

Cyclogram-based evaluation of inter-limb gait symmetry in Prader-Willi Syndrome

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ABSTRACT

Background: Prader-Willi syndrome (PWS) is characterized by a complex clinical condition, whose typical features lead to impaired motor and functional skills. To date, limited data is available as regards symmetry of gait in PWS.

Research question: The aim of this study was to characterize lower-limb asymmetry during gait in a group of Prader-Willi Syndrome (PWS) individuals by using the synchronized cyclograms and to compare it with those of two different control groups, a normal-weight group and an obese group.

Methods: A total of 18 PWS, 30 normal weight (NW) and 28 obese individuals (OG) matched for age, sex and height were assessed via 3D gait analysis. Gait spatio-temporal parameters were computed together with angle-angle diagrams, characterized in terms of their geometric features (i.e. area, orientation, and trend symmetry index).

Results: Individuals with PWS exhibit reduced speed, stride length and cadence and increased duration of both stance and double support phase than the other groups. OG was characterized by the same pattern when compared to NW. With respect to inter-limb symmetry, individuals with PWS exhibited significantly larger cyclogram areas at hip joint with respect to the other two groups (203.32 degrees² vs. 130.73 degrees² vs. 111.59 degrees²) and significantly higher orientation angle (4.17° vs. 2.11° vs. 1.22°) and Trend Symmetry (3.72 vs. 2.02 vs. 1.21) with respect to the other two groups at knee joint; no differences were found at ankle joint. Both individuals with PWS and those of OG exhibited reduced ROM at knee and ankle joints with respect with normal weight, but no statistically significant differences were observed between PWS and OG.

Significance: The obtained results may provide novel and useful insights to understand better the impairments in motor control associated with this pathological state, supporting clinics in the identification of the best rehabilitation program for this rare pathological state, aimed to improve stability and motor control.

1. Introduction

Prader-Willi Syndrome (PWS) is a multi-system sporadic chromosomal disorder, occurring with a prevalence of 1/10000 – 1/30000 [1] which results from the loss of the expression of the paternally active genes on chromosome 15q11.2-q13 in the 60–70 % of the cases and due to a maternal uniparental disomy of chromosome 15 in the 25–35 % of

the cases or imprinting defects and other chromosome 15 alterations (1–4 %) [2]. Such disorder is characterized by a complex clinical condition [3] and the PWS phenotype is currently thought to be due to a complex hypothalamic dysfunction [4].

PWS individuals are usually characterized by increased fat-lean mass ratio with respect to both normal weight and non-syndromic obese individuals [5–8]. Obesity leads to anomalies in the biomechanics of most

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simple and complex motor tasks, thus negatively affecting daily life activities, as well as increasing the risk of falls and other injuries [9–12].

From a biomechanical point of view, although hypotonia gradually improves with age [1,13], the combination of the previously mentioned typical features of PWS leads to impaired motor and functional skills [14,15] that are evident since the early childhood [16,17]. In the adulthood, the most evident anomalies in motor control involve postural control [11,12,15], transition from sitting to standing [6,18] and gait [13].

Several studies assessed the gait pattern in PWS using optoelectronic motion capture systems and force platforms [11,13,19]. It was observed a well-defined gait phenotype characterized by asymmetry and instability, abnormal spatio-temporal parameters (e.g. reduced cadence, step length and speed) [13,20,21], altered kinematic at knee and ankle joints and abnormal foot rotation and pronation [6,22]. With respect to kinetics, reduced push-off ability at ankle moment and ankle power was observed during terminal stance [6,11,21].

However, limited data is available as regards symmetry of gait, especially those regarding its kinematic aspects. Although there is agreement on the fact that human locomotion is intrinsically characterized by a certain degree of asymmetry, it was also suggested that excessive asymmetry may be indicative of either altered motor control or structural anomalies of the musculoskeletal system.

In this regard, gait symmetry is typically investigated using approaches aimed to obtain single discrete values (e.g. Robinson Index, Symmetry Angle) [23,24] based on the difference observed between the spatio-temporal parameters of the contralateral limbs, but completely neglecting the joint kinematics. Although practical and of straightforward interpretation, such indexes are characterized by low sensitivity and lack of standardization in terms of equations and variables. Moreover, they do not allow for the time-identification of the asymmetry during the gait cycle [25–28].

To partly overcome such drawbacks, in the last years new quantitative methods have been developed to achieve a more complete description of gait asymmetries, such as the waveform-based methods which rely on the use of all the information related to the angles of lower limbs during a gait cycle [23]. They provided encouraging results when applied to investigate inter-limb symmetry in a wide range of gait anomalies [29–33], associated to neurologic and orthopaedic conditions like hemiplegia [28,29], multiple-sclerosis [34] osteoarthritis [35] as well as in case of obesity [33]. Among the waveform-based methods, the approach based on the use of bilateral cyclograms is probably the most widespread. Basically, a cyclogram is a left-right angle-angle diagram that can be built for each joint of interest on the basis of the angular positions of two contralateral joints assumed during the gait cycle without considering the time. According to such approach, symmetry can be assessed through the calculation of several geometric properties of the cyclogram (e.g. perimeter, area, shape factor and orientation) [36, 37].

In this paper we propose a retrospective study aimed to characterize lower-limb joint kinematics asymmetry during gait in PWS group and to compare it with those of two different control groups, including healthy-weight and obese individuals respectively, to identify whether interlimb symmetry of PWS can be assimilated to those of non-PWS obese or if they exhibit specific features associated to their condition. As subjects with PWS were demonstrated to present reduced smoothness/symmetry by applying other investigation method [20] and some kinematic features during gait are similar in some aspects to those of obese individuals [33], which displayed inter-limb asymmetry, we hypothesized that the use of cyclograms could revealed interesting elements related to inter-limb asymmetry in patients with PWS.

2. Materials and Methods

2.1. Participants

Three groups of participants were enrolled in this study on a voluntary basis. Their characteristics are summarised in Table 1. Eighteen adults with PWS periodically hospitalized at San Giuseppe Hospital, Istituto Auxologico Italiano, Piancavallo (Verbania, Italy), were enrolled in the study. All exhibited the typical PWS clinical phenotype [1] and resulted free from severe cognitive impairments, assessed using the Mini Mental State Examination Italian Version (score over the cut-off value of 24) [38].

Two groups of healthy individuals, served as controls. The first consisted of 28 age and BMI-matched obese individuals (Obese Group: OG) who followed a 4-week multidisciplinary bodyweight reduction rehabilitation program. To be eligible for this study, the recruited obese individuals had to be free from any neurological or major musculoskeletal disorder potentially able to affect their walking abilities. The second control group consisted of 30 age-matched healthy subjects (Healthy Group: HG) recruited among the staff of the hospital, who were free from any neurological or musculoskeletal disorder able to impact on their gait pattern.

All participants were able to understand verbal cues and complete the test, as well as walking independently without aids. Written informed consent was obtained from all the participants and/or parents or legal representatives. The study was carried out in accordance with the ethical standards of the Institute and with the 1964 Helsinki declaration and its latest amendments.

2.2. Methods

The functional evaluation of the groups consisted on the execution of sessions of 3D Gait Analysis (GA). The participants were assessed at the Motion Analysis Laboratory of San Giuseppe Hospital, which was equipped with a 6-camera optoelectronic motion capture system (VICON, Oxford Metrics Ltd., Oxford, UK; sampling rate: 100 Hz) and two force platforms (Kistler, Winterthur, CH). Prior to the GA session, anthropometric measurements of each participant were collected. The kinematic evaluation of each subject was performed by using a set of 22 spherical retro-reflective markers placed on specific anatomical landmarks on patients' body according to the marker set-up proposed by Davis et al. [39] (Fig. 1).

Following the preparation, subjects were asked to walk barefoot at their own natural pace along a 8-m long walkway. Kinematic and kinetic data were collected for each patient from up to seven trials to guarantee the reproducibility of the results.

2.3. Data analysis

The 3D raw data were processed using the dedicated software Nexus (Nexus, version 1.8., Vicon, Oxford Metrics Ltd., Oxford, UK). For each participant, three out of seven trials consistent in terms of gait pattern

Table 1

Anthropometric and clinical features of participants. Values are expressed as mean (SD).

	Normal Weight (NW)	Obese (OG)	Prader-Willi (PWS)
Participants (M, F)	14 M, 16 F	12 M, 16 F	11 M, 7 F
Age (years)	29.5 (8.8)	29.7 (8.7)	27.6 (6.5)
Body Mass (kg)	61.7 (12.8)	111.4 (19.8) ^a	94.9 (21.0) ^{a,b}
Height (cm)	166.7 (9.3)	162.6 (12.5)	152.9 (6.0) ^{a,b}
BMI (kg m⁻²)	22.0 (3.0)	44.9 (18.5) ^a	40.5 (8.1) ^a

The symbols a and b denote statistically significant difference vs. Normal Weight and Obese group respectively

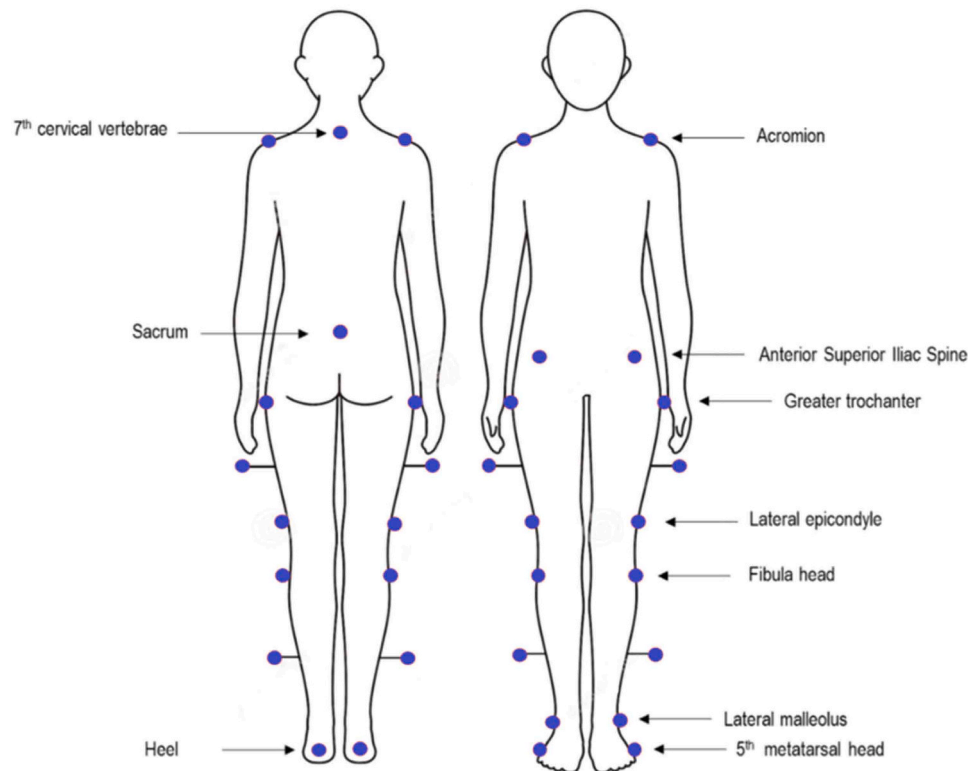


Fig. 1. Marker set-up according to Davis et al. [39].

(spatio-temporal and kinematic) were considered for analysis. The data associated with the selected trials were imported in Polygon (Polygon, version 2.4, Vicon, Oxford Metrics Ltd., Oxford, UK) to calculate the following variables:

- Spatio-temporal gait parameters (i.e., gait speed, stride length, cadence, stance and double support phase duration);
- Dynamic range of motion (ROM) of hip, knee and ankle joints, calculated as the difference between the minimum and the maximum flexion-extension angles (hip and knee) and dorsi-plantar flexion angle (ankle) observed during the gait cycle.
- Hip, knee and ankle kinematics on the sagittal plane (hip and knee flexion-extension and ankle dorsi-plantarflexion angles during the gait cycle). All the graphs obtained from GA were normalized as % of gait cycle.

Bilateral cyclograms features were calculated based on the previously described sagittal kinematics by means of a dedicated Matlab routine according to the procedure described by Goswami et al. [37]. In particular, the following parameters were considered (Fig. 2):

- Area (degrees²), namely the area of the left-right angle diagram [40]. In a perfectly symmetrical gait, left and right joints assume the same angular position during each period of the gait cycle and thus the area would result null. The area tends to increase with increasing asymmetry.
- Cyclogram orientation (ϕ , degrees), which is calculated as the absolute value of the angular difference between the 45° line (which represent perfect symmetry) and the orientation of the principal axis of inertia of the cyclogram [36,37]. Higher ϕ angles denote reduced inter-limb symmetry;
- Trend Symmetry (dimensionless) Index, calculated according to the procedure described by Crenshaw et al. [26]. This parameter assesses the similarity of right and left leg angular trend across the gait cycles,

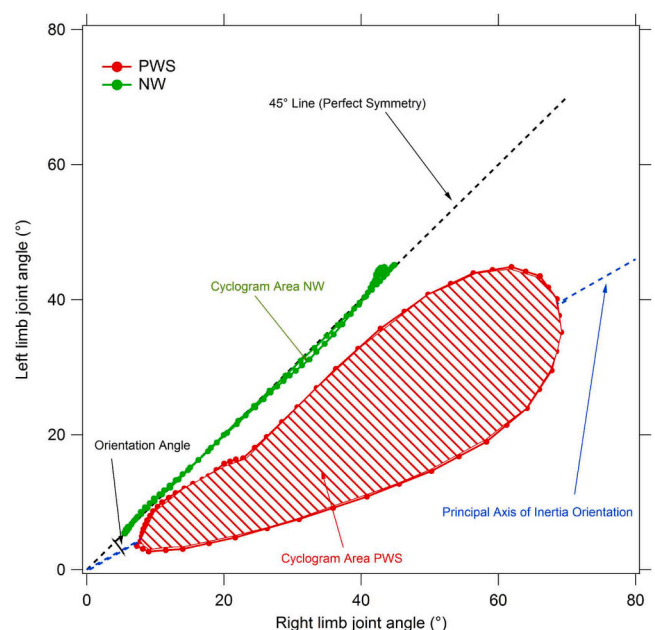


Fig. 2. Graphical representation of the main features of interlimb cyclograms for a participant with PWS (red curve) and a healthy control normal weight (green curve).

for each joint using an eigenvector analysis. Higher asymmetries result in increased Trend Symmetry values.

2.4. Statistical analysis

Data was tested using parametric statistical analysis following a preliminary checking for normality and homogeneity of variances (using

the Shapiro–Wilk’s and Levene’s test respectively). The existence of differences in gait patterns possibly introduced by PWS was investigated using a one-way multivariate analysis of covariance (MANCOVA) including BMI as a covariate. In case of spatio-temporal parameters, the independent variable was the group (i.e., PWS, OG, HG) while the dependent variables were the 5 spatio-temporal parameters previously listed. As regards the symmetry parameters the dependent variables were cyclogram area, orientation and Trend Symmetry calculated at hip, knee and ankle joints. At last, a third MANCOVA was carried out using the dynamic ROMs at hip, knee and ankle joints as dependent variables. The level of significance was set at $p = 0.05$, and the effect sizes were assessed using the eta-squared (η^2) coefficient. Post-hoc analysis was performed using univariate ANOVA by reducing the level of significance to $p = 0.01$ (0.05/5) for spatio-temporal parameters and $p = 0.017$ (0.05/3) for the symmetry parameters and dynamic ROMs after a Bonferroni correction for multiple comparisons. When necessary, Holm-Sidak test for pairwise comparison was carried out to assess intra- and inter-group differences.

3. Results

The results of the comparison between the three groups in terms of spatio-temporal parameters and dynamic ROMs are reported in Tables 2 and 3, while the symmetry parameters are reported in Table 4. As regards the spatio-temporal parameters of gait, after controlling for BMI, MANCOVA detected a significant main effect of group [$F(8,138) = 18.548, p < 0.001$, Wilks’ $\lambda = 0.23, \eta^2 = 0.52$]. In particular, the post-hoc analysis revealed that individuals with PWS exhibit reduced speed, stride length and cadence and increased duration of both stance and double support phase with respect to all the other groups. Obese non-PWS were characterized by the same pattern when compared to normal weight. As regards the symmetry parameters, main effect of group was detected for hip [$F(6,138) = 3.626, p = 0.02$, Wilks’ $\lambda = 0.75, \eta^2 = 0.13$] and knee [$F(6,138) = 3.48, p = 0.003$, Wilks’ $\lambda = 0.75, \eta^2 = 0.10$] but not for ankle [$F(6,138) = 1.43, p = 0.206$, Wilks’ $\lambda = 0.89, \eta^2 = 0.06$]. In this case, individuals with PWS exhibited significantly larger cyclogram areas at hip joint with respect to the other two groups and significantly higher orientation angle and Trend Symmetry with respect to the other two groups at knee joint. At last, a main significant effect of group was observed even as regards the dynamic ROMs. The post-hoc analysis revealed that both individuals of PWS and OG groups exhibited reduced ROM at knee and ankle joints with respect with normal weight, while no statistically significant differences were found when comparing PWS and obese non-PWS. The observed power associated with the main group effect for all the investigated parameters was in the range 0.8–0.95.

4. Discussion

The aim of the present study was to assess inter-limb asymmetry

Table 2
Comparison between spatio-temporal parameters of gait of normal weight, overweight and individuals with Prader-Willi Syndrome. Values are expressed as mean (SD).

	Normal Weight (NW)	Obese (OG)	Prader-Willi (PWS)
Gait speed (m s ⁻¹)	1.30 (0.20)	1.18 (0.13) ^a	0.98 (0.14) ^{a,b}
Stride length (m)	1.39 (0.13)	1.25 (0.10) ^a	1.01 (0.16) ^{a,b}
Cadence (steps min ⁻¹)	113.5 (11.0)	113.4 (6.8)	112.6 (9.8)
Stance phase (% of the gait cycle)	59.02 (1.44)	61.63 (1.34) ^a	63.83 (1.70) ^{a,b}
Double support (% of the gait cycle)	34.11 (1.50)	42.30 (2.04) ^a	45.62 (3.08) ^{a,b}

The symbols a and b denote a statistically significant difference vs. Normal Weight and Obese groups respectively after Bonferroni correction ($p < 0.01$)

Table 3
Comparison between dynamic ROM of normal weight, overweight and individuals with Prader-Willi Syndrome. Values are expressed as mean (SD).

	Normal Weight (NW)	Obese (OG)	Prader-Willi (PWS)
Ankle ROM (°)	46.76 (4.98)	44.17 (4.69)	45.96 (6.15)
Knee ROM (°)	62.00 (4.27)	54.90 (6.36) ^a	55.65 (8.44) ^a
Hip ROM (°)	32.57 (5.55)	28.28 (5.45) ^a	25.35 (2.77) ^a

The symbol a denotes statistically significant difference vs. Normal Weight group after Bonferroni correction ($p < 0.016$)

during gait in individuals with PWS individuals and compare it with those of non-genetically obese and normal weight individuals using cyclogram features. According to the kinematic features which lead to impaired motor and functional skill in patients with PWS and the limited data available in terms of their gait symmetry, we hypothesized that the use of cyclograms could revealed interesting characteristics related to inter-limb asymmetry in patients with PWS.

The results of our analysis show that individuals with PWS are slower, have shorter stride length as well as more prolonged stance and double support phase compared with both obese and normal weight participants as previously reported in similar studies [13,19]. This motor strategy is likely unconsciously adopted to reduce overload during single limb stance and to maintain the weight on both the limbs to increase the stability and efficiency of locomotion by reducing the risk of instability and falls. Foot acromicria represent an additional factor which might explain the observed increase in double support phase duration compared to non-syndromic obese controls. Taken together, such findings indicate a cautious, abnormal gait aiming at preserve balance and stability. Furthermore, dorsal kyphosis in PWS subjects [41, 42] that anteriorly tilt the pelvis associated with excessive fat on the abdomen can be responsible for forward displacement of the centre of gravity creating instability during standing and walking.

Although significantly higher than those calculated for normal weight individuals, dynamic ROMs during gait of both hip and knee joints of PWS are similar to those of obese individuals, while no differences were observed among the three groups as for the ankle joint, globally according with literature [13,19]. The significantly reduced dynamic ROMs at hip and knee joints, may be partly due to the continuous search for stability typical of individuals with PWS that is directly correlated with their BMI. As they need to keep both limbs in contact with the ground, this condition increases the amount of time spent in a closed lower-limb kinematic chain condition. In this situation, the degrees of freedom of the rigid lower body system are reduced and the constraint, especially on the knee joint, increases. At last, another factor possibly involved in the ROM reduction at knee joint might be the excessive amount of fat on the thigh and shank, which mechanically encumbers intersegmental rotation and counteracts the antigravity action exerted by the knee flexors [33,43].

The cyclogram analysis suggests the existence of a well-defined trend characterized by altered symmetry in individuals with PWS, whose parameters were found systematically higher than those of the other two groups for hip, knee and ankle, even though in this latter joint statistical significance was not achieved. To the best of our knowledge, no previous studies investigated inter-limb symmetry of lower limb joint kinematics in individuals with PWS individuals, and thus there are no available data for direct comparison. However, it should be noted that mass excess is a factor that “per se” may introduce relevant inter-limb asymmetry, as observed in previous studies [33]. Moreover, individual with PWS were found characterized by reduced Harmonic Ratio values when compared to health controls [15,20]. This parameter, which is calculated on the basis of the trunk accelerations during gait, has been suggested associated with step-by-step symmetry [44]. We believe that this global lack of symmetry, which manifests in different forms, might be representative of a reduced gait balance, probably directly connected to the presence of

Table 4

Comparison between symmetry parameters of gait of normal weight, overweight and individuals with Prader-Willi Syndrome. Values are expressed as mean (SD).

Parameter	Joint	Normal Weight (NW)	Obese (OG)	Prader-Willi (PWS)
Cyclogram area (degrees ²)	Hip	111.59 (84.69)	130.73 (78.73)	203.32 (118.80) ^{a,b}
Cyclogram orientation ϕ (degrees)		1.76 (1.18)	1.80 (1.15)	1.97 (1.76)
Trend Symmetry		1.74 (1.17)	1.58 (1.25)	1.98 (1.82)
Cyclogram area (degrees ²)	Knee	304.64 (212.24)	341.23 (219.24)	402.52 (209.17)
Cyclogram orientation ϕ (degrees)		1.22 (0.86)	2.11 (2.00)	4.17 (2.94) ^{a,b}
Trend Symmetry		1.21 (0.87)	2.02 (1.84)	3.72 (2.30) ^{a,b}
Cyclogram area (degrees ²)	Ankle	92.84 (61.10)	125.00 (98.06)	128.03 (108.02)
Cyclogram orientation ϕ (degrees)		2.48 (1.99)	3.77 (2.82)	5.23 (2.86)
Trend Symmetry		2.46 (1.97)	3.35 (3.04)	4.31 (3.33)

The symbols a and b denote statistically significant difference vs. Normal Weight and Obese groups respectively after Bonferroni correction ($p < 0.016$)

ligament laxity and muscle hypotonia, together with small feet [45] which are recurrent features of the pathology. Hypotonia in particular has been proven to be a major cause of unpaired postural control and gait instability in these patients [11,46]. The abnormal gait symmetry might be connected to the limited balance maintenance during the gait which requires continuous control, due to the presence of instability during the single support [15].

Summarizing, the findings of the present study show that individuals with PWS exhibit a peculiar gait pattern consistent with previous observations [13,20,21] which cannot be solely attributed to their obesity condition. Most likely, the altered spatio-temporal parameters and poor inter-limb symmetry are due to a combination between excessive body mass, short feet and stature, reduced muscle strength and impaired motor control, which are typical features of these individuals.

Of course, this study has some limitations. Firstly, the reduced number of participants limits, to some extent, the strength of the statistical results. However, PWS is a rare genetic condition and that large experimental samples are difficult to collect. Having data on larger cohorts would certainly improve the generalization of the results and would also help to detect the existence of sex-related differences, due to the different distribution of fat in men and women. Secondly, the tested sample was composed of young adults which are unable to verify whether that with aging articular problems (such as osteoarthritis) as well as more severe gait alterations could introduce progressive/cumulative effect of excessive joint loads, thus worsening the gait pattern and influencing negatively the inter-limb asymmetry. Finally, the standard marker set [39] used in this study was proven to suffer from reduced accuracy both in terms of marker placement and soft tissue artefact in case of obese individuals [47,48]. The main concern is related to the placement of the markers on Anterior Superior Iliac Spine (ASIS) and/or greater trochanter markers to define joint centers of pelvis and hip, leading to their inaccurate estimates and errors in the resulting kinematic/kinetic parameters, in particular for hip and knee [49]. However, it should be also noticed that parameters such as dynamic ROMs during gait are only slightly affected by these errors [50] so that their values can be considered reliable even in obese individuals. Further investigations are needed to clearly identify the optimal marker configuration and skeletal model development procedures, to properly eliminate (or at least greatly reduce) errors that may be associated with marker placement. However, it is important to underline that despite these limitations this represents the first study focusing on inter-limb asymmetry using the so-called “bilateral cyclograms” method in PWS subjects.

5. Conclusion

The assessment of inter-limb symmetry during the whole gait cycle may provide novel and useful insights to better highlight gait limitations of PWS patients in addition to spatio-temporal parameters or traditional kinematic features. This study warrants continued research to refine the best characterization of walking strategy in PWS by applying innovative procedures to better describe the functional limitation during walking of

patients with PWS.

Institutional review board statement

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Ethics Committees of the Istituto Auxologico Italiano, Ospedale San Giuseppe, Piancavallo (VB), Italy (GAITNEW 31C302, protocol code CE 2013_04_23_03).

Declaration of Competing Interest

we are undersigned authors of the manuscript as Original Research entitled “Cyclogram-based Evaluation of Inter-limb Gait Symmetry in Prader-Willi Syndrome” by Massimiliano Pau, Serena Cerfoglio, Paolo Capodaglio, Flavia Marrone, Graziano Grugni, Micaela Porta, Bruno Leban, Manuela Galli and Veronica Cimolin, submitted to Gait & Posture for publication hereby attest and affirm that the material within has not been and will not be submitted for publication elsewhere and that they were fully involved in the study and preparation of the manuscript.

All authors haven't any conflicts of interest and any financial interest.

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