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Computer Methods and Programs in Biomedicine

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--Manuscript Draft--

Manuscript Number:	CMPB-D-21-02079R2
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Keywords:	wearable sensors; motor biomarkers; preterm children; motor development; variability; complexity; gait
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	Manuela Fabbri
	Duccio Maria Cordelli
	Rita Stagni
Manuscript Region of Origin:	Europe
Abstract:	Background and Objectives Preterm children have an increased risk of motor difficulties. Gait analysis and wearable technologies allow the assessment of motor performance in toddlers, identifying early deviations from typical development. Using a sensor-based approach, gait performance of full-term and preterm toddlers at different risk of motor delay was analysed. The aim was to measure quantitative differences among groups. Methods Twenty-nine two-year old children born preterm (≤36 gestational weeks) and 17 full-term controls, matched for age and walking experience, participated in the study. Preterm children were further divided based on risk of motor delay: preterm at high risk (n=8, born at ≤28 gestational weeks or with ≤1000g of body weight), and at moderate risk (n=21). Children were asked to walk along a corridor while wearing 3 inertial sensors on the lower back and on the ankles. Gait temporal parameters, their variability, and nonlinear metrics of trunk kinematics (i.e. recurrence quantification analysis, multiscale entropy) were extracted from the collected data and compared among groups. Results Children born preterm showed significantly longer stance and double support phases, higher variability of temporal parameters, and lower multiscale entropy values than peers born full-term. No difference was found for the other parameters when comparing preterm and full-term children. When comparing children grouped according to risk of delay, with increasing risk, children showed longer stride-, stance- and double-support-time, higher variability of temporal parameters, higher recurrence - and lower multiscale entropy values. Conclusions Sensor-based gait analysis allowed differentiating the gait performance of preterm from full-term toddlers, and of preterm toddlers at different risk of motor delay. When analysing the present results with respect to the expected trajectory of locomotor development, children born preterm, in particular those at higher risk of motor delay,

	exhibited a less mature motor control performance during gait: lower stability (i.e. longer support phases), and higher variability, although not structured towards the exploration of more complex movements (i.e. higher recurrence- and lower multiscale entropy values). These indexes can serve as biomarkers for monitoring locomotor development, and early detecting risk to develop persistent motor impairments.
Suggested Reviewers:	Alicia Spittle, PhD alicia.spittle@mcri.edu.au Expert on early detection and early intervention for infants with or/at high risk of neurodevelopmental impairments
	Jennifer L Mcginley, PhD mcginley@unimelb.edu.au Expert in gait and mobility outcome measures for clinical practice and research, translation of biomechanical evidence to inform practice and in clinical trials of interventions to improve functional mobility.
	Phil Dixon, PhD philippe.dixon@umontreal.ca Expert on analyses of human movement and physiological signals from wearable sensors across a wide range of populations.
Opposed Reviewers:	
Response to Reviewers:	First, we would like to thank again the editor and the reviewers for their comments and for their careful revision that helped us in improving the paper. We modified the manuscript accordingly and we hope that now it will be suitable for publication on Computers Methods and Programs in Biomedicine. In the following lines, we reported direct answers to reviewers' comments, showing what we modified. All the parts of the manuscript that were modified from the previous version are highlighted in yellow in the text. Editor and Reviewer comments: Reviewer #1: In general, the authors have addressed my previous concerns and improved the paper a lot. Again, I think this direction is interesting but we should treat the conclusion very carefully considering the limited number of subject involved in the experiment. We thank the reviewer for the positive and constructive comments. - We modified the conclusive paragraph as follows. "However, the limited number of participants included in the present study has to be taken into consideration when drawing the conclusions of the study: the present results demonstrated the feasibility of the proposed quantitative sensor-based approach [17] for monitoring gait performance in PT children, confirming, in a relatively small group of children, the hypotheses that PT children at risk of motor delay show a less mature gait performance, corresponding to a delayed maturation of the control of the trunk (i.e. lower complexity) and a higher variability of gait temporal parameters. The proposed approach will support the implementation of further longitudinal studies on more numerous groups, in order to attain a more robust and deeper understanding of motor development pathways in PT children, assessing the predictive capacity and usability of the identified quantitative parameters as biomarkers of locomotor development and risk of motor delays." Additionally, it is hard to quantify how the attached device would affect the children in gait (although in the paper, the authors claim that the children were distracted and unware of them). Maybe camera-based CV technology is an option in the future. - Authors thank the reviewer for the consideration regarding the ecological aspects of using wearable sensors in toddlers. We would like to highlight that we are not the 'first' in using sensors for analysing motor development in children, and that in gait/human movement analysis, wearable inertial sensors are considered an unobtrusive solution when compared to the classic 3D gait analysis performed with reflective markers (with which most of the classic and fundamental literature regarding gait development has been conducted). With the purpose of a widespread monitoring in mind, video camera-

based solutions (not requiring markers) would add data issues related to the collection of images of the children, which are sensitive data, and moreover would lead to relevant inaccuracy with respect to the measurement of the analysed variables (e.g. trunk acceleration). The wearable sensors are very small and light (even for small children), are worn by the children under the clothes, and the acquisitions are performed not immediately after wearing the sensors, waiting for the child to forget them. In addition to this, wearable sensor allow to acquire children out of the lab, in a more familiar and ecological environment, thus facilitating the accurate acquisition of kinematic data of natural motor behaviours.
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Reviewer #2: Overall
The changes made to this paper have turned it into a much more understandable paper. However, there are still a substantial number of minor changes, which are needed to bring the paper up to a level which is easy to read. Currently as a reader I found myself flicking up and down to clarify the meaning of the metrics used. Also the paper still requires significant copy editing.
In addition to this text I have also provided an annotated word version of the paper.

- The authors would like to thank the reviewer for the constructive comments and the attention towards our manuscript. Point to point answers are provided in the following document as well as direct reference to the changes made to the manuscript.
Careful proofreading and copyediting of the manuscript was performed.
Unfortunately, we could not find the annotated word version of the paper either attached to the email or on editorial manager.

Minor

Overall
There are a significant amount of copy errors which interrupt the flow of the paper.

- We carefully proofread the text in order to correct all the copy errors.

This paper uses many abbreviations. To understand this paper you must understand the abbreviations. Details of these abbreviations have now been provided. However, they have been put into a supplementary material section. These abbreviations should be put into the main body of the paper or future readers may struggle to understand. Typically the supplementary material is a separate download from the main paper so they will become divorced.

- Agreed. We inserted the tables with acronyms and method description in the main texts as suggested (Table 2a and 2b).

Some of the Abbreviations provided in the abbreviations tables do not match up with those used in the paper for instance DS is used throughout. However in the table DS(%) is shown. i.e. the double support time, expressed as a percentage of Stride Time (Stride T)

- We checked abbreviations both in the text and in the tables in order to verify their matching and corrected them when needed. We agree that the insertion of Table 2a

	and b with acronyms in the main text supports the understanding of the paper. Results Table captions: In the previous review it was suggested that the captions should be improved, to make them standalone. The text has been extended but, not all are standalone. Some are in need of an introductory sentence. Here is an example from one of the cited papers which provides an example of how they should be formatted: 'Fig. 1. Changes in behaviors and test of infant motor performance scores during the development of midline head control. White bars represent the infants born full term. Black bars represent the infants born preterm. A: Duration of leg lift in the No Toy Condition. B: Frequency of leg lift in the No Toy Condition. C: Duration of head in midline in the No Toy Condition. D: TIMP z-score.' Table 2. I assume '** (Hrisk-PT > Mrisk-PT)' represents a trend. What does '**' on its own mean? there is no trend? This should be explained in the caption. This is part of the caption for Table 3. 'Asterisks indicate significant differences (*p<0.1; ** p<0.05). Significant differences described between brackets. ' However, there is no single * in Table 3 - Agreed. We further extended the Caption of Table1a, Table 3 and Table 4 (Tables 2 and 3 in the previous version of the manuscript). We described the meanings of asterisks with respect to the specific statistical test and of observed trends described between brackets. Table 2. On the left, estimated temporal parameters (25th, 50th, and 75th percentiles) for FT and PT children. Asterisks indicate significant differences between FT and PT (*p<0.1; ** p<0.05). Significant differences are described between brackets. On the right, estimated temporal parameters (25th, 50th, and 75th percentiles) for PT children at high risk (Hrisk-PT) and children at moderate risk (Mrisk-PT) of motor delays. Asterisks indicate a significant effect of risk of motor delay when comparing FT, Mrisk-PT and Hrisk-PT (*p<0.1; ** p<0.05). Significant differences between groups resulting from the multiple comparison test are described between brackets. Table 3. On the left, estimated nonlinear parameters (25th, 50th, and 75th percentiles) for FT and PT children. Asterisks indicate significant differences between FT and PT (** p<0.05). Significant differences are described between brackets. On the right, estimated nonlinear parameters (25th, 50th, and 75th percentiles) for PT children at high risk (Hrisk-PT) and children at moderate risk (Mrisk-PT) of motor delays. Asterisks indicate a significant effect of risk of motor delay when comparing FT, Mrisk-PT and Hrisk-PT (** p<0.05). Significant differences between groups resulting from the multiple comparison test are described

11th March 2022

Dear Professor Filippo Molinari
Editor in Chief
Computer Methods and Programs in Biomedicine

Ref: CMPB-D-21-02079

Title: "***Gait performance in toddlers born preterm: a sensor based quantitative characterization***"

by M.C. Bisi, M. Fabbri, D.M. Cordelli and R. Stagni.

We received communication of requested minor revision for the above-mentioned manuscript and are now resubmitting the revised version of the manuscript.
We would like to thank again the editor and the reviewers for their comments and for their careful revision that helped us in improving the paper.
We are providing a point by point response to the reviewers' comments and the revised version of the manuscript, where modified sections are highlighted.
We hope that this revised version of the manuscript can be suitable for publication on *Computer Methods and Programs in Biomedicine*.
We declare that this material has not been and will not be submitted for publication elsewhere except as an abstract and that there are no competing interests to declare.
Each author has been fully involved with the work, has read and concurs with the content in the final manuscript.

Best regards,

Maria Cristina Bisi
Manuela Fabbri
Duccio Maria Cordelli
Rita Stagni

POINT-BY-POINT RESPONSES TO REVIEWERS' COMMENTS:

First, we would like to thank again the editor and the reviewers for their comments and for their careful revision that helped us in improving the paper. We modified the manuscript accordingly and we hope that now it will be suitable for publication on *Computers Methods and Programs in Biomedicine*.

In the following lines, we reported direct answers to reviewers' comments, showing what we modified.

All the parts of the manuscript that were modified from the previous version are highlighted in yellow in the text.

Editor and Reviewer comments:

Reviewer #1: In general, the authors have addressed my previous concerns and improved the paper a lot. Again, I think this direction is interesting but we should treat the conclusion very carefully considering the limited number of subject involved in the experiment.
We thank the reviewer for the positive and constructive comments.

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Highlights

Sensor-based gait assessment of preterm toddlers.

Characterization of gait of toddlers at high, moderate, and low risk of motor delay.

Analysed quantitative metrics allowed differentiating between groups.

Preterm toddlers at higher risk of motor delay exhibited a less mature gait.

Identified metrics can serve as biomarkers for monitoring preterm motor development.

Figure 1

Click here to access/download;Figure;Figure1.jpg

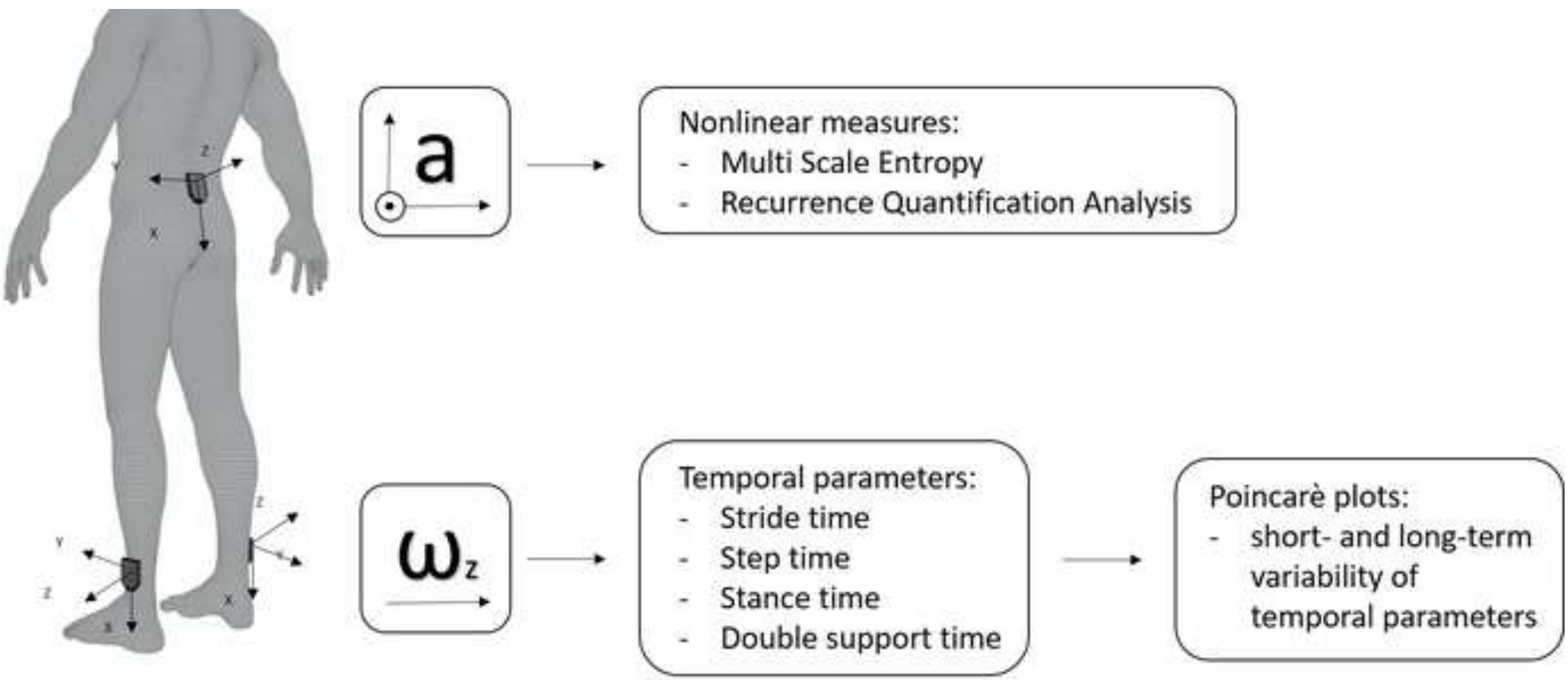
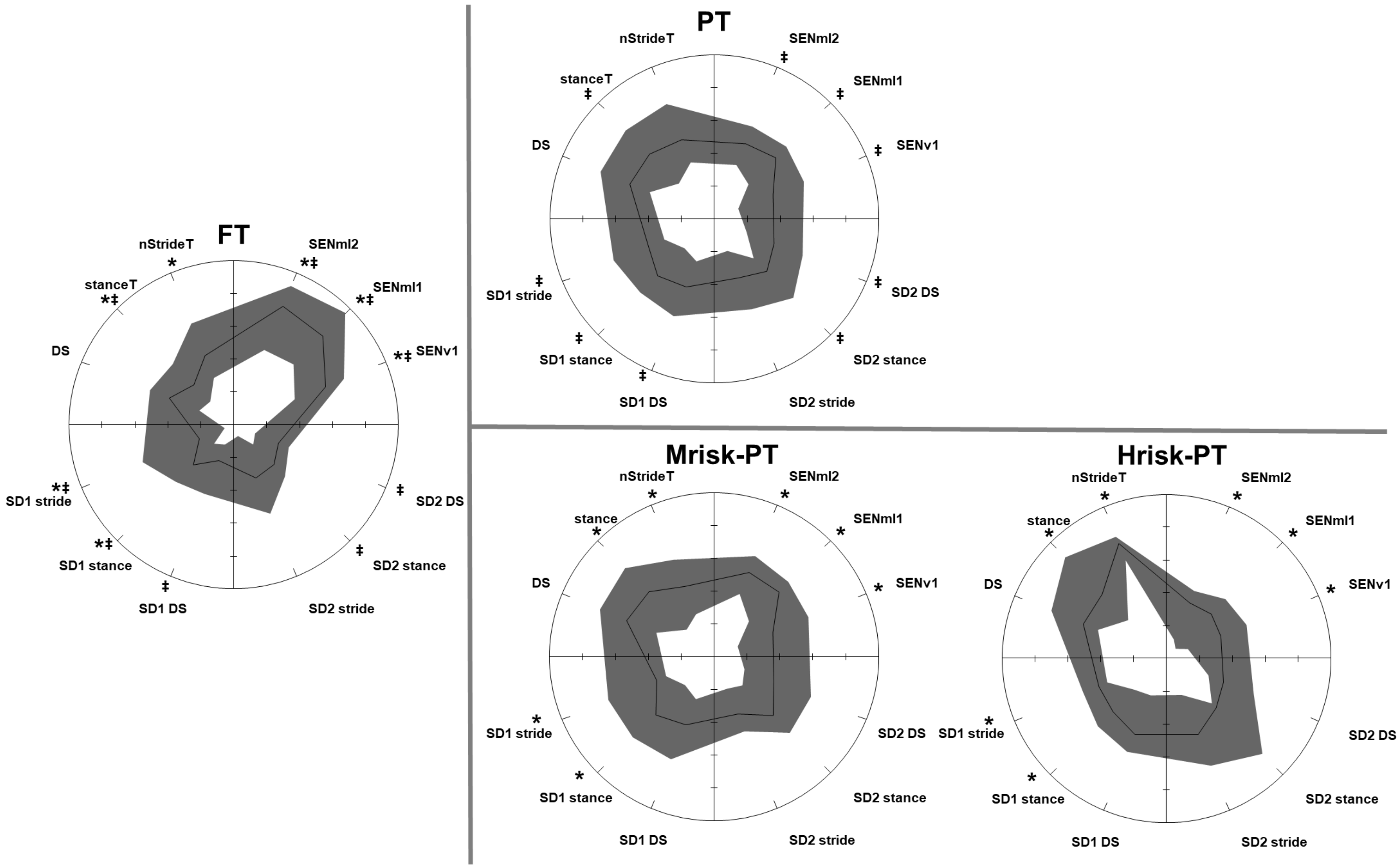


Figure 2. **Polar bands (median, 25th and 75th percentiles) for FT and PT children and for Mrisk-PT and Hrisk-PT. Double dagger indicate significant differences between FT and PT (p<0.05), asterisks significant effect of risk of motor delay when considering FT, Mrisk-PT and Hrisk-PT (p<0.05).**



							at birth		at 24 months	
	age (months)	**corrected age**	**gender**	**twins**	**walking experience (months)**	**weeks of pregnancy**	**body mass (kg)**	**length (cm)**	**body mass (kg)**	**BSID-III cognitive standardized scores**
Hrisk-PT	22.3	18.3	F	n	4.3	23+4	0.530	84	9.2	85*
	27.4	24.2	F	y	12.2	26+2	0.900	86	11	105
	27.4	24.2	M	y	11.2	26+2	1.020	86	13	90
	28.8	25.7	F	n	9.7	27+2	0.755	80	10.5	85
	30.2	27.2	F	y	15.2	27+2	1.040	92	13	80
	30.2	27.2	F	y	16.2	27+2	1.085	90	15	105
	27.6	24.8	F	n	12.8	28+2	1.020	77	9.5	90
	26.9	24.1	F	n	12.1	28+2	0.810	85	11	100
Mrisk-PT	30.0	27.2	F	n	14.2	28+4	1.430	91	12.4	100
	28.8	26.0	M	n	15.0	28+3	1.170	89	12.5	95
	27.6	25.3	F	y	13.3	30+1	1.470	90	11	100
	27.6	25.3	M	y	14.3	30+1	1.410	92	12	95
	26.3	24.0	F	n	8.0	30	1.200	90	12	95
	25.3	22.9	F	y	6.9	30+3	1.480	86	12.5	95
	25.3	22.9	F	y	6.9	30+3	1.411	86	11.5	90
	26.7	24.6	M	n	14.6	31	1.990	90	12.5	95
	27.1	25.0	F	n	12.0	31	1.530	84	11.4	100
	27.0	25.1	M	n	15.1	31+2	1.600	89	13	95
	21.3	19.2	M	y	7.2	31+3	1.795	88	13	75
	21.3	19.2	M	y	7.2	31+3	1.410	85	12.5	75
	26.2	24.4	F	n	11.4	32	1.580	85	11.3	NA**
	27.3	25.4	F	y	10.4	32	1.590	88.5	12.3	100
	27.3	25.4	F	y	11.4	32	1.490	88.5	12.3	100
	26.7	24.6	F	n	2.6	31+6	1.400	92	13	105
	27.4	25.6	F	y	10.6	32+3	1.675	80.5	10.1	95
	27.5	25.6	F	y	12.6	32+3	1.375	80.5	10.1	90
	26.7	24.9	F	n	14.9	32+4	2.090	87	12.5	95

27.3	25.5	F	n	13.5	32+6	1.690	85	12	100
26.2	25.1	F	n	12.1	35	1.545	82	10	90

* test administered when the child was 29 months old

** test score not avaiable

Table 1 a) Preterm (PT) participants' details, divided into children at high risk (Hrisk-PT) and children at moderate risk (Mrisk-PT) of motor delays: age and adjusted age (months), gender (male(M)/female(F)), twins (yes(y)/no(n)), walking experience (months), weeks of pregnancy, body mass at birth (kg), length (cm) and body mass (kg) at 24 months, Bayley Scales of Infant Development-3rd Edition (BSID-III) cognitive standardized score at 24 months.

					at birth	at 24 months	
age (months)	**gender**	**twins**	**walking experience (months)**	**weeks of pregnancy**	**body mass (kg)**	**length (cm)**	**body mass (kg)**
32.0	M	n	19.0	38+4	3.790	96	14.4
28.0	F	n	10.0	41	3.55	86	12.2
28.0	F	n	15.0	40	2.685	85.5	10.8
25.0	F	n	14.0	38	2.800	85	12.5
29.0	F	n	16.0	41	3.270	91	13.4
31.0	M	n	18.0	40	3.560	92	13.3
29.0	F	n	17.0	36	3.960	97	15.7
31.0	F	n	19.0	39	3.520	91	14.5
20.0	M	n	7.0	38+3	3.090	82	11.2
21.0	F	n	8.0	39	3.265	83	13.2
19.0	M	n	7.0	40	3.500	85	12.5
19.0	F	n	3.0	37+4	2.645	95	14.2
33.0	M	n	24.0	40+3	4.050	96.5	14.8
27.0	M	n	15.0	38	4.000	92	15.9
14.0	M	n	2.0	38	3.190	92	16.1
34.0	M	n	19.0	38+2	2.600	96	17.5

27.0	M	n	13.0	41	3.215	90	14

Table 1. b) Full-term (FT) participants' details: age (months), gender (male(M)/female(F)), twins (yes(y)/no(n)), walking experience (months), weeks of pregnancy, body mass at birth (kg), length (cm) and body mass (kg) at 24 months.

Table 2a. Temporal parameters: acronyms, descriptions and details for parameter calculation

Temporal parameters		
Acronym	**Measure (unit)**	**Description**
Stride T	Stride time (s)	Time difference between two consecutive initial contacts of the same foot
nstrideT	normalized stride time (adimentional)	Adimentional stride time, calculated according to Hof [33]
step T	Step time (s)	Time difference between the initial contact of one foot and the initial contact of the opposite foot
nstepT	normalized step time (adimentional)	Adimentional step time, calculated according to Hof [33]
stanceT	stance time (% of StrideT)	Time difference between initial contact and the consecutive terminal contact of the same foot, expressed in percentage of StrideT
DS	double support time (% of StrideT)	Time difference between the initial contact of one foot and the terminal contact of the opposite foot, expressed in percentage of StrideT
SD1 StrideT	short term variability of StrideT	Poincaré plots were created plotting temporal parameters data between successive gait cycles, showing variability of temporal parameters data. The plots display the correlation between temporally consecutive data in a graphical manner: SD1 and SD2 are calculated as width and length of the long and short axis, respectively, describing the elliptical nature of the plots, and represent the short-term and long-term variability of the analysed temporal parameter [34].
SD2 StrideT	long term variability of StrideT	
SD1 StepT	short term variability of StepT	
SD2 StepT	long term variability of StrideT	
SD1 StanceT	short term variability of StrideT	
SD2 StanceT	long term variability of StrideT	
SD1 DS	short term variability of StrideT	
SD2 DS	long term variability of StrideT	

Table 2b. Nonlinear parameters: acronyms, descriptions and details for parameter calculation

Nonlinear parameters

Acronym	**Measure**	**Description**
MSE	multiscale entropy	MSE was calculated as the Sample Entropy (SEN) of trunk acceleration components (SENv, SENml, SENap) at time scales (τ) from 1 to 6.
SEN	sample entropy	Trunk acceleration time series have been normalized to have standard deviation 1. Consecutive coarse-grained time series were calculated by averaging increasing numbers of data points in non-overlapping windows of length τ. Each element of the coarse grained time series yj(τ), was calculated starting from the original time series {x1,…,xi,…, xN}, according to $y_j^{(\tau)} = {}^1/_\tau \sum_{i=(j-1)\tau+1}^{j\tau} x_i,$ where τ represents the scale factor and 1≤j≤N⁄τ. For each coarse grained time series, SEN was calculated as the conditional probability that two sequences of m consecutive data points (m=2) similar to each other will remain similar (i.e. distance of data points inferior to a fixed radius (radius fixed at 0.2), when one more consecutive point is included.
RQA	Recurrence quantification Analysis	State space was reconstructed by using the delay embedded state space of each trunk acceleration component separately (V, AP and ML). Embedding dimension was fixed at 5; time delay was obtained using the first minimum of the average mutual information algorithm and set at 10 samples (corresponding to 0.078 s given the sampling frequency of 128Hz). Distance between all the points of the embedded time series was calculated. If this distance was less than or equal to a threshold the point is a recurrence. The recurrence plot was obtained by selecting a threshold of 40% of the max distance, and all cells with values below this threshold were identified as recurrent points.
RR	Recurrence Rate	RR was calculated as the number of recurrent points in the recurrence plot expressed as a percentage of the number of possibly recurrent points (percentage of points within a threshold distance of one another)
DET	Determinism	DET was calculated as the percentage of recurrent points falling on upward diagonal line segments. Number of points forming a line segment was fixed at 4.

AvgL	Averaged Diagonal Line Length	AvgL was calculated as the average upward diagonal line length, where the diagonal lines are defined following determinism definition

	FT			PT				Mrisk-PT			Hrisk-PT			
	25th	50th	75th	25th	50th	75th		25th	50th	75th	25th	50th	75th	
Stride T	0.74	0.82	0.87	0.75	0.80	0.89		0.72	0.78	0.84	0.84	0.88	0.92	** (Hrisk-PT > Mrisk-PT)
nstrideT	2.48	2.61	2.86	2.54	2.71	2.98		2.39	2.65	2.77	2.83	3.00	3.05	** (Hrisk-PT > FT; Hrisk-PT > Mrisk-PT)
step T	0.37	0.41	0.44	0.37	0.40	0.44		0.37	0.38	0.43	0.42	0.44	0.45	*
nstepT	1.24	1.32	1.42	1.27	1.35	1.50		1.22	1.32	1.42	1.42	1.50	1.51	** (Hrisk-PT > FT; Hrisk-PT > Mrisk-PT)
stanceT	56.4	58.2	59.9	57.4	60.2	62.0	** (PT > FT)	56.6	60.2	62.0	58.2	60.2	62.6	**
DS	13.1	17.2	19.8	17.2	20.0	24.0	* (PT > FT)	16.3	20.4	24.0	17.8	19.8	24.1	
SD1 StrideT	0.04	0.04	0.06	0.05	0.06	0.08	** (PT > FT)	0.05	0.07	0.08	0.05	0.06	0.07	** (FT < Mrisk-PT)
SD2 StrideT	0.05	0.08	0.11	0.07	0.09	0.12		0.06	0.08	0.11	0.07	0.10	0.13	
SD1 StepT	0.02	0.03	0.04	0.03	0.04	0.07	** (PT > FT)	0.03	0.05	0.08	0.03	0.04	0.04	** (FT < Mrisk-PT)
SD2 StepT	0.04	0.04	0.07	0.05	0.06	0.08	** (PT > FT)	0.04	0.06	0.18	0.05	0.06	0.07	
SD1 StanceT	2.53	3.05	3.94	3.16	4.16	4.82	** (PT > FT)	3.16	4.18	4.97	3.21	3.93	4.33	** (FT < Mrisk-PT)
SD2 StanceT	3.22	3.68	4.17	3.72	4.31	5.41	** (PT > FT)	3.40	4.31	5.25	3.92	4.82	5.69	*
SD1 DS	3.41	4.06	5.44	4.34	5.39	6.60	** (PT > FT)	4.34	5.39	6.81	4.12	5.71	6.46	*
SD2 DS	4.10	5.21	5.73	4.63	5.94	7.35	** (PT > FT)	4.54	5.94	7.77	5.10	5.81	7.29	

Table 3. On the left, estimated temporal parameters (25th, 50th, and 75th percentiles) for FT and PT children. Asterisks indicate significant differences between FT and PT (*p<0.1; ** p<0.05). Significant differences are described between brackets.

On the right, estimated temporal parameters (25th, 50th, and 75th percentiles) for PT children at high risk (Hrisk-PT) and children at moderate risk (Mrisk-PT) of motor delays. Asterisks indicate a significant effect of risk of motor delay when comparing FT, Mrisk-PT and Hrisk-PT (*p<0.1; ** p<0.05). Significant differences between groups resulting from the multiple comparison test are described between brackets.

	FT			PT				Mrisk-PT			Hrisk-PT			
	25th	50th	75th	25th	50th	75th		25th	50th	75th	25th	50th	75th	
DETml	5.11	5.50	5.69	5.29	5.47	5.69		5.28	5.42	5.55	5.62	5.82	6.04	** (Hrisk-PT > Mrisk-PT)
SENv (τ=1)	0.47	0.54	0.58	0.38	0.46	0.54	** (PT < FT)	0.38	0.46	0.55	0.38	0.45	0.51	**
SENml (τ=1)	0.51	0.60	0.67	0.43	0.51	0.55	** (PT < FT)	0.43	0.52	0.55	0.35	0.46	0.51	** (Hrisk-PT < FT)
SENml (τ=2)	0.83	1.01	1.09	0.74	0.83	0.90	** (PT < FT)	0.78	0.87	0.93	0.60	0.75	0.80	** (Hrisk-PT < FT)

Table 4. On the left, estimated nonlinear parameters (25th, 50th, and 75th percentiles) for FT and PT children. Asterisks indicate significant differences between FT and PT ($p<0.05$). Significant differences are described between brackets.**

On the right, estimated nonlinear parameters (25th, 50th, and 75th percentiles) for PT children at high risk (Hrisk-PT) and children at moderate risk (Mrisk-PT) of motor delays. Asterisks indicate a significant effect of risk of motor delay when comparing FT, Mrisk-PT and Hrisk-PT ($p<0.05$).**

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The Authors declare that there is no conflict of interest.

Best regards,

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Gait performance in toddlers born preterm: a sensor based quantitative characterization

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Abstract (350 words)

Background and Objectives

Preterm children have an increased risk of motor difficulties. Gait analysis and wearable technologies allow the assessment of motor performance in toddlers, identifying early deviations from typical development. Using a sensor-based approach, gait performance of full-term and preterm toddlers at different risk of motor delay was analysed. The aim was to measure quantitative differences among groups.

Methods

Twenty-nine two-year old children born preterm (≤36 gestational weeks) and 17 full-term controls, matched for age and walking experience, participated in the study. Preterm children were further divided based on risk of motor delay: preterm at high risk (n=8, born at ≤28 gestational weeks or with ≤1000g of body weight), and at moderate risk (n=21).

Children were asked to walk along a corridor while wearing 3 inertial sensors on the lower back and on the ankles. Gait temporal parameters, their variability, and nonlinear metrics of trunk kinematics (i.e. recurrence quantification analysis, multiscale entropy) were extracted from the collected data and compared among groups.

Results

Children born preterm showed significantly longer stance and double support phases, higher variability of temporal parameters, and lower multiscale entropy values than peers born full-term. No difference was found for the other parameters when comparing preterm and full-term children. When comparing children grouped according to risk of delay, with increasing risk, children showed longer stride-, stance- and double-support-time, higher variability of temporal parameters, higher recurrence - and lower multiscale entropy values.

Conclusions

Sensor-based gait analysis allowed differentiating the gait performance of preterm from full-term toddlers, and of preterm toddlers at different risk of motor delay. When analysing the present results with respect to the expected trajectory of locomotor development, children born preterm, in particular those at higher risk of motor delay, exhibited a less mature motor control performance during gait: lower stability (i.e. longer support phases), and higher variability, although not structured towards the exploration of more complex movements (i.e. higher recurrence- and lower multiscale entropy values). These indexes can serve as biomarkers for monitoring locomotor development and early detecting risk to develop persistent motor impairments.

Keywords: Wearable sensors; motor biomarkers; preterm children; motor development; variability; complexity.

Introduction

The earlier a baby is born the greater the risk of long-term consequences, with over 50% of children born <30 weeks facing motor, cognitive, and behavioural impairments [1]. Thanks to advances in medical care, younger and more vulnerable children born preterm (PT) have increased opportunities of survival, with evidence of an increasing number of PT infants worldwide (an estimated 11.1% of all livebirths in 2010 were born PT [2]).

One of the most frequent issues encountered by PT children is an increased risk of motor difficulties ranging from mild impairments to cerebral palsy, with prevalence 3 to 4 times greater than in the general population [3]. While a substantial evidence base has been established for risk factors, causal pathways, and neurological mechanisms for cerebral palsy [4], the knowledge regarding the non-cerebral palsy motor impairments is still limited, although affecting a much larger number of PT children (up to 50% of children born <30 weeks) [1]. Mild motor deficits, such as Developmental Coordination Disorder, can have long-term consequences, compromising physical function, academic achievement, and other health outcomes (e.g. higher risks of obesity, cardiorespiratory problems, diabetes, and problems related to social integration) [5]. Thus, to implement effective interventions for the future wellbeing of this growing population, the understanding as well as the early and timely identification of mild motor difficulties is crucial, given the key periods of brain plasticity and musculoskeletal development.

WHO defines preterm birth as any birth before 37 completed weeks of gestation and divides this further on the basis of gestational age (extremely/very preterm < 32 weeks of gestation; moderate/late preterm 32 - <37 weeks). These subdivisions are important since decreasing gestation age is associated with increasing short and long term consequences [2]. However, this subdivision is defined to support clinical data collection and management in general and not for subject-specific identification of risk of motor delays.

Nowadays, identification of potential gross motor impairment in toddlers is primarily based on motor-milestone history and clinical examination, which have demonstrated poor specificity [6]. Motor milestone assessments are made challenging by variability in parental report and the wide age range of normal in milestone attainment [6]. Clinical examinations, even when based on structured assessments of gross motor function (e.g. The Peabody Developmental Motor Scale-2 and Bayley Scales of Infant Development-3rd Edition), are long (90min for the full BSID-III 18–22 month olds) and expensive, require trained personnel, thus limiting assessments only to the highest-risk children. Given these limitations, there is the need of quantitative and objective tests, easy to be administered, for a widespread application.

As recently highlighted in the review by Albesher et al., [7], walking is a central part of most basic and leisure daily activities; therefore, knowledge of the timing of walking onset and any alteration of gait is essential to understand the needs of children born PT. Several research studies [6,8–10] analysed and quantified gait of PT children during the first months of independent walking using lab-based measurement methods (i.e. instrumental walkways, 3-D motion analysis and force platforms) [7]. These studies showed that gait in toddlers born PT is generally characterized as being delayed and qualitatively less coordinated [8,11]. At 18 months of age, they exhibited shorter stride length than full-term (FT) peers [10], but it is not clear if these differences persist as children reach preschool and school age [7]. Recently, spatiotemporal gait parameters have been proposed as useful in building a clinically relevant, straightforward assessment of toddler gross motor development [6], but the need of laboratory assessment hinders their applicability for routine monitoring. Despite relevant findings [8–11], the quantitative characterization of gait in children born PT is still scarce and concentrates on the first few months after the child attains walking and at school age, while studies on walking characteristics of PT children in between those ages are lacking [7]. Wearable sensors can be a viable solution to overcome laboratory limitations and effectively fill this gap: they are easy to use, light, unobtrusive, and can be worn under the clothes, for long periods, facilitating the experiments with toddlers [12]. Human movement analysis methods exploiting measurements based on wearable inertial sensors allow the quantitative assessment of human movement in outpatient conditions at different ages, effectively integrating the information derived from qualitative observation with quantitative biomarkers [13] to attain a quantitative monitoring of motor development in PT children.

Sensor-based approaches allowed the estimation of temporal gait parameters in different children populations with typical and atypical development [13] as well as toddlers at the onset of walking [12]. On the other hand, the analysis and monitoring of motor control development requires to address the maturation of different underlying control mechanisms, such as automaticity and complexity, that can be investigated by means of advanced metrics [13,14].

To this purpose, nonlinear metrics, derived from dynamical system theory, provide tools for investigating the dynamics of motor control resulting from interactions between nervous system, musculoskeletal system, and the surrounding environment while performing of a specific task [15].

Among these nonlinear metrics, previous works from the same authors showed that multiscale entropy (MSE) [16] and recurrence quantification analysis (RQA) of trunk 3D acceleration during gait, allowed to quantitatively assess motor development during the life-span [17,18], highlighting differences related to age maturation [17], and providing information complementary to standard clinical tests in toddlers and school-children [19,20]. In particular, RQA and MSE have been associated to the quantification of motor regularity and complexity during locomotion and their changes with age to changes in the maturation of motor control [19,20]. Increase or decrease of these metrics with (age) maturation depends on the analysed motor task and, specifically, on the stage of motor learning process of the population under study with respect to the specific task [20,21]. When considering toddlers at the onset of independent walking, MSE was found to increase with maturation and/or walking experience, as during the first stage of the fundamental movement phase [22], there is a gradual increase in agility, adaptability, and ability to make complex movements, which children show manifesting more and more flexibility in performance [18,23].

When considering PT children motor development, entropy-based metrics have been applied for the analysis of infant postural control maturation [24–27], highlighting that infants born PT show a decreased postural complexity compared to infants born FT. These results, although not specifically referred to gait, support the use of nonlinear metrics for the investigation of motor development to highlight consequences of PT births and/or risk of possible delays.

The aim of the present study was to assess gait performance of toddlers born PT as compared to a control group born at FT, using a sensor-based approach that allows quantifying a cluster of metrics [17] that include gait temporal parameters, their variability, as well as nonlinear metrics quantitatively characterising the dynamics of the lower trunk, related to the control of the progression of the centre of mass [19]. Only PT children without diagnosis of cerebral palsy were included in the study. Based on previous literature [7,23,25], it was hypothesized that PT children at risk of motor delay would show a less mature gait performance, corresponding to a delayed maturation of the control of the trunk and a higher variability of gait temporal parameters.

Materials and methods

Study subjects

PT children were recruited at the Ceredilico – IRCCS Institute of Neurological Sciences of Bologna, where they were already enrolled in a neurodevelopment follow-up program. Children born at FT were recruited at a local kindergarten (Istituto San Giuseppe, Lugo, Ravenna). The local Ethical Committee approved this study (ASL_BO n° 0018081 08/02/2017), and informed consent was obtained from the participants' parents.

Twenty-nine two-year old PT (median/min-max value of months of adjusted age: 25/18-27; months of walking experience: 12/2-16; gestational weeks: 30.5/24-35) and 17 FT children (median/min-max value of age: 28/14-34; months of walking experience: 15/2-24; ≥38 gestational weeks) participated in the study.

All PT children had a diagnosis of "Disorders related to short gestation and low birth weight", ICD10-GM-2018 P07, and no other diagnosed developmental delay. Children with congenital malformations and/or blindness were excluded. PT children were further divided into two groups based on the risk of motor delay. Since gestational age and body weight at birth are both determinant of long-term neurodevelopmental outcomes [28,29], the children born extremely PT (≤28 gestational weeks [2]) or with extremely low body weight (≤1000g [30]) were considered at high risk (Hrisk-PT), and the other PT children at moderate risk (Mrisk-PT). FT children had no diagnosed developmental delay. Characteristics of PT and FT children participating in the study are shown in in Table 1a and 1b, respectively.

Table 1 a) Preterm (PT) participants' details, divided into children at high risk (Hrisk-PT) and children at moderate risk (Mrisk-PT) of motor delays: age and adjusted age (months), gender (male(M)/female(F)), twins (yes(y)/no(n)), walking experience (months), weeks of pregnancy, body mass at birth (kg), length (cm) and body mass (kg) at 24 months, Bayley Scales of Infant Development-3rd Edition (BSID-III) cognitive standardized score at 24 months.

							at birth	at 24 months		
	age (months)	corrected age	gender	twins	walking experience (months)	weeks of pregnancy	body mass (kg)	length (cm)	body mass (kg)	BSID-III cognitive standardized scores
Hrisk-PT	22.3	18.3	F	n	4.3	23+4	0.53	84	9.2	85*
	27.4	24.2	F	y	12.2	26+2	0.9	86	11	105
	27.4	24.2	M	y	11.2	26+2	1.02	86	13	90
	28.8	25.7	F	n	9.7	27+2	0.755	80	10.5	85
	30.2	27.2	F	y	15.2	27+2	1.04	92	13	80
	30.2	27.2	F	y	16.2	27+2	1.085	90	15	105
	27.6	24.8	F	n	12.8	28+2	1.02	77	9.5	90
	26.9	24.1	F	n	12.1	28+2	0.81	85	11	100
Mrisk-PT	30	27.2	F	n	14.2	28+4	1.43	91	12.4	100
	28.8	26	M	n	15	28+3	1.17	89	12.5	95
	27.6	25.3	F	y	13.3	30+1	1.47	90	11	100
	27.6	25.3	M	y	14.3	30+1	1.41	92	12	95
	26.3	24	F	n	8	30	1.2	90	12	95
	25.3	22.9	F	y	6.9	30+3	1.48	86	12.5	95
	25.3	22.9	F	y	6.9	30+3	1.411	86	11.5	90
	26.7	24.6	M	n	14.6	31	1.99	90	12.5	95
	27.1	25	F	n	12	31	1.53	84	11.4	100
	27	25.1	M	n	15.1	31+2	1.6	89	13	95
	21.3	19.2	M	y	7.2	31+3	1.795	88	13	75
	21.3	19.2	M	y	7.2	31+3	1.41	85	12.5	75
	26.2	24.4	F	n	11.4	32	1.58	85	11.3	NA**
	27.3	25.4	F	y	10.4	32	1.59	88.5	12.3	100
	27.3	25.4	F	y	11.4	32	1.49	88.5	12.3	100
	26.7	24.6	F	n	2.6	31+6	1.4	92	13	105
	27.4	25.6	F	y	10.6	32+3	1.675	80.5	10.1	95
	27.5	25.6	F	y	12.6	32+3	1.375	80.5	10.1	90
	26.7	24.9	F	n	14.9	32+4	2.09	87	12.5	95
	27.3	25.5	F	n	13.5	32+6	1.69	85	12	100
	26.2	25.1	F	n	12.1	35	1.545	82	10	90

* test administered when the child was 29 months old

** test score not avaiable

Table 1. b) Full-term (FT) participants' details: age (months), gender (male(M)/female(F)), twins (yes(y)/no(n)), walking experience (months), weeks of pregnancy, body mass at birth (kg), length (cm) and body mass (kg) at 24 months.

					at birth	at 24 months	
age (months)	**gender**	**twins**	**walking experience (months)**	**weeks of pregnancy**	**body mass (kg)**	**length (cm)**	**body mass (kg)**
32.0	M	n	19.0	38+4	3.790	96	14.4
28.0	F	n	10.0	41	3.55	86	12.2
28.0	F	n	15.0	40	2.685	85.5	10.8
25.0	F	n	14.0	38	2.800	85	12.5
29.0	F	n	16.0	41	3.270	91	13.4
31.0	M	n	18.0	40	3.560	92	13.3
29.0	F	n	17.0	36	3.960	97	15.7
31.0	F	n	19.0	39	3.520	91	14.5
20.0	M	n	7.0	38+3	3.090	82	11.2
21.0	F	n	8.0	39	3.265	83	13.2
19.0	M	n	7.0	40	3.500	85	12.5
19.0	F	n	3.0	37+4	2.645	95	14.2
33.0	M	n	24.0	40+3	4.050	96.5	14.8
27.0	M	n	15.0	38	4.000	92	15.9
14.0	M	n	2.0	38	3.190	92	16.1
34.0	M	n	19.0	38+2	2.600	96	17.5
27.0	M	n	13.0	41	3.215	90	14

FT, Mrisk-PT, and Hrisk-PT showed no difference in terms of age (when considering both adjusted and not adjusted age for PT children) and walking experience (Kruskalwallis test, level of significance 5%).

Experimental setup

Three tri-axial wireless inertial sensors (OPAL, Apdm, USA) were mounted on the lower back (at L5 level) and on the shanks (above lateral malleolus) using Velcro straps (Figure 1) [12]; 3D acceleration and angular velocity were recorded at 128Hz. Tests were performed at the clinical centre Ceredilico

– IRCCS Institute of Neurological Sciences of Bologna during the day of the follow up visit for PT children, and at the kindergarten (Istituto San Giuseppe, Lugo, Ravenna) for FT children.

Sensors had coloured stickers attached on in order to help participants familiarize. After sensor positioning, children were distracted with toys and free walks. Tests started only when participants were comfortable and forgot about the sensors (given the unobtrusiveness of the sensors, this took typically less than 2 minutes).

The participants were asked to walk at self-selected speed along a 15 m long corridor while moms or nannies called them at the other end of the corridor. The trials were video recorded to later check if they either were helping themselves with something (wall, shelves etc.), were curving, stopping, running, or crying. In those cases, the identified steps were excluded from the analysis.

Data analysis

Only inline straight strides were considered for data analysis.

Foot contacts and foot offs were identified from the angular velocity around the medio-lateral axis of the leg, identifying local minima at the beginning and at the end of the swing phase [12,31,32]. For all participants, 14 consecutive strides were analysed, being the maximum number of inline strides identified for all subjects.

The following temporal parameters were calculated as described in Bisi & Stagni [17] and [31]:

- Stride-time (StrideT, in seconds) and normalized stride- (nStrideT, adimentional [33]);
- Step- (StepT, in seconds) and normalized step- (nStepT, adimentional [33]),
- stance- (StanceT, expressed in % of StrideT),
- double support- time (DS, expressed in % of StrideT).

Symmetry between right and left StrideT, StanceT and StepT was tested per each subject using the Kruskal–Wallis test with a level of significance of 5%. As no significant difference between right and left parameters was found, data from both legs were considered together for each participant.

Intra-subject variability was evaluated using Poincarè plots [34], calculating short (SD1) and long term (SD2) variability [35] of the estimated temporal parameters (i.e. StrideT, StepT, StanceT, DS).

Recurrence Quantification Analysis, and Multiscale Entropy (MSE) were calculated for the three trunk acceleration components (vertical, V, medio-lateral, ML, and antero-posterior, AP) [17].

MSE was calculated as the Sample Entropy (SEN) of trunk acceleration components (SENv, SENml, SENap) at time scales (τ) from 1 to 6: i) coarse-grained time series were calculated by averaging increasing numbers of data points in non-overlapping windows of length τ, τ=1:6; ii) length of sequences to be compared, *m*, was fixed at 2, and tolerance for accepting matches, *radius*, at 0.2 [20]. To guarantee reliability of MSE results [36], sensitivity to radius values was verified (*radius* = 0.10, 0.15, 0.20, 0.25, and 0.30) for each τ for the two groups, and relative consistency was verified for radius values below and above the selected one.

For Recurrence Quantification Analysis (RQA) [37], the state space was constructed by using the delay-embedded state space of each component of the trunk acceleration separately (embedding dimension, 5, time delay, 10 samples) [20]. After the generation of recurrence plots (threshold, 40%) [20], the following features were extracted for each acceleration component: recurrence rate (RR), determinism (DET) and averaged diagonal line length (AvgL).

Figure 1 shows sensor placement and a schematic flowchart of data analysis.

Full description of parameters extractions for both temporal and nonlinear parameters is provided in Table 2a and 2b, respectively.

Figure 1

Fig.1. On the left, inertial sensor positions (lower trunk and shanks) and axis orientations. On the right, data analysis flowchart.

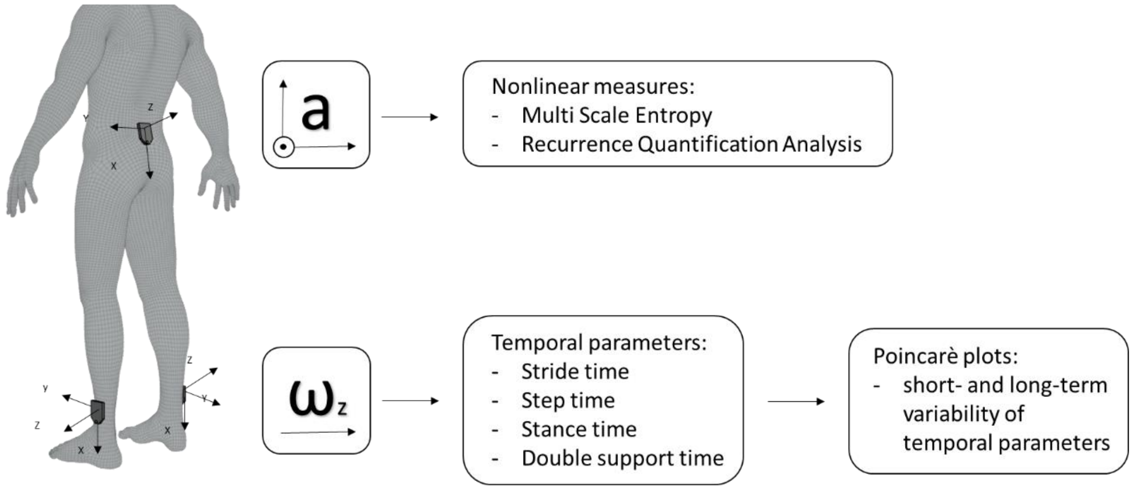


Table 2a. Temporal parameters: acronyms, descriptions and details for parameter calculation.

Temporal parameters

Acronym	Measure (unit)	Description
Stride T	Stride time (s)	Time difference between two consecutive initial contacts of the same foot
nstrideT	normalized stride time (adimentional)	Adimentional stride time, calculated according to Hof [33]
step T	Step time (s)	Time difference between the initial contact of one foot and the initial contact of the opposite foot
nstepT	normalized step time (adimentional)	Adimentional step time, calculated according to Hof [33]
stanceT	stance time (% of StrideT)	Time difference between initial contact and the consecutive terminal contact of the same foot, expressed in percentage of StrideT
DS	double support time (% of StrideT)	Time difference between the initial contact of one foot and the terminal contact of the opposite foot, expressed in percentage of StrideT
SD1 StrideT	short term variability of StrideT	Poincaré plots were created plotting temporal parameters data between successive gait cycles, showing variability of temporal parameters data. The plots display the correlation between temporally consecutive data in a graphical manner: SD1 and SD2 are calculated as width and length of the long and short axis, respectively, describing the elliptical nature of the plots, and represent the short-term and long-term variability of the analysed temporal parameter [34].
SD2 StrideT	long term variability of StrideT	
SD1 StepT	short term variability of StepT	
SD2 StepT	long term variability of StrideT	
SD1 StanceT	short term variability of StrideT	
SD2 StanceT	long term variability of StrideT	
SD1 DS	short term variability of StrideT	
SD2 DS	long term variability of StrideT	

Table 2b. Nonlinear parameters: acronyms, descriptions and details for parameter calculation.

Nonlinear parameters Acronym	Measure	Description
MSE	multiscale entropy	MSE was calculated as the Sample Entropy (SEN) of trunk acceleration components (SENv, SENml, SENap) at time scales (τ) from 1 to 6.
SEN	sample entropy	Trunk acceleration time series have been normalized to have standard deviation 1. Consecutive coarse-grained time series were calculated by averaging increasing numbers of data points in non-overlapping windows of length τ. Each element of the coarse grained time series yj(τ), was calculated starting from the original time series {x1,...,xi,..., xN}, according to $y_j^{(\tau)} = 1/\tau \sum_{i=(j-1)\tau+1}^{j\tau} x_i$, where τ represents the scale factor and $1 \leq j \leq N/\tau$. For each coarse grained time series, SEN was calculated as the conditional probability that two sequences of m consecutive data points (m=2) similar to each other will remain similar (i.e. distance of data points inferior to a fixed radius (radius fixed at 0.2), when one more consecutive point is included.
RQA	Recurrence quantification Analysis	State space was reconstructed by using the delay embedded state space of each trunk acceleration component separately (V, AP and ML). Embedding dimension was fixed at 5; time delay was obtained using the first minimum of the average mutual information algorithm and set at 10 samples (corresponding to 0.078 s given the sampling frequency of 128Hz). Distance between all the points of the embedded time series was calculated. If this distance was less than or equal to a threshold the point is a recurrence. The recurrence plot was obtained by selecting a threshold of 40% of the max distance, and all cells with values below this threshold were identified as recurrent points.
RR	Recurrence Rate	RR was calculated as the number of recurrent points in the recurrence plot expressed as a percentage of the number of possibly recurrent points (percentage of points within a threshold distance of one another)
DET	Determinism	DET was calculated as the percentage of recurrent points falling on upward diagonal line segments. Number of points forming a line segment was fixed at 4.
AvgL	Averaged Diagonal Line Length	AvgL was calculated as the average upward diagonal line length, where the diagonal lines are defined following determinism definition

Statistical analysis

Jarque-Bera test was performed to test the normal distribution of the estimated parameters in the different groups (i.e. FT, PT, Hrisk-PT, Mrisk-PT): since the normal distribution was not verified on all groups, Kruskal-Wallis test (level of significance, 0.1) was used to analyse influence of (i) PT birth and (ii) risk of motor delay on the calculated parameters (i.e. temporal parameter, variability of temporal parameters, RQA, MSE).

Statistical analysis was performed to test:

(i) Influence of preterm birth: PT vs FT;

(ii) Influence of risk of motor delay: FT, Mrisk-PT and Hrisk-PT. When a significant effect was found, a multiple comparison test [38] was performed to evaluate which of the analysed groups showed significant differences from the others. Dunn–Sidak correction was considered for post hoc analysis [39].

Results

Temporal parameters

No significant difference was found for StrideT, nStrideT, StepT, and nStepT when comparing FT and PT. When comparing the 3 groups based on risk of motor delay, a significant effect was found for both StrideT and nStrideT (p=0.007 and p=0.001, respectively) and for stepT and nStepT (p=0.09 and p=0.05, respectively): StrideT, nStrideT, stepT, and nStepT all resulted shorter for groups at lower risk of motor delay; post-hoc analysis showed that Hrisk-PT had significantly longer StrideT than Mrisk-PT and longer nStrideT than Mrisk-PT and FT, and had significantly longer nStepT than Mrisk-PT and FT children.

PT children also showed significantly longer StanceT (p=0.02) and DS (p=0.06) with respect to FT. When considering the three groups based on risk of motor delay, a significant effect was found on StanceT, showing longer stance for increasing risk of motor delay (p=0.04); however, post-hoc analysis highlighted no significant differences between groups.

Intra-subject variability of all temporal parameters resulted significantly higher in PT children than in FT control peers for all estimated parameters except for SD2 of StrideT (p=0.3). When dividing PT participants based on risk of motor delay, a significant effect was found for SD1 of StrideT (p=0.03), SD1 of StepT (p=0.03), SD1 and SD2 of StanceT (p=0.04 and p=0.07, respectively), and SD1 of DS (p=0.07), highlighting an increasing trend of variability with increasing risk of motor delay; post-hoc analysis showed that FT children had significantly lower values of SD1 of StrideT, of StepT and of StanceT than Mrisk-PT.

Median values and 25th and 75th percentiles of temporal parameters for each group are reported in Table 3.

	FT			PT				Mrisk-PT			Hrisk-PT			
	25th	50th	75th	25th	50th	75th		25th	50th	75th	25th	50th	75th	
Stride T	0.74	0.82	0.87	0.75	0.80	0.89		0.72	0.78	0.84	0.84	0.88	0.92	** (Hrisk-PT > Mrisk-PT)
nstrideT	2.48	2.61	2.86	2.54	2.71	2.98		2.39	2.65	2.77	2.83	3.00	3.05	** (Hrisk-PT > FT; Hrisk-PT > Mrisk-PT)
step T	0.37	0.41	0.44	0.37	0.40	0.44		0.37	0.38	0.43	0.42	0.44	0.45	*
nstepT	1.24	1.32	1.42	1.27	1.35	1.50		1.22	1.32	1.42	1.42	1.50	1.51	** (Hrisk-PT > FT; Hrisk-PT > Mrisk-PT)
stanceT	56.4	58.2	59.9	57.4	60.2	62.0	** (PT > FT)	56.6	60.2	62.0	58.2	60.2	62.6	**
DS	13.1	17.2	19.8	17.2	20.0	24.0	* (PT > FT)	16.3	20.4	24.0	17.8	19.8	24.1	
SD1 StrideT	0.04	0.04	0.06	0.05	0.06	0.08	** (PT > FT)	0.05	0.07	0.08	0.05	0.06	0.07	** (FT < Mrisk-PT)
SD2 StrideT	0.05	0.08	0.11	0.07	0.09	0.12		0.06	0.08	0.11	0.07	0.10	0.13	
SD1 StepT	0.02	0.03	0.04	0.03	0.04	0.07	** (PT > FT)	0.03	0.05	0.08	0.03	0.04	0.04	** (FT < Mrisk-PT)
SD2 StepT	0.04	0.04	0.07	0.05	0.06	0.08	** (PT > FT)	0.04	0.06	0.18	0.05	0.06	0.07	
SD1 StanceT	2.53	3.05	3.94	3.16	4.16	4.82	** (PT > FT)	3.16	4.18	4.97	3.21	3.93	4.33	** (FT < Mrisk-PT)
SD2 StanceT	3.22	3.68	4.17	3.72	4.31	5.41	** (PT > FT)	3.40	4.31	5.25	3.92	4.82	5.69	*
SD1 DS	3.41	4.06	5.44	4.34	5.39	6.60	** (PT > FT)	4.34	5.39	6.81	4.12	5.71	6.46	*
SD2 DS	4.10	5.21	5.73	4.63	5.94	7.35	** (PT > FT)	4.54	5.94	7.77	5.10	5.81	7.29	

Table 3. On the left, estimated temporal parameters (25th, 50th, and 75th percentiles) for FT and PT children. Asterisks indicate significant differences between FT and PT (*p<0.1; ** p<0.05). Significant differences are described between brackets.

On the right, estimated temporal parameters (25th, 50th, and 75th percentiles) for PT children at high risk (Hrisk-PT) and children at moderate risk (Mrisk-PT) of motor delays. Asterisks indicate a significant effect of risk of motor delay when comparing FT, Mrisk-PT and Hrisk-PT (*p<0.1; ** p<0.05). Significant differences between groups resulting from the multiple comparison test are described between brackets.

Non-linear metrics

No significant difference was found for RQA parameters when comparing FT and PT. When considering the three groups based on risk of motor delay, among RQA parameters, a significant effect was found for DETml (p=0.02) showing higher values in children at higher risk of motor delay: post-hoc analysis showed DETml to be significantly higher in Hrisk-PT than Mrisk-PT.

When comparing FT vs PT, SEN values calculated in the frontal plans, i.e. V and ML direction, showed significant differences for τ=1 (p=0.01), and τ=1 and 2 (p=0.007 and 0.01), respectively. In particular PT children showed lower complexity values than FT peers. No significant difference was found for the other values of τ and in AP direction (for all the values of τ). When considering participants divided into three groups, a significant effect of risk of motor delay was found again for SEN values calculated in the frontal plane, i.e. V and ML direction, in particular for τ=1 (p=0.03) on the V axis, and τ = from 1 to 4 (p<0.02) on the ML axis. In all cases, lower SEN values were found for increasing risk of motor delay. Post hoc analysis highlighted that, in ML direction, Hrisk-PT children had significantly lower SEN values than FT.

Median values and 25th and 75th percentiles of nonlinear metrics for each group are reported in Table 4.

	FT			PT				Mrisk-PT			Hrisk-PT			
	25th	**50th**	**75th**	**25th**	**50th**	**75th**		**25th**	**50th**	**75th**	**25th**	**50th**	**75th**	
DETml	5.11	5.50	5.69	5.29	5.47	5.69		5.28	5.42	5.55	5.62	5.82	6.04	** (Hrisk-PT > Mrisk-PT)
SENv (τ=1)	0.47	0.54	0.58	0.38	0.46	0.54	** (PT < FT)	0.38	0.46	0.55	0.38	0.45	0.51	**
SENml (τ=1)	0.51	0.60	0.67	0.43	0.51	0.55	** (PT < FT)	0.43	0.52	0.55	0.35	0.46	0.51	** (Hrisk-PT < FT)
SENml (τ=2)	0.83	1.01	1.09	0.74	0.83	0.90	** (PT < FT)	0.78	0.87	0.93	0.60	0.75	0.80	** (Hrisk-PT < FT)

Table 4. On the left, estimated nonlinear parameters (25th, 50th, and 75th percentiles) for FT and PT children. Asterisks indicate significant differences between FT and PT (p<0.05). Significant differences are described between brackets.**

On the right, estimated nonlinear parameters (25th, 50th, and 75th percentiles) for PT children at high risk (Hrisk-PT) and children at moderate risk (Mrisk-PT) of motor delays. Asterisks indicate a significant effect of risk of motor delay when comparing FT, Mrisk-PT and Hrisk-PT (p<0.05).**

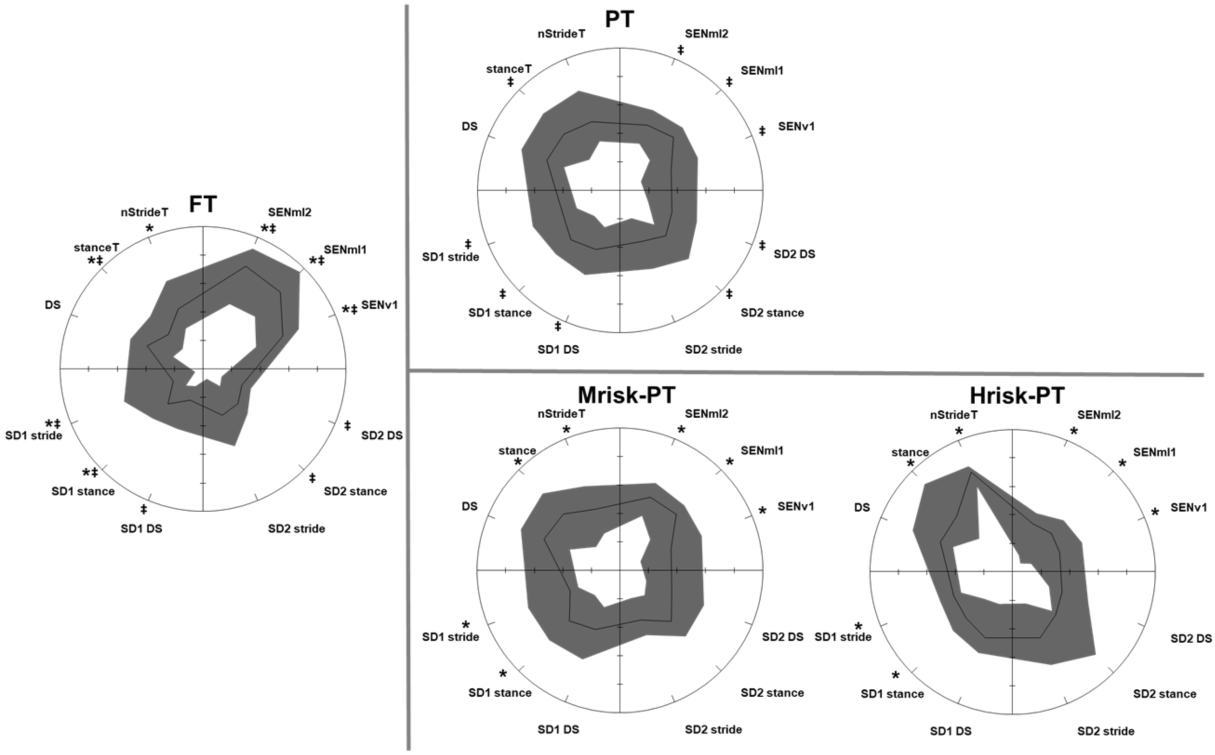
Significant differences between groups resulting from the multiple comparison test are described between brackets.

Based on statistical analysis results, the following significant parameters were selected for a polar representation [17]:

1) 'Temporal parameters': nStrideT, StanceT, DS.
2) 'Motor complexity': SENv (τ=1), SENml (τ=1), SENml (τ=2).
3) 'Short term variability': SD1 for strideT, stanceT and DS.
4) 'Long term variability': SD2 for strideT, stanceT and DS.

Figure 2 shows polar reference bands representing median, 25th and 75th percentiles of each parameter for FT and PT, and for Mrisk-PT and Hrisk-PT.

Figure 2. Polar bands (median, 25th and 75th percentiles) for FT and PT children and for Mrisk-PT and Hrisk-PT. Double dagger indicate significant differences between FT and PT (p<0.05), asterisks significant effect of risk of motor delay when considering FT, Mrisk-PT and Hrisk-PT (p<0.05).



Discussion

In the present work, a sensor-based approach was used to characterize and compare gait performance of toddlers born PT with FT controls, allowing to quantify differences in temporal parameters, their variability, and non-linear metrics for the quantification of motor control. PT children showed significantly longer StanceT, higher variability of temporal parameters (SD1 of StrideT, StepT, StanceT and DS, SD2 of StepT, StanceT and DS), and lower motor complexity than FT (lower MSE values in the frontal plane). When dividing PT children according to risk of motor delay (Hrisk-PT and Mrisk-PT), the estimated parameters confirmed the expected trends, showing a significant effect of risk of motor delay and Mrisk-PT values in between those of FT and Hrisk-PT (see Tables 3 and 4).

Although literature providing quantitative characterization of gait characteristics in PT children is scarce [7], some of the results of the comprehensive analysis performed in the present work confirm previous findings. The proposed sensor-based approach showed a tendency towards longer (not significant) StepT in HriskPT (median, 0.44s) with respect to Mrisk-PT and FT (median, 0.38s and 0.41s) and significantly longer nStepT (median nStepT 1.50 for Hrisk-PT, 1.32 for Mrisk-PT, 1.32 for FT). In addition, stride duration (i.e. StrideT and nStrideT) resulted significantly longer in Hrisk-PT than in Mrisk-PT and FT, while they did not significantly differ between PT and FT. This result confirms the longer step duration already observed in PT children with moderate motor delay when compared to FT children [7,8]. No significant differences were found between Mrisk-PT and FT for these parameters.

Moreover, significantly longer StanceT and a tendency towards longer DS (not significant) were found for PT children when compared to FT. PT children at 18 months were previously shown to have a stance duration inversely correlated to walking experience [10] and those with lower gross motor function to have longer StanceT and DS phases [8]. The combination of the mentioned [8,10] and present findings suggests that PT children manifest a delayed gait maturation, characterized by longer support phases, which can be interpreted as driven by the need of a stabilizing strategy [35]. Both short- and long-term intra-subject variability of temporal parameters showed a decrease from HriskPT to Mrisk-PT to FT children. Increased gait variability was already reported in the literature for PT schoolchildren when analysing stride velocity- and stride length variability [9]. Considering gait development, the increased gait variability in PT can be interpreted as the manifestation of a less mature gait performance, as a decrease in StrideT variability with age maturation (from toddlers to schoolchildren) is expected [18,40].

Among non-linear metrics, RQA showed DETml significantly higher in Hrisk-PT than Mrisk-PT and FT, and MSE highlighted significantly lower values of SEN in PT children on the V and the ML direction. These results suggest that PT children manifest a more regular and less complex pattern of gait on the frontal plane, corresponding to a more simple early form of gait [12] and a possible delay in the manifestation of flexibility and ability to make complex movements [41].

With respect to previous works from the same authors [17,18], highlighting the significance of MSE for τ values higher than 4 when characterizing gait at different ages from school children to adults, in the population analysed in the present work, the lowest time scales resulted the ones highlighting significant differences between groups (e.g. τ=1 for V and τ=1,2 for ML). Considering that coarse graining procedures (i.e. averaging on a moving window, as performed for the calculation of MSE) on gait acceleration signal for increasing values of τ values can be related to low pass filtering at decreasing cut-off frequencies (e.g. τ =4 corresponding to 16 Hz, τ =5 corresponding to 13 Hz etc), this result suggests that, when considering toddlers, differences between PT and FT are related to faster signal components. This could suggest that proprioceptive-based control loops (short-loops) associated to postural control play a more relevant role for the characterization of the early development of gait, while visuo-vestibular based control loops (long-loops), characterized by longer time scale, influence and characterize the development of gait later in life (e.g. starting from middle and/or late childhood) [42]. Clearly, specific future studies are necessary to investigate this hypothesis and improve the understanding of underlying physiology of motor control development. It has to be highlighted that MSE on the ML axis (τ = from 1 to 4) was the only metric allowing to differentiate both PT from FT and Hrisk-PT from the other two groups, supporting the potential of this metric in the assessment of motor control development. As previously suggested for postural control in infants [24], also in gait, decreased early complexity not only may contribute to motor delays but may also limit exploration of the environment impacting cognitive development.

To authors' knowledge, this is the first study investigating gait performance differences in PT children using wearable sensors, highlighting the possibility of identifying early motor biomarkers with non-intrusive technology [13]. This solution will facilitate longitudinal monitoring, which, as suggested in literature [7], is fundamental to understand the relationship between early biomarkers of gait and long-term developmental problems and/or to understand if affected children catch up later or continue to have issues.

The advantages of the polar representation of the results is again confirmed in this application as in previous studies [17,19]: when aiming at characterizing a specific population, it allows to relate the proposed metrics at first glance to an 'age equivalent' in order to understand if possible delays in motor development are present and in which area (variability, motor complexity etc.). Clearly, given the very young age of the participants of the present study, only natural walking was considered. In the future, using the same approach, it will be possible to analyse locomotor performance of PT schoolchildren, by assessing gait and tandem gait, as proposed in the literature [19].

Possible limitations of the present study regard the number and the characteristics of the participants: i) the number of participants per group, especially when considering Hrisk-PT and

Mrisk-PT separately, is relatively small and ii) even if groups had no significant differences in term of age and walking experience, when compared to PT children, FT characteristics were more dispersed (PT, 24 ± 2 months of adjusted age, FT, 26 ± 5 months). Nonetheless, the number of participants is similar to that of previous studies investigating gait in PT [7], and the larger dispersion of the FT group characteristics is more likely to have hindered rather than promoted the identification of significant differences with respect to the PT group; despite a higher variability of FT characteristics, the inter-subject variability of FT children gait results was comparable to that of PT children (see band widths in Figure 2), highlighting that locomotor development has a similar trajectory in children with typical development, while it is more heterogeneous in PT children.

However, the limited number of participants included in the present study has to be taken into consideration when drawing the conclusions of the study: the present results demonstrated the feasibility of the proposed quantitative sensor-based approach [17] for monitoring gait performance in PT children, confirming, in a relatively small group of children, the hypothesis that PT children at risk of motor delay show a less mature gait performance, corresponding to a delayed maturation of the control of the trunk (i.e. lower complexity) and a higher variability of gait temporal parameters. The proposed approach will support the implementation of further longitudinal studies on more numerous groups, in order to attain a more robust and deeper understanding of motor development pathways in PT children, assessing the predictive capacity and usability of the identified quantitative parameters as biomarkers of locomotor development and risk of motor delays.

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Gait performance in toddlers born preterm: a sensor based quantitative characterization

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Abstract (350 words)

Background and Objectives

Preterm children have an increased risk of motor difficulties. Gait analysis and wearable technologies allow the assessment of motor performance in toddlers, identifying early deviations from typical development. Using a sensor-based approach, gait performance of full-term and preterm toddlers at different risk of motor delay was analysed. The aim was to measure quantitative differences among groups.

Methods

Twenty-nine two-year old children born preterm (≤36 gestational weeks) and 17 full-term controls, matched for age and walking experience, participated in the study. Preterm children were further divided based on risk of motor delay: preterm at high risk (n=8, born at ≤28 gestational weeks or with ≤1000g of body weight), and at moderate risk (n=21).

Children were asked to walk along a corridor while wearing 3 inertial sensors on the lower back and on the ankles. Gait temporal parameters, their variability, and nonlinear metrics of trunk kinematics (i.e. recurrence quantification analysis, multiscale entropy) were extracted from the collected data and compared among groups.

Results

Children born preterm showed significantly longer stance and double support phases, higher variability of temporal parameters, and lower multiscale entropy values than peers born full-term. No difference was found for the other parameters when comparing preterm and full-term children. When comparing children grouped according to risk of delay, with increasing risk, children showed longer stride-, stance- and double-support-time, higher variability of temporal parameters, higher recurrence - and lower multiscale entropy values.

Conclusions

Sensor-based gait analysis allowed differentiating the gait performance of preterm from full-term toddlers, and of preterm toddlers at different risk of motor delay. When analysing the present results with respect to the expected trajectory of locomotor development, children born preterm, in particular those at higher risk of motor delay, exhibited a less mature motor control performance during gait: lower stability (i.e. longer support phases), and higher variability, although not structured towards the exploration of more complex movements (i.e. higher recurrence- and lower multiscale entropy values). These indexes can serve as biomarkers for monitoring locomotor development and early detecting risk to develop persistent motor impairments.

Keywords: Wearable sensors; motor biomarkers; preterm children; motor development; variability; complexity.

Introduction

The earlier a baby is born the greater the risk of long-term consequences, with over 50% of children born <30 weeks facing motor, cognitive, and behavioural impairments [1]. Thanks to advances in medical care, younger and more vulnerable children born preterm (PT) have increased opportunities of survival, with evidence of an increasing number of PT infants worldwide (an estimated 11.1% of all livebirths in 2010 were born PT [2]).

One of the most frequent issues encountered by PT children is an increased risk of motor difficulties ranging from mild impairments to cerebral palsy, with prevalence 3 to 4 times greater than in the general population [3]. While a substantial evidence base has been established for risk factors, causal pathways, and neurological mechanisms for cerebral palsy [4], the knowledge regarding the non-cerebral palsy motor impairments is still limited, although affecting a much larger number of PT children (up to 50% of children born <30 weeks) [1]. Mild motor deficits, such as Developmental Coordination Disorder, can have long-term consequences, compromising physical function, academic achievement, and other health outcomes (e.g. higher risks of obesity, cardiorespiratory problems, diabetes, and problems related to social integration) [5]. Thus, to implement effective interventions for the future wellbeing of this growing population, the understanding as well as the early and timely identification of mild motor difficulties is crucial, given the key periods of brain plasticity and musculoskeletal development.

WHO defines preterm birth as any birth before 37 completed weeks of gestation and divides this further on the basis of gestational age (extremely/very preterm < 32 weeks of gestation; moderate/late preterm 32 - <37 weeks). These subdivisions are important since decreasing gestation age is associated with increasing short and long term consequences [2]. However, this subdivision is defined to support clinical data collection and management in general and not for subject-specific identification of risk of motor delays.

Nowadays, identification of potential gross motor impairment in toddlers is primarily based on motor-milestone history and clinical examination, which have demonstrated poor specificity [6]. Motor milestone assessments are made challenging by variability in parental report and the wide age range of normal in milestone attainment [6]. Clinical examinations, even when based on structured assessments of gross motor function (e.g. The Peabody Developmental Motor Scale-2 and Bayley Scales of Infant Development-3rd Edition), are long (90min for the full BSID-III 18–22 month olds) and expensive, require trained personnel, thus limiting assessments only to the highest-risk children. Given these limitations, there is the need of quantitative and objective tests, easy to be administered, for a widespread application.

As recently highlighted in the review by Albesher et al., [7], walking is a central part of most basic and leisure daily activities; therefore, knowledge of the timing of walking onset and any alteration of gait is essential to understand the needs of children born PT. Several research studies [6,8–10] analysed and quantified gait of PT children during the first months of independent walking using lab-based measurement methods (i.e. instrumental walkways, 3-D motion analysis and force platforms) [7]. These studies showed that gait in toddlers born PT is generally characterized as being delayed and qualitatively less coordinated [8,11]. At 18 months of age, they exhibited shorter stride length than full-term (FT) peers [10], but it is not clear if these differences persist as children reach preschool and school age [7]. Recently, spatiotemporal gait parameters have been proposed as useful in building a clinically relevant, straightforward assessment of toddler gross motor development [6], but the need of laboratory assessment hinders their applicability for routine monitoring. Despite relevant findings [8–11], the quantitative characterization of gait in children born PT is still scarce and concentrates on the first few months after the child attains walking and at school age, while studies on walking characteristics of PT children in between those ages are lacking [7]. Wearable sensors can be a viable solution to overcome laboratory limitations and effectively fill this gap: they are easy to use, light, unobtrusive, and can be worn under the clothes, for long periods, facilitating the experiments with toddlers [12]. Human movement analysis methods exploiting measurements based on wearable inertial sensors allow the quantitative assessment of human movement in outpatient conditions at different ages, effectively integrating the information derived from qualitative observation with quantitative biomarkers [13] to attain a quantitative monitoring of motor development in PT children.

Sensor-based approaches allowed the estimation of temporal gait parameters in different children populations with typical and atypical development [13] as well as toddlers at the onset of walking [12]. On the other hand, the analysis and monitoring of motor control development requires to address the maturation of different underlying control mechanisms, such as automaticity and complexity, that can be investigated by means of advanced metrics [13,14].

To this purpose, nonlinear metrics, derived from dynamical system theory, provide tools for investigating the dynamics of motor control resulting from interactions between nervous system, musculoskeletal system, and the surrounding environment while performing of a specific task [15].

Among these nonlinear metrics, previous works from the same authors showed that multiscale entropy (MSE) [16] and recurrence quantification analysis (RQA) of trunk 3D acceleration during gait, allowed to quantitatively assess motor development during the life-span [17,18], highlighting differences related to age maturation [17], and providing information complementary to standard clinical tests in toddlers and school-children [19,20]. In particular, RQA and MSE have been associated to the quantification of motor regularity and complexity during locomotion and their changes with age to changes in the maturation of motor control [19,20]. Increase or decrease of these metrics with (age) maturation depends on the analysed motor task and, specifically, on the stage of motor learning process of the population under study with respect to the specific task [20,21]. When considering toddlers at the onset of independent walking, MSE was found to increase with maturation and/or walking experience, as during the first stage of the fundamental movement phase [22], there is a gradual increase in agility, adaptability, and ability to make complex movements, which children show manifesting more and more flexibility in performance [18,23].

When considering PT children motor development, entropy-based metrics have been applied for the analysis of infant postural control maturation [24–27], highlighting that infants born PT show a decreased postural complexity compared to infants born FT. These results, although not specifically referred to gait, support the use of nonlinear metrics for the investigation of motor development to highlight consequences of PT births and/or risk of possible delays.

The aim of the present study was to assess gait performance of toddlers born PT as compared to a control group born at FT, using a sensor-based approach that allows quantifying a cluster of metrics [17] that include gait temporal parameters, their variability, as well as nonlinear metrics quantitatively characterising the dynamics of the lower trunk, related to the control of the progression of the centre of mass [19]. Only PT children without diagnosis of cerebral palsy were included in the study. Based on previous literature [7,23,25], it was hypothesized that PT children at risk of motor delay would show a less mature gait performance, corresponding to a delayed maturation of the control of the trunk and a higher variability of gait temporal parameters.

Materials and methods

Study subjects

PT children were recruited at the Ceredilico – IRCCS Institute of Neurological Sciences of Bologna, where they were already enrolled in a neurodevelopment follow-up program. Children born at FT were recruited at a local kindergarten (Istituto San Giuseppe, Lugo, Ravenna). The local Ethical Committee approved this study (ASL_BO n° 0018081 08/02/2017), and informed consent was obtained from the participants' parents.

Twenty-nine two-year old PT (median/min-max value of months of adjusted age: 25/18-27; months of walking experience: 12/2-16; gestational weeks: 30.5/24-35) and 17 FT children (median/min-max value of age: 28/14-34; months of walking experience: 15/2-24; ≥38 gestational weeks) participated in the study.

All PT children had a diagnosis of "Disorders related to short gestation and low birth weight", ICD10-GM-2018 P07, and no other diagnosed developmental delay. Children with congenital malformations and/or blindness were excluded. PT children were further divided into two groups based on the risk of motor delay. Since gestational age and body weight at birth are both determinant of long-term neurodevelopmental outcomes [28,29], the children born extremely PT (≤28 gestational weeks [2]) or with extremely low body weight (≤1000g [30]) were considered at high risk (Hrisk-PT), and the other PT children at moderate risk (Mrisk-PT). FT children had no diagnosed developmental delay. Characteristics of PT and FT children participating in the study are shown in in Table 1a and 1b, respectively.

Table 1 a) Preterm (PT) participants' details, divided into children at high risk (Hrisk-PT) and children at moderate risk (Mrisk-PT) of motor delays: age and adjusted age (months), gender (male(M)/female(F)), twins (yes(y)/no(n)), walking experience (months), weeks of pregnancy, body mass at birth (kg), length (cm) and body mass (kg) at 24 months, Bayley Scales of Infant Development-3rd Edition (BSID-III) cognitive standardized score at 24 months.

							at birth	at 24 months		
	age (months)	corrected age	gender	twins	walking experience (months)	weeks of pregnancy	body mass (kg)	length (cm)	body mass (kg)	BSID-III cognitive standardized scores
Hrisk-PT	22.3	18.3	F	n	4.3	23+4	0.53	84	9.2	85*
	27.4	24.2	F	y	12.2	26+2	0.9	86	11	105
	27.4	24.2	M	y	11.2	26+2	1.02	86	13	90
	28.8	25.7	F	n	9.7	27+2	0.755	80	10.5	85
	30.2	27.2	F	y	15.2	27+2	1.04	92	13	80
	30.2	27.2	F	y	16.2	27+2	1.085	90	15	105
	27.6	24.8	F	n	12.8	28+2	1.02	77	9.5	90
	26.9	24.1	F	n	12.1	28+2	0.81	85	11	100
Mrisk-PT	30	27.2	F	n	14.2	28+4	1.43	91	12.4	100
	28.8	26	M	n	15	28+3	1.17	89	12.5	95
	27.6	25.3	F	y	13.3	30+1	1.47	90	11	100
	27.6	25.3	M	y	14.3	30+1	1.41	92	12	95
	26.3	24	F	n	8	30	1.2	90	12	95
	25.3	22.9	F	y	6.9	30+3	1.48	86	12.5	95
	25.3	22.9	F	y	6.9	30+3	1.411	86	11.5	90
	26.7	24.6	M	n	14.6	31	1.99	90	12.5	95
	27.1	25	F	n	12	31	1.53	84	11.4	100
	27	25.1	M	n	15.1	31+2	1.6	89	13	95
	21.3	19.2	M	y	7.2	31+3	1.795	88	13	75
	21.3	19.2	M	y	7.2	31+3	1.41	85	12.5	75
	26.2	24.4	F	n	11.4	32	1.58	85	11.3	NA**
	27.3	25.4	F	y	10.4	32	1.59	88.5	12.3	100
	27.3	25.4	F	y	11.4	32	1.49	88.5	12.3	100
	26.7	24.6	F	n	2.6	31+6	1.4	92	13	105
	27.4	25.6	F	y	10.6	32+3	1.675	80.5	10.1	95
	27.5	25.6	F	y	12.6	32+3	1.375	80.5	10.1	90
	26.7	24.9	F	n	14.9	32+4	2.09	87	12.5	95
	27.3	25.5	F	n	13.5	32+6	1.69	85	12	100
	26.2	25.1	F	n	12.1	35	1.545	82	10	90

* test administered when the child was 29 months old

** test score not avaiable

Table 1. b) Full-term (FT) participants' details: age (months), gender (male(M)/female(F)), twins (yes(y)/no(n)), walking experience (months), weeks of pregnancy, body mass at birth (kg), length (cm) and body mass (kg) at 24 months.

					at birth	at 24 months	
age (months)	**gender**	**twins**	**walking experience (months)**	**weeks of pregnancy**	**body mass (kg)**	**length (cm)**	**body mass (kg)**
32.0	M	n	19.0	38+4	3.790	96	14.4
28.0	F	n	10.0	41	3.55	86	12.2
28.0	F	n	15.0	40	2.685	85.5	10.8
25.0	F	n	14.0	38	2.800	85	12.5
29.0	F	n	16.0	41	3.270	91	13.4
31.0	M	n	18.0	40	3.560	92	13.3
29.0	F	n	17.0	36	3.960	97	15.7
31.0	F	n	19.0	39	3.520	91	14.5
20.0	M	n	7.0	38+3	3.090	82	11.2
21.0	F	n	8.0	39	3.265	83	13.2
19.0	M	n	7.0	40	3.500	85	12.5
19.0	F	n	3.0	37+4	2.645	95	14.2
33.0	M	n	24.0	40+3	4.050	96.5	14.8
27.0	M	n	15.0	38	4.000	92	15.9
14.0	M	n	2.0	38	3.190	92	16.1
34.0	M	n	19.0	38+2	2.600	96	17.5
27.0	M	n	13.0	41	3.215	90	14

FT, Mrisk-PT, and Hrisk-PT showed no difference in terms of age (when considering both adjusted and not adjusted age for PT children) and walking experience (Kruskalwallis test, level of significance 5%).

Experimental setup

Three tri-axial wireless inertial sensors (OPAL, Apdm, USA) were mounted on the lower back (at L5 level) and on the shanks (above lateral malleolus) using Velcro straps (Figure 1) [12]; 3D acceleration and angular velocity were recorded at 128Hz. Tests were performed at the clinical centre Ceredilico

– IRCCS Institute of Neurological Sciences of Bologna during the day of the follow up visit for PT children, and at the kindergarten (Istituto San Giuseppe, Lugo, Ravenna) for FT children.

Sensors had coloured stickers attached on in order to help participants familiarize. After sensor positioning, children were distracted with toys and free walks. Tests started only when participants were comfortable and forgot about the sensors (given the unobtrusiveness of the sensors, this took typically less than 2 minutes).

The participants were asked to walk at self-selected speed along a 15 m long corridor while moms or nannies called them at the other end of the corridor. The trials were video recorded to later check if they either were helping themselves with something (wall, shelves etc.), were curving, stopping, running, or crying. In those cases, the identified steps were excluded from the analysis.

Data analysis

Only inline straight strides were considered for data analysis.

Foot contacts and foot offs were identified from the angular velocity around the medio-lateral axis of the leg, identifying local minima at the beginning and at the end of the swing phase [12,31,32]. For all participants, 14 consecutive strides were analysed, being the maximum number of inline strides identified for all subjects.

The following temporal parameters were calculated as described in Bisi & Stagni [17] and [31]:

- Stride-time (StrideT, in seconds) and normalized stride- (nStrideT, adimentional [33]);
- Step- (StepT, in seconds) and normalized step- (nStepT, adimentional [33]),
- stance- (StanceT, expressed in % of StrideT),
- double support- time (DS, expressed in % of StrideT).

Symmetry between right and left StrideT, StanceT and StepT was tested per each subject using the Kruskal–Wallis test with a level of significance of 5%. As no significant difference between right and left parameters was found, data from both legs were considered together for each participant.

Intra-subject variability was evaluated using Poincarè plots [34], calculating short (SD1) and long term (SD2) variability [35] of the estimated temporal parameters (i.e. StrideT, StepT, StanceT, DS).

Recurrence Quantification Analysis, and Multiscale Entropy (MSE) were calculated for the three trunk acceleration components (vertical, V, medio-lateral, ML, and antero-posterior, AP) [17].

MSE was calculated as the Sample Entropy (SEN) of trunk acceleration components (SENv, SENml, SENap) at time scales (τ) from 1 to 6: i) coarse-grained time series were calculated by averaging increasing numbers of data points in non-overlapping windows of length τ, τ=1:6; ii) length of sequences to be compared, *m*, was fixed at 2, and tolerance for accepting matches, *radius*, at 0.2 [20]. To guarantee reliability of MSE results [36], sensitivity to radius values was verified (*radius* = 0.10, 0.15, 0.20, 0.25, and 0.30) for each τ for the two groups, and relative consistency was verified for radius values below and above the selected one.

For Recurrence Quantification Analysis (RQA) [37], the state space was constructed by using the delay-embedded state space of each component of the trunk acceleration separately (embedding dimension, 5, time delay, 10 samples) [20]. After the generation of recurrence plots (threshold, 40%) [20], the following features were extracted for each acceleration component: recurrence rate (RR), determinism (DET) and averaged diagonal line length (AvgL).

Figure 1 shows sensor placement and a schematic flowchart of data analysis.

Full description of parameters extractions for both temporal and nonlinear parameters is provided in Table 2a and 2b, respectively.

Figure 1

Fig.1. On the left, inertial sensor positions (lower trunk and shanks) and axis orientations. On the right, data analysis flowchart.

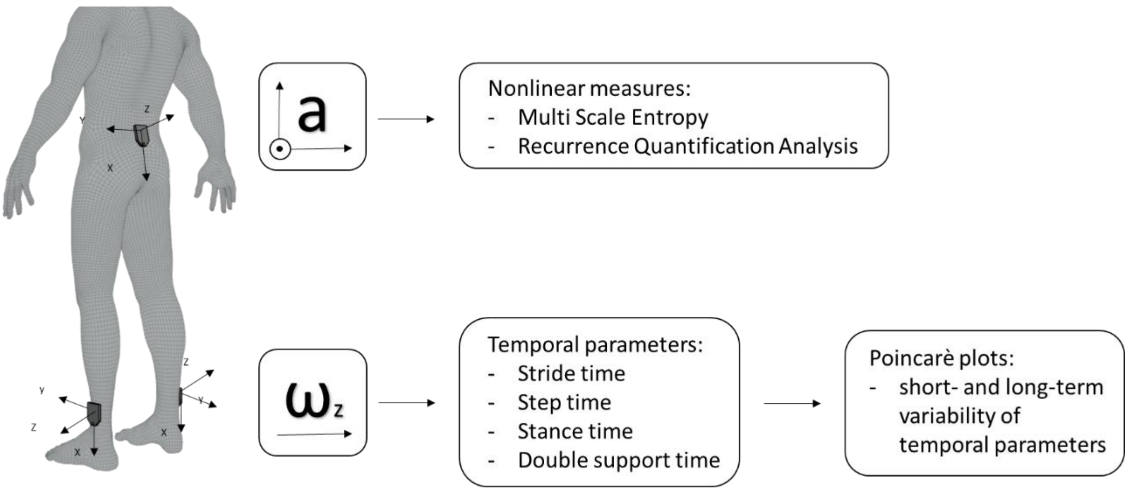


Table 2a. Temporal parameters: acronyms, descriptions and details for parameter calculation.

Table 2a. Temporal parameters: acronyms, descriptions and details for parameter calculation

Temporal parameters		
Acronym	Measure (unit)	Description
Stride T	Stride time (s)	Time difference between two consecutive initial contacts of the same foot
nstrideT	normalized stride time (adimentional)	Adimentional stride time, calculated according to Hof [33]
step T	Step time (s)	Time difference between the initial contact of one foot and the initial contact of the opposite foot
nstepT	normalized step time (adimentional)	Adimentional step time, calculated according to Hof [33]
stanceT	stance time (% of StrideT)	Time difference between initial contact and the consecutive terminal contact of the same foot, expressed in percentage of StrideT
DS	double support time (% of StrideT)	Time difference between the initial contact of one foot and the terminal contact of the opposite foot, expressed in percentage of StrideT
SD1 StrideT	short term variability of StrideT	Poincaré plots were created plotting temporal parameters data between successive gait cycles, showing variability of temporal parameters data. The plots display the correlation between temporally consecutive data in a graphical manner: SD1 and SD2 are calculated as width and length of the long and short axis, respectively, describing the elliptical nature of the plots, and represent the short-term and long-term variability of the analysed temporal parameter [34].
SD2 StrideT	long term variability of StrideT	
SD1 StepT	short term variability of StepT	
SD2 StepT	long term variability of StrideT	
SD1 StanceT	short term variability of StrideT	
SD2 StanceT	long term variability of StrideT	
SD1 DS	short term variability of StrideT	
SD2 DS	long term variability of StrideT	

Table 2b. Nonlinear parameters: acronyms, descriptions and details for parameter calculation.

Nonlinear parameters		
Acronym	**Measure**	**Description**
MSE	multiscale entropy	MSE was calculated as the Sample Entropy (SEN) of trunk acceleration components (SENv, SENml, SENap) at time scales (τ) from 1 to 6.
SEN	sample entropy	Trunk acceleration time series have been normalized to have standard deviation 1. Consecutive coarse-grained time series were calculated by averaging increasing numbers of data points in non-overlapping windows of length τ. Each element of the coarse grained time series yj(τ), was calculated starting from the original time series {x1,…,xi,…, xN}, according to $y_j^{(\tau)} = 1/\tau \sum_{i=(j-1)\tau+1}^{j\tau} x_i$, where τ represents the scale factor and 1≤j≤N/τ. For each coarse grained time series, SEN was calculated as the conditional probability that two sequences of m consecutive data points (m=2) similar to each other will remain similar (i.e. distance of data points inferior to a fixed radius (radius fixed at 0.2), when one more consecutive point is included.
RQA	Recurrence quantification Analysis	State space was reconstructed by using the delay embedded state space of each trunk acceleration component separately (V, AP and ML). Embedding dimension was fixed at 5; time delay was obtained using the first minimum of the average mutual information algorithm and set at 10 samples (corresponding to 0.078 s given the sampling frequency of 128Hz). Distance between all the points of the embedded time series was calculated. If this distance was less than or equal to a threshold the point is a recurrence. The recurrence plot was obtained by selecting a threshold of 40% of the max distance, and all cells with values below this threshold were identified as recurrent points.
RR	Recurrence Rate	RR was calculated as the number of recurrent points in the recurrence plot expressed as a percentage of the number of possibly recurrent points (percentage of points within a threshold distance of one another)
DET	Determinism	DET was calculated as the percentage of recurrent points falling on upward diagonal line segments. Number of points forming a line segment was fixed at 4.
AvgL	Averaged Diagonal Line Length	AvgL was calculated as the average upward diagonal line length, where the diagonal lines are defined following determinism definition

Statistical analysis

Jarque-Bera test was performed to test the normal distribution of the estimated parameters in the different groups (i.e. FT, PT, Hrisk-PT, Mrisk-PT): since the normal distribution was not verified on all groups, Kruskal-Wallis test (level of significance, 0.1) was used to analyse influence of (i) PT birth and (ii) risk of motor delay on the calculated parameters (i.e. temporal parameter, variability of temporal parameters, RQA, MSE).

Statistical analysis was performed to test:

(i) Influence of preterm birth: PT vs FT;

(ii) Influence of risk of motor delay: FT, Mrisk-PT and Hrisk-PT. When a significant effect was found, a multiple comparison test [38] was performed to evaluate which of the analysed groups showed significant differences from the others. Dunn–Sidak correction was considered for post hoc analysis [39].

Results

Temporal parameters

No significant difference was found for StrideT, nStrideT, StepT, and nStepT when comparing FT and PT. When comparing the 3 groups based on risk of motor delay, a significant effect was found for both StrideT and nStrideT (p=0.007 and p=0.001, respectively) and for stepT and nStepT (p=0.09 and p=0.05, respectively): StrideT, nStrideT, stepT, and nStepT all resulted shorter for groups at lower risk of motor delay; post-hoc analysis showed that Hrisk-PT had significantly longer StrideT than Mrisk-PT and longer nStrideT than Mrisk-PT and FT, and had significantly longer nStepT than Mrisk-PT and FT children.

PT children also showed significantly longer StanceT (p=0.02) and DS (p=0.06) with respect to FT. When considering the three groups based on risk of motor delay, a significant effect was found on StanceT, showing longer stance for increasing risk of motor delay (p=0.04); however, post-hoc analysis highlighted no significant differences between groups.

Intra-subject variability of all temporal parameters resulted significantly higher in PT children than in FT control peers for all estimated parameters except for SD2 of StrideT (p=0.3). When dividing PT participants based on risk of motor delay, a significant effect was found for SD1 of StrideT (p=0.03), SD1 of StepT (p=0.03), SD1 and SD2 of StanceT (p=0.04 and p=0.07, respectively), and SD1 of DS (p=0.07), highlighting an increasing trend of variability with increasing risk of motor delay; post-hoc analysis showed that FT children had significantly lower values of SD1 of StrideT, of StepT and of StanceT than Mrisk-PT.

Median values and 25th and 75th percentiles of temporal parameters for each group are reported in Table 3.

	FT			PT				Mrisk-PT			Hrisk-PT			
	25th	50th	75th	25th	50th	75th		25th	50th	75th	25th	50th	75th	
Stride T	0.74	0.82	0.87	0.75	0.80	0.89		0.72	0.78	0.84	0.84	0.88	0.92	** (Hrisk-PT > Mrisk-PT)
nstrideT	2.48	2.61	2.86	2.54	2.71	2.98		2.39	2.65	2.77	2.83	3.00	3.05	** (Hrisk-PT > FT; Hrisk-PT > Mrisk-PT)
step T	0.37	0.41	0.44	0.37	0.40	0.44		0.37	0.38	0.43	0.42	0.44	0.45	*
nstepT	1.24	1.32	1.42	1.27	1.35	1.50		1.22	1.32	1.42	1.42	1.50	1.51	** (Hrisk-PT > FT; Hrisk-PT > Mrisk-PT)
stanceT	56.4	58.2	59.9	57.4	60.2	62.0	** (PT > FT)	56.6	60.2	62.0	58.2	60.2	62.6	**
DS	13.1	17.2	19.8	17.2	20.0	24.0	* (PT > FT)	16.3	20.4	24.0	17.8	19.8	24.1	
SD1 StrideT	0.04	0.04	0.06	0.05	0.06	0.08	** (PT > FT)	0.05	0.07	0.08	0.05	0.06	0.07	** (FT < Mrisk-PT)
SD2 StrideT	0.05	0.08	0.11	0.07	0.09	0.12		0.06	0.08	0.11	0.07	0.10	0.13	
SD1 StepT	0.02	0.03	0.04	0.03	0.04	0.07	** (PT > FT)	0.03	0.05	0.08	0.03	0.04	0.04	** (FT < Mrisk-PT)
SD2 StepT	0.04	0.04	0.07	0.05	0.06	0.08	** (PT > FT)	0.04	0.06	0.18	0.05	0.06	0.07	
SD1 StanceT	2.53	3.05	3.94	3.16	4.16	4.82	** (PT > FT)	3.16	4.18	4.97	3.21	3.93	4.33	** (FT < Mrisk-PT)
SD2 StanceT	3.22	3.68	4.17	3.72	4.31	5.41	** (PT > FT)	3.40	4.31	5.25	3.92	4.82	5.69	*
SD1 DS	3.41	4.06	5.44	4.34	5.39	6.60	** (PT > FT)	4.34	5.39	6.81	4.12	5.71	6.46	*
SD2 DS	4.10	5.21	5.73	4.63	5.94	7.35	** (PT > FT)	4.54	5.94	7.77	5.10	5.81	7.29	

Table 3. On the left, estimated temporal parameters (25th, 50th, and 75th percentiles) for FT and PT children. Asterisks indicate significant differences between FT and PT (*p<0.1; ** p<0.05). Significant differences are described between brackets.

On the right, estimated temporal parameters (25th, 50th, and 75th percentiles) for PT children at high risk (Hrisk-PT) and children at moderate risk (Mrisk-PT) of motor delays. Asterisks indicate a significant effect of risk of motor delay when comparing FT, Mrisk-PT and Hrisk-PT (*p<0.1; ** p<0.05). Significant differences between groups resulting from the multiple comparison test are described between brackets.

Non-linear metrics

No significant difference was found for RQA parameters when comparing FT and PT. When considering the three groups based on risk of motor delay, among RQA parameters, a significant effect was found for DETml (p=0.02) showing higher values in children at higher risk of motor delay: post-hoc analysis showed DETml to be significantly higher in Hrisk-PT than Mrisk-PT.

When comparing FT vs PT, SEN values calculated in the frontal plans, i.e. V and ML direction, showed significant differences for τ=1 (p=0.01), and τ=1 and 2 (p=0.007 and 0.01), respectively. In particular PT children showed lower complexity values than FT peers. No significant difference was found for the other values of τ and in AP direction (for all the values of τ). When considering participants divided into three groups, a significant effect of risk of motor delay was found again for SEN values calculated in the frontal plane, i.e. V and ML direction, in particular for τ=1 (p=0.03) on the V axis, and τ = from 1 to 4 (p<0.02) on the ML axis. In all cases, lower SEN values were found for increasing risk of motor delay. Post hoc analysis highlighted that, in ML direction, Hrisk-PT children had significantly lower SEN values than FT.

Median values and 25th and 75th percentiles of nonlinear metrics for each group are reported in Table 4.

	FT			PT				Mrisk-PT			Hrisk-PT			
	25th	50th	75th	25th	50th	75th		25th	50th	75th	25th	50th	75th	
DETml	5.11	5.50	5.69	5.29	5.47	5.69		5.28	5.42	5.55	5.62	5.82	6.04	** (Hrisk-PT > Mrisk-PT)
SENv (τ=1)	0.47	0.54	0.58	0.38	0.46	0.54	** (PT < FT)	0.38	0.46	0.55	0.38	0.45	0.51	**
SENml (τ=1)	0.51	0.60	0.67	0.43	0.51	0.55	** (PT < FT)	0.43	0.52	0.55	0.35	0.46	0.51	** (Hrisk-PT < FT)
SENml (τ=2)	0.83	1.01	1.09	0.74	0.83	0.90	** (PT < FT)	0.78	0.87	0.93	0.60	0.75	0.80	** (Hrisk-PT < FT)

Table 4. On the left, estimated nonlinear parameters (25th, 50th, and 75th percentiles) for FT and PT children. Asterisks indicate significant differences between FT and PT (p<0.05). Significant differences are described between brackets.**

On the right, estimated nonlinear parameters (25th, 50th, and 75th percentiles) for PT children at high risk (Hrisk-PT) and children at moderate risk (Mrisk-PT) of motor delays. Asterisks indicate a significant effect of risk of motor delay when comparing FT, Mrisk-PT and Hrisk-PT (p<0.05).**

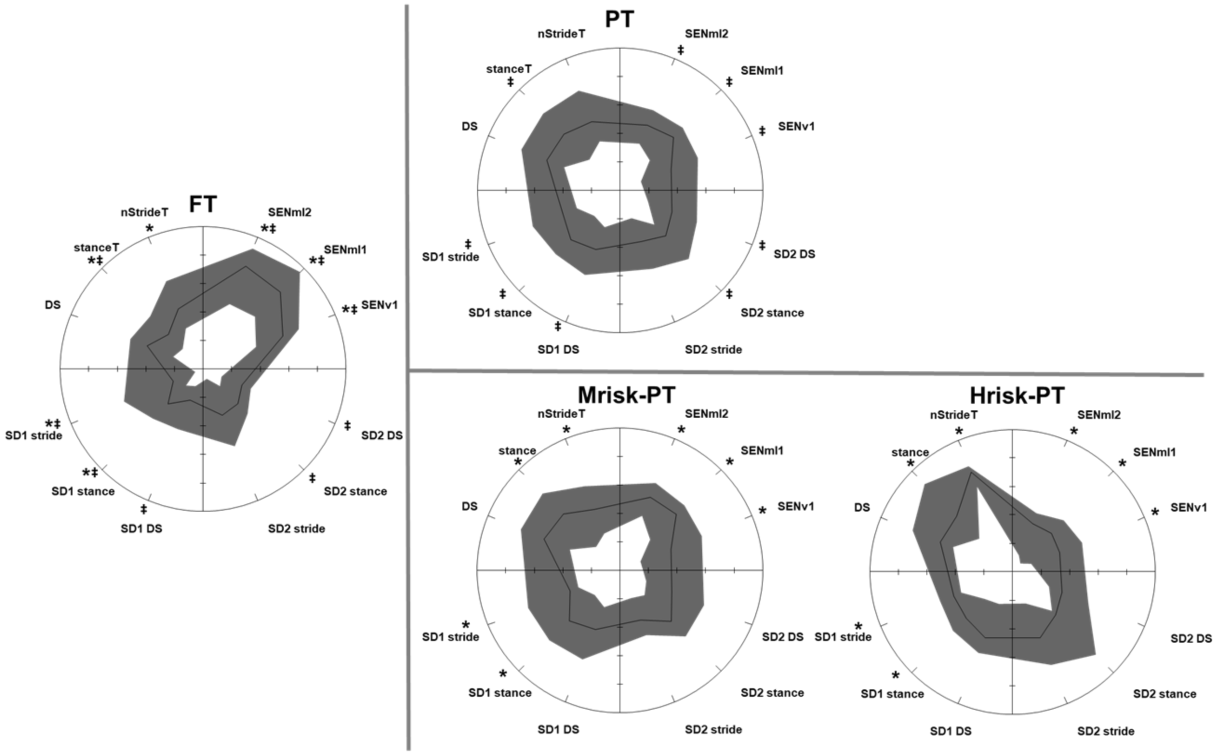
Significant differences between groups resulting from the multiple comparison test are described between brackets.

Based on statistical analysis results, the following significant parameters were selected for a polar representation [17]:

1) 'Temporal parameters': nStrideT, StanceT, DS.
2) 'Motor complexity': SENv (τ=1), SENml (τ=1), SENml (τ=2).
3) 'Short term variability': SD1 for strideT, stanceT and DS.
4) 'Long term variability': SD2 for strideT, stanceT and DS.

Figure 2 shows polar reference bands representing median, 25th and 75th percentiles of each parameter for FT and PT, and for Mrisk-PT and Hrisk-PT.

Figure 2. Polar bands (median, 25th and 75th percentiles) for FT and PT children and for Mrisk-PT and Hrisk-PT. Double dagger indicate significant differences between FT and PT (p<0.05), asterisks significant effect of risk of motor delay when considering FT, Mrisk-PT and Hrisk-PT (p<0.05).



Discussion

In the present work, a sensor-based approach was used to characterize and compare gait performance of toddlers born PT with FT controls, allowing to quantify differences in temporal parameters, their variability, and non-linear metrics for the quantification of motor control. PT children showed significantly longer StanceT, higher variability of temporal parameters (SD1 of StrideT, StepT, StanceT and DS, SD2 of StepT, StanceT and DS), and lower motor complexity than FT (lower MSE values in the frontal plane). When dividing PT children according to risk of motor delay (Hrisk-PT and Mrisk-PT), the estimated parameters confirmed the expected trends, showing a significant effect of risk of motor delay and Mrisk-PT values in between those of FT and Hrisk-PT (see Tables 3 and 4).

Although literature providing quantitative characterization of gait characteristics in PT children is scarce [7], some of the results of the comprehensive analysis performed in the present work confirm previous findings. The proposed sensor-based approach showed a tendency towards longer (not significant) StepT in HriskPT (median, 0.44s) with respect to Mrisk-PT and FT (median, 0.38s and 0.41s) and significantly longer nStepT (median nStepT 1.50 for Hrisk-PT, 1.32 for Mrisk-PT, 1.32 for FT). In addition, stride duration (i.e. StrideT and nStrideT) resulted significantly longer in Hrisk-PT than in Mrisk-PT and FT, while they did not significantly differ between PT and FT. This result confirms the longer step duration already observed in PT children with moderate motor delay when compared to FT children [7,8]. No significant differences were found between Mrisk-PT and FT for these parameters.

Moreover, significantly longer StanceT and a tendency towards longer DS (not significant) were found for PT children when compared to FT. PT children at 18 months were previously shown to have a stance duration inversely correlated to walking experience [10] and those with lower gross motor function to have longer StanceT and DS phases [8]. The combination of the mentioned [8,10] and present findings suggests that PT children manifest a delayed gait maturation, characterized by longer support phases, which can be interpreted as driven by the need of a stabilizing strategy [35]. Both short- and long-term intra-subject variability of temporal parameters showed a decrease from HriskPT to Mrisk-PT to FT children. Increased gait variability was already reported in the literature for PT schoolchildren when analysing stride velocity- and stride length variability [9]. Considering gait development, the increased gait variability in PT can be interpreted as the manifestation of a less mature gait performance, as a decrease in StrideT variability with age maturation (from toddlers to schoolchildren) is expected [18,40].

Among non-linear metrics, RQA showed DETml significantly higher in Hrisk-PT than Mrisk-PT and FT, and MSE highlighted significantly lower values of SEN in PT children on the V and the ML direction. These results suggest that PT children manifest a more regular and less complex pattern of gait on the frontal plane, corresponding to a more simple early form of gait [12] and a possible delay in the manifestation of flexibility and ability to make complex movements [41].

With respect to previous works from the same authors [17,18], highlighting the significance of MSE for τ values higher than 4 when characterizing gait at different ages from school children to adults, in the population analysed in the present work, the lowest time scales resulted the ones highlighting significant differences between groups (e.g. τ=1 for V and τ=1,2 for ML). Considering that coarse graining procedures (i.e. averaging on a moving window, as performed for the calculation of MSE) on gait acceleration signal for increasing values of τ values can be related to low pass filtering at decreasing cut-off frequencies (e.g. τ =4 corresponding to 16 Hz, τ =5 corresponding to 13 Hz etc), this result suggests that, when considering toddlers, differences between PT and FT are related to faster signal components. This could suggest that proprioceptive-based control loops (short-loops) associated to postural control play a more relevant role for the characterization of the early development of gait, while visuo-vestibular based control loops (long-loops), characterized by longer time scale, influence and characterize the development of gait later in life (e.g. starting from middle and/or late childhood) [42]. Clearly, specific future studies are necessary to investigate this hypothesis and improve the understanding of underlying physiology of motor control development. It has to be highlighted that MSE on the ML axis (τ = from 1 to 4) was the only metric allowing to differentiate both PT from FT and Hrisk-PT from the other two groups, supporting the potential of this metric in the assessment of motor control development. As previously suggested for postural control in infants [24], also in gait, decreased early complexity not only may contribute to motor delays but may also limit exploration of the environment impacting cognitive development.

To authors' knowledge, this is the first study investigating gait performance differences in PT children using wearable sensors, highlighting the possibility of identifying early motor biomarkers with non-intrusive technology [13]. This solution will facilitate longitudinal monitoring, which, as suggested in literature [7], is fundamental to understand the relationship between early biomarkers of gait and long-term developmental problems and/or to understand if affected children catch up later or continue to have issues.

The advantages of the polar representation of the results is again confirmed in this application as in previous studies [17,19]: when aiming at characterizing a specific population, it allows to relate the proposed metrics at first glance to an 'age equivalent' in order to understand if possible delays in motor development are present and in which area (variability, motor complexity etc.). Clearly, given the very young age of the participants of the present study, only natural walking was considered. In the future, using the same approach, it will be possible to analyse locomotor performance of PT schoolchildren, by assessing gait and tandem gait, as proposed in the literature [19].

Possible limitations of the present study regard the number and the characteristics of the participants: i) the number of participants per group, especially when considering Hrisk-PT and

Mrisk-PT separately, is relatively small and ii) even if groups had no significant differences in term of age and walking experience, when compared to PT children, FT characteristics were more dispersed (PT, 24 ± 2 months of adjusted age, FT, 26 ± 5 months). Nonetheless, the number of participants is similar to that of previous studies investigating gait in PT [7], and the larger dispersion of the FT group characteristics is more likely to have hindered rather than promoted the identification of significant differences with respect to the PT group; despite a higher variability of FT characteristics, the inter-subject variability of FT children gait results was comparable to that of PT children (see band widths in Figure 2), highlighting that locomotor development has a similar trajectory in children with typical development, while it is more heterogeneous in PT children.

However, the limited number of participants included in the present study has to be taken into consideration when drawing the conclusions of the study: the present results demonstrated the feasibility of the proposed quantitative sensor-based approach [17] for monitoring gait performance in PT children, confirming, in a relatively small group of children, the hypothesis that PT children at risk of motor delay show a less mature gait performance, corresponding to a delayed maturation of the control of the trunk (i.e. lower complexity) and a higher variability of gait temporal parameters. The proposed approach will support the implementation of further longitudinal studies on more numerous groups, in order to attain a more robust and deeper understanding of motor development pathways in PT children, assessing the predictive capacity and usability of the identified quantitative parameters as biomarkers of locomotor development and risk of motor delays.

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Title Page

Gait performance in toddlers born preterm: a sensor based quantitative characterization

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