.25	-161.64	86.63	-175.77	-168.29	91.89	-173.04	-161.81	92.52	0.001	0.532	0.008
%GC when the sagittal hip M equals 0 (%)	-55.76	-50.14	30.88	-68.35	-60.87	38.18	-64.85	-53.63	38.43	< 0.001	0.778	0.002
Max dorsiflexion M in LR (Nm/kg)	11.06	16.68	-2.53	-6.97	0.52	7.48	-4.01	7.22	8.01	< 0.001	0.593	< 0.001
Max ankle power generation in preswing (W/kg)	158.02	163.63	-76.01	129.77	137.26	-60.89	133.72	144.95	-60.86	< 0.001	0.977	< 0.001
Max hip power generation in stance (Nm/kg)	151.66	157.27	-72.83	123.83	131.31	-57.92	127.33	138.56	-57.67	< 0.001	0.780	< 0.001

Abbreviations; in alphabetic order: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; %GC = percentage of gait cycle; LogLik = Log-Likelihood, LR = loading response; M = moment; Max = maximal; model 1 = simple linear regression model; model 2 = random intercepts model; model 3 = random intercepts and slopes model; Nm/kg = Newton meters per kilogram bodyweight; ROM = range of motion; sec = seconds; W/kg = Watts per kilogram bodyweight; ° = degrees.

[1] p-value from the Likelihood-Ratio test.

[a] ankle angle with dorsiflexion as a positive and plantar flexion as a negative value.

Table 2.

Comparison between the 3 models for the best statistical fit: muscle strength parameters in relation to increasing age (second hypothesis)

Muscle strength measure (Nm/kg)	**model 1**			**model 2**			**model 3**			**model 1 vs. 2**	**model 2 vs. 3**	**model 1 vs. 3**
	AIC	*BIC*	*LogLik*	*AIC*	*BIC*	*LogLik*	*AIC*	*BIC*	*LogLik*	*p-value*[1]	*p-value*[1]	*p-value*[1]
Hip flexors	32.45	37.44	-13.22	30.65	37.30	-11.32	33.24	43.22	-10.62	0.051	0.494	0.157
Hip extensors	-17.41	-12.42	11.70	-16.07	-9.42	12.04	-13.66	-3.68	12.83	0.414	0.453	0.588
Hip abductors	-23.34	-18.35	14.67	-23.99	-17.33	15.99	-20.05	-10.07	16.02	0.104	0.972	0.439
Knee extensors	21.71	27.32	-7.85	16.06	23.54	-4.03	19.86	31.08	-3.93	0.006	0.905	0.049
Knee flexors	-48.63	-43.02	27.32	-52.55	-45.07	30.28	-49.85	-38.62	30.93	0.015	0.523	0.065
Dorsiflexors	-123.37	-117.75	64.68	-130.68	-123.19	69.34	-130.02	-118.79	71.01	0.002	0.188	0.005
Plantar flexors	-84.47	-78.86	45.24	-83.83	-76.34	45.91	-83.34	-72.11	47.67	0.244	0.173	0.182

Abbreviations; in alphabetic order: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; LogLik = Log-Likelihood, model 1 = simple linear regression model; model 2 = random intercepts model; model 3 = random intercepts and slopes model; Nm/kg = Newton meters per kilograms bodyweight.

[1] p-value from selection of the Linear mixed effects models comparison with the best fit.

Table 3.
Comparison between the 3 models for the best statistical fit: gait parameters in relation to increasing muscle weakness (third hypothesis)

Gait measure (unit)	Muscle weakness measure (Nm/kg)	model 1			model 2			model 3			model 1 vs. 2	model 2 vs. 3	model 1 vs. 3
		AIC	*BIC*	*LogLik*	*AIC*	*BIC*	*LogLik*	*AIC*	*BIC*	*LogLik*	*p-value*[1]	*p-value*[1]	*p-value*[1]
Step width, Hof	Hip abductors	-121.23	-116.47	63.61	-120.65	-114.31	64.32	-116.68	-107.18	64.34	0.233	0.985	0.694
Max hip extension angle in stance (°)	Hip extensors Knee extensors	268.35	274.68	-130.17	246.04	253.96	-118.02	252.99	268.83	-116.50	< 0.001	0.693	< 0.001
Gait Profile Score (°)	TCS	174.53	179.28	-84.26	168.47	174.80	-80.23	166.98	176.49	-77.49	0.005	0.065	0.004
Cadence (/sec)	TCS	6.39	11.14	-0.20	-1.66	4.68	4.83	1.39	10.89	5.30	0.002	0.622	0.012
Max anterior pelvic tilt (°)	Hip extensors Knee extensors	240.12	246.46	-116.06	222.72	230.64	-106.36	225.13	240.97	-102.57	< 0.001	0.180	< 0.001
Max dorsiflexion angle in swing (°)	Dorsiflexors	307.18	312.73	-150.59	292.55	299.95	-142.28	294.30	305.40	-141.15	< 0.001	0.324	< 0.001
Max hip extension M in stance (Nm/kg)	Hip extensors	-7.825	-3.07	6.913	-12.19	-5.86	10.10	-8.81	0.70	10.40	0.012	0.736	0.073
ROM pelvic obliquity (°)	Hip abduction	210.44	215.19	-102.22	195.95	202.29	-93.98	198.46	207.96	-93.23	< 0.001	0.473	< 0.001
Walking velocity, Hof	TCS	-97.59	-92.84	51.79	-101.03	-94.70	54.52	-98.20	-88.70	55.10	0.020	0.558	0.085
Max hip abduction angle in stance (°)	Hip abductors	181.48	186.24	-87.74	174.90	181.24	-83.45	178.90	188.4	-83.45	0.003	0.999	0.035
Max ankle power absorption in LR (W/kg)	Dorsiflexors Plantar flexors Knee extensors	12.89	22.14	-1.45	-1.10	10.01	6.55	-6.10	21.65	18.05	< 0.001	0.006	< 0.001
Ankle angle at initial contact (°)[a]	Dorsiflexors Knee extensors	301.92	309.32	-146.96	287.58	296.83	-138.79	295.36	313.86	-137.68	< 0.001	0.817	0.005
Max dorsiflexion angle in stance (°)	Plantar flexors Knee extensors	298.81	306.21	-145.40	288.15	297.40	-139.07	294.60	313.10	-137.30	< 0.001	0.616	0.013
ROM pelvic rotation (°)	TCS	249.96	254.71	-121.98	219.09	225.42	-105.54	222.98	232.48	-105.49	< 0.001	0.949	< 0.001
Max plantar flexion M in preswing (Nm/kg)	Plantar flexors	-40.65	-35.10	23.33	-65.63	-58.23	36.81	-61.64	-50.54	36.82	< 0.001	0.991	< 0.001
Max knee extension M in stance (Nm/kg)	Knee extensors	-43.20	-37.65	24.60	-42.69	-35.29	25.35	-38.82	-27.72	25.41	0.221	0.939	0.654
Max hip abduction M in stance (Nm/kg)	Hip abductors	-53.6	-48.88	29.82	-53.35	-47.02	30.68	-49.43	-39.93	30.71	0.190	0.963	0.616

Max hip power generation in stance (Nm/kg)	Hip extensors	115.14	119.89	-54.57	89.23	95.56	-40.62	93.09	102.59	-40.55	< 0.001	0.934	< 0.001
Max hip abduction angle in swing (°)	Dorsiflexors Plantar flexors Hip flexors	209.96	217.87	-99.98	197.31	206.81	-92.66	213.13	236.88	-91.57	< 0.001	0.988	0.078
Step length, Hof	TCS	-81.66	-76.91	43.83	-93.45	-87.12	50.73	-91.28	-81.78	51.64	< 0.001	0.402	0.001
Max knee flexion angle in swing (°)	Dorsiflexors	318.01	323.56	-156.01	319.29	326.69	-155.65	312.78	323.88	-150.39	0.397	0.005	0.011
%GC when the sagittal hip M equals 0 (%)	Hip extensors	267.80	272.55	-130.90	269.50	275.83	-130.75	273.34	282.85	-130.67	0.583	0.926	0.929
Max dorsiflexion M in LR (Nm/kg)	Dorsiflexors	-164.76	-159.21	85.38	-170.45	-163.05	89.23	-166.45	-155.35	89.23	0.006	1.000	0.053
Max ankle power generation in preswing (W/kg)	Plantar flexors	155.75	161.30	-74.87	121.14	128.54	-56.57	124.63	135.73	-56.32	< 0.001	0.774	< 0.001
Max knee extension angle in swing (°)	Knee extensors	281.88	287.43	-137.94	270.57	277.97	-131.29	271.19	282.29	-129.60	< 0.001	0.185	< 0.001

Abbreviations; in alphabetic order: AIC = The Akaike Information Criterion; BIC = Bayesian Information Criterion; %GC = percentage of gait cycle; LogLik = Log-Likelihood, LR = loading response; M = moment; Max = maximal; model 1 = simple linear regression model; model 2 = random intercepts model; model 3 = random intercepts and slopes model; Nm/kg = Newton meters per kilograms bodyweight; ROM = range of motion; sec = seconds; TCS = total composite score; W/kg = Watts per kilogram bodyweight; ° = degrees.

[1] p-value from selection of the Linear mixed effects models comparison with the best fit.

[a] ankle angle with dorsiflexion as a positive and plantar flexion as a negative value.

Appendix 8.
Overview of the residuals' distribution of the parameters, outcomes from the Shapiro-Wilk test

Table 1.
Overview of the residuals' distribution of the gait parameters in relation to increasing age, listed by ascending order (first hypothesis)

Gait measure (unit)	p-value[1]	Corrected BH α-level	Gait measure (unit)	p-value[1]	Corrected BH α-level
%GC when the sagittal hip M equals 0 (%)	<0.001	0.002	Max ankle power generation in preswing (W/kg)	0.428	0.028
Max knee flexion angle in swing (°)	<0.001	0.004	ROM pelvic obliquity (°)	0.440	0.0230
Max hip flexion M in stance (Nm/kg)	<0.001	0.006	Step length, Hof	0.533	0.032
Max dorsiflexion M in LR (Nm/kg)	<0.001	0.007	Max dorsiflexion angle in stance (°)	0.619	0.033
Max hip power generation in stance (Nm/kg)	0.012	0.009	Walking velocity, Hof	0.637	0.035
Max hip extension M in stance (Nm/kg)	0.082	0.011	Max hip abduction M in stance (Nm/kg)	0.652	0.037
ROM pelvic rotation (°)	0.103	0.013	Max knee flexion M in stance (Nm/kg)	0.676	0.039
Max hip abduction angle in stance (°)	0.111	0.019	Max anterior pelvic tilt (°)	0.727	0.041
Max knee extension angle in swing (°)	0.212	0.018	Max hip abduction angle in swing (°)	0.762	0.043
Max ankle power absorption in LR (W/kg)	0.212	0.016	Max knee extension M in stance (Nm/kg)	0.845	0.044
Max plantar flexion M in preswing (Nm/kg)	0.277	0.020	Max dorsiflexion angle in swing (°)	0.889	0.046
Cadence (/sec)	0.278	0.022	Ankle angle at initial contact (°)[a]	0.960	0.048
Step width, Hof	0.338	0.024	Gait Profile Score (°)	0.981	0.050
Max hip extension angle in stance (°)	0.421	0.026			

Abbreviations; in alphabetic order: BH = Benjamini-Hochberg procedure; %GC = percentage of gait cycle; LR = loading response; M = moment; Max = maximal;; Nm/kg = Newton meters per kilogram bodyweight; ROM = range of motion; sec = seconds; W/kg = Watts per kilogram bodyweight; ° = degrees.

[a] ankle angle with dorsiflexion as a positive and plantar flexion as a negative value.

[1] p-value from the Shapiro-Wilk test.

Table 2.

Overview of the residuals' distribution of the muscle strength parameters in relation to increasing age, listed by ascending p-values (second hypothesis)

Muscle strength measure (Nm/kg)	p-value[1]	Corrected BH α-level
Plantar flexors	0.039	0.007
Dorsiflexors	0.055	0.014
Hip extensors	0.069	0.021
Hip abductors	0.106	0.029
Knee flexors	0.205	0.043
Knee extensors	0.271	0.038
Hip flexors	0.680	0.050

Abbreviations; in alphabetic order: BH = Benjamini-Hochberg procedure; Nm/kg = Newton meters per kilogram bodyweight.

[1] p-value from the Shapiro-Wilk test.

Table 3.

Overview of the residual's distribution of the gait parameters in relation to muscle weakness, listed by ascending p-values (third hypothesis)

Gait measure (unit)	p-value[1]	Corrected BH α-level	Gait measure (unit)	p-value[1]	Corrected BH α-level
%GC when the sagittal hip M equals 0 (%)	<0.001	0.002	Max hip extension angle in stance (°)	0.329	0.028
Max dorsiflexion M in LR (Nm/kg)	0.005	0.004	Max knee flexion angle in swing (°)	0.354	0.030
Max hip power generation in stance (Nm/kg)	0.012	0.006	Cadence (/sec)	0.457	0.032
%GC when the sagittal hip M equals 0 (%)	0.034	0.008	Step length, Hof	0.528	0.034
Max hip extension M in stance (Nm/kg)	0.038	0.010	Max knee extension angle in swing (°)	0.609	0.036
Max dorsiflexion angle in stance (°)	0.072	0.012	ROM pelvic rotation (°)	0.663	0.038
Max hip abduction angle in swing (°)	0.088	0.014	Max hip abduction M in stance (Nm/kg)	0.751	0.040
Step width, Hof	0.137	0.016	ROM pelvic obliquity (°)	0.912	0.042
Max ankle power absorption in LR (W/kg)	0.195	0.018	Ankle angle at initial contact (°)[a]	0.915	0.044
Max plantar flexion M in preswing (Nm/kg)	0.199	0.020	Max dorsiflexion angle in swing (°)	0.931	0.046
Max hip abduction angle in stance (°)	0.201	0.022	Gait Profile Score (°)	0.990	0.048
Max anterior pelvic tilt (°)	0.224	0.024	Walking velocity, Hof	0.995	0.050
Max ankle power generation in preswing (W/kg)	0.306	0.026			

Abbreviations; in alphabetic order: BH = Benjamini-Hochberg procedure; %GC = percentage of gait cycle; LR = loading response; M = moment; Max = maximal; Nm/kg = Newton meters per kilogram bodyweight; ROM = range of motion; sec = seconds;W/kg = Watts per kilogram bodyweight; ° = degrees.

[a] ankle angle with dorsiflexion as a positive and plantar flexion as a negative value.

[1] p-value from the Shapiro-Wilk test.

Appendix 9.
Overview of the outcomes from Linear mixed effects models

Table 1.
Overview of the gait parameter outcomes in relation to increasing age from Linear mixed effects models (hypothesis one)

	FIXED EFFECTS				RANDOM EFFECTS		RESIDUALS
Gait measure	***Intercept (CI)***	***p-value[1]***	***Regression coefficient (CI)***	***p-value[1]***	***SD random intercept (CI) - SD random slope (CI)[2]***	***ICC random intercept***	***SD residuals (CI)***
Cadence (/sec)	2.78 (2.53, 3.03)	<0.001	-0.06* (-0.08, -0.04)	<0.001	0.14 (0.09, 0.21)	0.52	0.13 (0.10, 0.17)
Step length, Hof	0.86 (0.77, 0.96)	<0.001	-0.01* (-0.02, -0.01)	<0.001	0.05 (0.03, 0.08)	0.58	0.04 (0.04, 0.06)
Walking velocity, Hof	0.52 (0.45, 0.59)	<0.001	-0.01* (-0.02, -0.01)	<0.001	0.03 (0.02, 0.06)	0.44	0.04 (0.03, 0.05)
Step width, Hof	0.18 (0.14, 0.216)	<0.001	0.01* (0.01, 0.01)	<0.001			0.04 (0.03, 0.05)
Max anterior pelvic tilt (°)	3.43 (-3.59, 10.46)	0.330	1.57* (0.94, 2.21)	<0.001	4.26 (2.92, 6.22)	0.75	2.49 (1.94, 3.19)
ROM pelvic obliquity (°)	1.49 (-3.35, 6.32)	0.539	0.91* (0.47, 1.35)	<0.001	2.83 (1.90, 4.23)	0.69	1.91 (1.49, 2.45)
ROM pelvic rotation (°)	5.55 (-3.76, 14.85)	0.236	0.92 (0.08, 1.76)	0.0327	5.93 (4.11, 8.55)	0.81	2.84 (2.22, 3.65)
Max hip extension angle in stance (°)	-29.55 (-40.27, -18.84)	<0.001	-2.92* (1.95, 3.89)	<0.001	6.27 (4.22, 9.31)	0.68	4.26 (3.33, 5.47)
Max hip abduction angle in stance (°)	-1.76 (-5.95, 2.44)	0.404	0.43 (-0.81, -0.05)	0.028	2.43 (1.60, 3.67)	0.66	1.72 (1.34, 2.22)
Max hip abduction angle in swing (°)	-6.72 (-12.13, 1.32)	0.016	0.32 (-0.81, 0.17)	0.195	3.18 (2.13, 4.75)	0.70	2.09 (1.63, 2.69)
Max knee extension angle in swing (°)	30.12 (22.94, 37.30)	<0.001	0.07 (-0.73, 0.87)	0.869	11.48 (6.98, 18.88) 1.36 (0.85, 2.18)[2]		2.64 (2.05, 3.40)
Max knee flexion angle in swing (°)	62.88 (56.14, 69.62)	<0.001	0.35 (-0.28, 0.97)	0.273			6.64 (5.44, 8.11)
Ankle angle at initial contact (°)[a]	12.42 (5.92, 18.92)	<0.001	-1.25 (-1.84, -0.66)	0.033	3.50 (2.21, 5.57)	0.53	3.21 (2.49, 4.13)
Max dorsiflexion angle in stance (°)	21.89 (14.44, 29.34)	<0.001	-0.74 (-1.42, -0.06)	0.033	4.18 (2.70, 6.45)	0.59	3.35 (2.60, 4.31)
Max dorsiflexion angle in swing (°)	18.04 (10.81, 25.27)	<0.001	-1.46* (-2.12, -0.81)	<0.001	4.06 (2.65, 6.22)	0.61	3.24 (2.52, 4.16)
Gait Profile Score (°)	2.26 (0.33, 4.19)	0.022	0.51* (0.33, 0.69)	<0.001			1.90 (1.56, 2.32)
Max hip abduction M in stance (Nm/kg)	0.43 (0.31, 0.55)	<0.001	0.01 (0.00, 0.02)	0.146			0.12 (0.10, 0.14)
Max hip extension M in stance (Nm/kg)	1.04 (0.77, 1.31)	<0.001	-0.05* (-0.08, -0.03)	<0.001	0.13 (0.08, 0.22)	0.40	0.16 (0.13, 0.21)
Max hip flexion M in stance (Nm/kg)	-0.95 (-1.14, -0.76)	<0.001	-0.03* (0.01, 0.04)	0.004			0.18 (0.15, 0.22)
Max knee extension M in stance (Nm/kg)	12.92 (4.06, 21.78)	0.005	-0.35 (-1.18, 0.47)	0.393			8.73 (7.15, 10.66)

Max knee flexion M in stance (Nm/kg)	0.55 (0.30, 0.80)	<0.001	-0.02 (-0.04, 0.00)	0.121	0.13 (0.08, 0.21)	0.50	0.13 (0.10, 0.17)
Max plantar flexion M in preswing (Nm/kg)	-0.17 (-0.29, 0.06)	0.004	0.01 (-0.00, 0.02)	0.058			0.11 (0.09, 0.14)
Max ankle power absorption in LR (W/kg)	-0.06 (-0.11, 0.00)	0.052	-0.002 (-0.00, 0.01)	0.430	0.03 (0.02, 0.05)	0.55	0.03 (0.02, 0.04)
%GC when the sagittal hip M equals 0 (%)	0.82 (0.64, 1.00)	<0.001	0.02 (0.00, 0.03)	0.038	0.10 (0.06, 0.16)	0.59	0.08 (0.06, 0.11)
Max dorsiflexion M in LR (Nm/kg)	-0.13 (-0.48, 0.23)	0.463	0.04 (-0.07, -0.01)	0.024	0.20 (0.13, 0.31)	0.65	0.15 (0.12, 0.19)
Max ankle power generation in preswing (W/kg)	1.30 (-0.46, 3.06)	0.143	0.04 (-0.12, 0.20)	0.601	1.11 (0.76, 1.62)	0.80	0.56 (0.43, 0.72)
Max hip power generation in stance (Nm/kg)	2.50 (0.90, 4.09)	0.003	-0.10 (-0.24, 0.05)	0.181	0.99 (0.68, 1.44)	0.77	0.54 (0.42, 0.69)

Abbreviations; in alphabetic order: CI = confidence interval; deg = degrees; %GC = percentage of the gait cycle; ICC = Intraclass Correlation Coefficient; LR = loading response; M = moment; Max = maximal; Nm/kg = Newton meters per kilogram bodyweight; ROM = range of motion; SD = standard deviation; sec = seconds; W/kg = Watts per kilogram bodyweight; ° = degrees.

[a] ankle angle with dorsiflexion as a positive and plantar flexion as a negative value.

* statistically significant relationship between the gait parameter and increasing age.

[1] p-value from regression analysis in Linear mixed effects models.

[2] SD random slope (CI): if this was also included in the model (valid for one parameter).

Table 2.
Overview of the muscle strength outcomes in relation to increasing age from Linear mixed effects models (hypothesis two)

	FIXED EFFECTS				RANDOM EFFECTS		RESIDUALS
Muscle strength measure (Nm/kg)	***Intercept (CI)***	***p-value[1]***	***Regression coefficient (CI)***	***p-value[1]***	***SD random intercept (CI)***	***ICC random intercept***	***SD residuals (CI)***
Hip flexors	1.06 (0.66, 1.47)	<0.001	-0.02 (-0.06, 0.02)	0.284			0.34 (0.27, 0.42)
Hip extensors	0.61 (0.40, 0.83)	<0.001	-0.03* (-0.05, -0.01)	0.004			0.18 (0.14, 0.22)
Hip abductors	0.55 (0.36, 0.75)	<0.001	-0.01 (-0.03, 0.01)	0.239			0.17 (0.13, 0.21)
Knee extensors	0.95 (0.66, 1.23)	<0.001	-0.04* (-0.06, -0.01)	0.013	0.19 (0.11, 0.32)	0.44	0.29 (0.23, 0.35)
Knee flexors	0.48 (0.35, 0.62)	<0.001	-0.01 (-0.03, 0.00)	0.066	0.08 (0.04, 0.14)	0.33	0.14 (0.11, 0.17)
Dorsiflexors	0.21 (0.13, 0.29)	<0.001	-0.01 (-0.01, 0.00)	0.089	0.04 (0.03, 0.07)	0.46	0.05 (0.04, 0.06)
Plantar flexors	0.45 (0.35, 0.54)	<0.001	-0.01* (-0.02, -0.01)	0.003			0.10 (0.08, 0.12)

Abbreviations; in alphabetic order: CI = confidence interval; ICC = Intraclass Correlation Coefficient; Nm/kg = Newton meters per kilogram bodyweight; SD = standard deviation.

* statistically significant relationship between the muscle strength parameter and increasing age.

[1] p-value from regression analysis in Linear mixed effects models.

Table 3a.
Overview of the gait parameters outcomes in relation to muscle weakness from Linear Mixed Models – fixed effects (hypothesis three)

		FIXED EFFECTS			
Gait measure (unit)	***Muscle weakness measure (Nm/kg)***	***Intercept (CI)***	***p-value[1]***	***Regression coefficient (CI)***	***p-value[1]***
Step width, Hof	Hip abductors	0.35 (0.32, 0.39)	<0.001	0.14* (0.06, 0.22)	0.001
Max hip extension angle in stance (°)	Hip extensors	-6.32 (-13.00, 0.37)	0.063	-22.47* (-32.33, -12.61)	< 0.001
	Knee extensors			5.40 (-3.77, 14.56)	0.239
Gait Profile Score (°)	TCS	9.67 (6.07, 13.27)	<0.001	4.91 (-1.90, 11.71)	0.152
Cadence (/sec)	TCS	2.08 (1.80, 2.35)	<0.001	-0.17 (-0.75, 0.42)	0.57
Max anterior pelvic tilt (°)	Hip extensors	24.53 (19.93, 29.13)	<0.001	7.59 (-0.22, 15.40)	0.056
	Knee extensors			3.26 (-3.78, 10.30)	0.353
Max dorsiflexion angle in swing (°)	Dorsiflexors	3.03 (-1.49, 7.55)	0.183	1.42 (-22.173, 25.018)	0.904
Max hip extension M in stance (Nm/kg)	Hip extensors	0.35 (0.23, 0.48)	<0.001	-0.36 (-0.67, -0.05)	0.022
ROM pelvic obliquity (°)	Hip abductors	12.65 (9.19, 16.10)	<0.001	2.80 (-3.65, 9.24)	0.384
Walking velocity, Hof	TCS	0.33 (0.26, 0.39)	<0.001	-0.12 (-0.27, 0.02)	0.099
Max hip abduction angle in stance (°)	Hip abductors	5.30 (2.76, 7.85)	<0.001	-3.11 (-8.14, 1.93)	0.218
Max ankle power absorption in LR (W/kg)	Dorsiflexors	0.30 (0.14, 0.47)	<0.001	-0.6 (-1.57, 0.38)	0.224
	Plantar flexors			-0.36 (-1.08, 0.37)	0.324
	Knee extensors			-0.05 (-0.41, 0.31)	0.774
Ankle angle at initial contact (°)[a]	Dorsiflexors	0.18 (-4.56, 4.911)	0.941	10.49 (-11.91, 32.89)	0.350
	Knee extensors			-1.36 (-6.21, 3.50)	0.575
Max dorsiflexion angle in stance (°)	Plantar flexors	15.57 (10.17, 20.96)	<0.001	4.18 (-9.43, 17.79)	0.619
	Knee extensors			0.13 (-4.84, 5.10)	0.957
ROM pelvic rotation (°)	TCS	15.75 (9.83, 21.68)	<0.001	-0.36 (-11.89, 11.17)	0.950
Max plantar flexion M in preswing (Nm/kg)	Plantar flexors	1.03 (0.92, 1.15)	<0.001	0.09 (-0.22, 0.40)	0.578
Max knee extension M in stance (Nm/kg)	Knee extensors	0.10 (0.01, 0.19)	0.034	-0.46* (-0.60, -0.33)	<0.001
Max hip abduction M in stance (Nm/kg)	Hip abductors	0.74 (0.64 0.84)	<0.001	0.41* (0.20, 0.61)	<0.001
Max hip power generation in stance (Nm/kg)	Hip extensors	1.27 (0.62, 1.93)	<0.001	-0.32 (-1.35, 0.70)	0.525
	Dorsiflexors	7.55 (3.29, 11.80)	0.001	-3.25 (-22.27, 15.78)	0.731

Max hip abduction angle in swing (°)	Plantar flexors			-4.58 (-13.78, 4.62)	0.318
	Hip flexors			-1.23 (-5.04, 2.58)	0.515
Step length, Hof	TCS	0.69 (0.61, 0.77)	<0.001	-0.03 (-0.19, 0.13)	0.706
Max knee flexion angle in swing (°)	Dorsiflexors	69.85 (64.46, 75.24)	<0.001	27.94 (-24.84, 80.72)	0.292
%GC when the sagittal hip M equals 0 (%)	Hip extensors	7.54 (2.06, 13.01)	0.008	-5.40 (-20.65, 9.85)	0.477
Max dorsiflexion M in LR (Nm/kg)	Dorsiflexors	0.04 (0.01, 0.07)	0.009	0.0 (-0.12, 0.23)	0.525
Max ankle power generation in preswing (W/kg)	Plantar flexors	1.72 (0.86, 2.59)	<0.001	0.0 (-2.01, 2.17)	0.940
Max knee extension angle in swing (°)	Knee extensors	25.32 (22.09, 28.54)	<0.001	-4.89 (-9.07, -0.70)	0.023

Abbreviations; in alphabetic order: CI = confidence interval; %GC = percentage of the gait cycle; LR = loading response; M = moment; Max = maximal; Nm/kg = Newton meters per kilogram bodyweight; ROM = range of motion; sec = seconds; TCS = Total Composite Score; W/kg = Watt per kilogram bodyweight; ° = degrees.

[a] ankle angle with dorsiflexion as a positive and plantar flexion as a negative value.

* statistically significant relationship between the gait parameter and muscle weakness parameter.

[1] p-value from multiple regression analysis in Linear mixed effects models.

Table 3b.
Overview of the gait parameters outcomes in relation to muscle weakness from Linear mixed effects models – random effects, residuals and multicollinearity (hypothesis three)

		RANDOM EFFECTS			RESIDUALS	MULTI COLLINEARITY
Gait measure (unit)	***Muscle weakness measure (Nm/kg)***	***SD random intercept (CI)***	***ICC Random intercept***	***SD random interslope (CI)***	***SD residual (CI)***	***VIF***
Step width, Hof	Hip abductors				0.04 (0.03, 0.05)	
Max hip extension angle in stance (°)	Hip extensors	9.26 (6.24, 13.72)	0.87		3.56 (2.62, 4.85)	1.77
	Knee extensors					1.77
Gait Profile Score (°)	TCS	5.04 (2.63, 9.64)	/	8.24 (3.42, 19.85)	1.57 (1.18, 2.10)	
Cadence (/sec)	TCS	0.22 (0.14, 0.36)	0.71		0.14 (0.10, 0.20	
Max anterior pelvic tilt (°)	Hip extensors	5.69 (3.78, 8.56)	0.80		2.85 (2.10, 3.88)	1.77
	Knee extensors					1.77
Max dorsiflexion angle in swing (°)	Dorsiflexors	5.96 (3.94, 9.01)	0.76		3.32 (2.55, 4.33)	
Max hip extension M in stance (Nm/kg)	Hip extensors	0.15 (0.09, 0.26)	0.55		0.14 (0.10, 0.19)	
ROM pelvic obliquity (°)	Hip abductors	3.60 (2.37, 5.47)	0.74		2.16 (1.60, 2.93)	
Walking velocity, Hof	TCS	0.04 (0.02, 0.08)	0.54		0.04 (0.03, 0.06)	
Max hip abduction angle in stance (°)	Hip abductors	2.19 (1.35, 3.54)	0.60		1.80 (1.32, 2.44)	
Max ankle power absorption in LR (W/kg)	Dorsiflexors	0.20 (0.07, 0.59)	/	1.59 (0.98, 2.57)	0.05 (0.03, 0.07)	1,13
	Plantar flexors			1.29 (0.74, 2.26)		1,10
	Knee extensors			0.66 (0.43, 1.02)		1,10
Ankle angle at initial contact (°)[a]	Dorsiflexors	5.49 (3.62, 8.34)	0.76		3.10 (2.37, 4.04)	1.07
	Knee extensors					
Max dorsiflexion angle in stance (°)	Plantar flexors	4.62 (3.00, 7.12)	0.65		3.38 (2.60, 4.38)	1.04
	Knee extensors					
ROM pelvic rotation (°)	TCS	6.76 (4.63, 9.87)	0.88		2.47 (1.82, 3.34)	

Max plantar flexion M in preswing (Nm/kg)	Plantar flexors	0.13 (0.09, 0.19)	0.74		0.07 (0.06, 0.10)	
Max knee extension M in stance (Nm/kg)	Knee extensors				0.14 (0.12, 0.18)	
Max hip abduction M in stance (Nm/kg)	Hip abductors				0.11 (0.08, 0.13)	
Max hip power generation in stance (Nm/kg)	Hip extensors	1.09 (0.74, 1.60)	0.87		0.41 (0.30, 0.56)	
Max hip abduction angle in swing (°)	Dorsiflexors	3.77 (2.46, 5.77)	0.78		1.99 (1.45, 2.72)	1,17
	Plantar flexors					1,10
	Hip flexors					1,24
Step length, Hof	TCS	0.06 (0.04, 0.10)	0.72		0.04 (0.03, 0.05)	
Max knee flexion angle in swing (°)	Dorsiflexors	5.14 (2.18, 12.14)		72.90 (41.69, 127.47)	4.43 (3.37, 5.82)	
%GC when the sagittal hip M equals 0 (%)	Hip extensors				9.18 (7.29, 11.57)	
Max dorsiflexion M in LR (Nm/kg)	Dorsiflexors	0.03 (0.02, 0.06)	0.62		0.03 (0.02, 0.04)	
Max ankle power generation in preswing (W/kg)	Plantar flexors	1.18 (0.82, 1.69)	0.86		0.49 (0.38, 0.63)	
Max knee extension angle in swing (°)	Knee extensors	3.94 (2.56, 6.06)	0.66		2.85 (2.20, 3.70)	

Abbreviations; in alphabetic order: CI = confidence interval; deg = degrees; %GC = percentage of the gait cycle; ICC = Intraclass Correlation Coefficient; LR = loading response; M = moment; Max = maximal; Nm/kg = Newton meters per kilogram bodyweight; ROM = range of motion; SD = standard deviation; sec = seconds; TCS = Total Composite Score; VIF = Variance Inflation Factor; W/kg = Watts per kilogram bodyweight; ° = degrees.

[a] ankle angle with dorsiflexion as a positive and plantar flexion as a negative value.