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FUNCTIONAL EVALUATION AND EXERCISE TRAINING FOR PEOPLE LIVING WITH CEREBELLAR ATAXIA

THE ATAEXER TRIAL

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Abstract

IMPORTANCE Cerebellar ataxia reflects a poor coordination during movements, with a progressive deterioration of gait and balance control which are reported to be the most disabling conditions affecting independence in daily activities with a considerable negative impact on quality of life. No satisfying pharmacological treatment exists, and rehabilitation programmes are necessary.

OBJECTIVE To provide a hybrid training intervention model, consisting in a supervised outpatient training intervention, integrated with a home-based multicomponent exercise programme for people living with cerebellar ataxia. This study is the first to evaluate such a training model focused also on coordination and rhythm auditory stimulation in this population on clinical, functional and patient-related outcomes.

DESIGN AND PARTICIPANTS Self-controlled clinical trial, in which patients with at least mild cerebellar ataxia able to walk independently were eligible, and some apparently healthy and age-matched subjects were also enrolled at baseline as controls.

INTERVENTION Patients were assigned to an eight-week phase of usual care as control period ($t_0 - t_1$) and a following eight-week intervention phase ($t_1 - t_2$) with an exercise training programme consisting in four training sessions per week provided either in a supervised or non-supervised setting.

MAIN OUTCOMES AND MEASURES The primary outcome was the change in the walking efficiency as cost of transport at the preferred walking speed, secondary outcomes were the ataxia severity measured by clinical scales and patient-reported, as well as muscular endurance and strength, balance control and walking ability.

RESULTS 7 individuals with mild cerebellar ataxia and 9 healthy subjects completed the study. Adherence to the ATAEXER Trial was 100% and session attendance was 90%. Discriminability between ataxic and healthy subjects were a characteristic of almost all measured parameters, and the whole panel of outcome category improved with the exercise programme. The cost of transport only improved significantly after the intervention phase (0.202 at t_0, 0.206 at t_1 and 0.183 mL·(kg·m)$^{-1}$ at t_2). Walking ability during a stress-walk at fast speed and corresponding spatio-temporal parameters, as well as muscular endurance appeared most strongly associated to measures of clinical and self-reported ataxia severity (R_{bo} = 0.77 to 0.86), while static balance control and muscular strength appeared less correlated.

CONCLUSIONS AND RELEVANCE These findings provide clinicians with evidence to embrace a specific exercise training programme as a standard in clinical care pathway targeting patients with cerebellar ataxia. In addition, according to the framework to guide the selection and development of digital measures of health, a set of evaluations has been recommended looking at (i) discriminability between healthy and cerebellar ataxic individuals, (ii) association with ataxia severity and (iii) responsiveness to an exercise training programme.

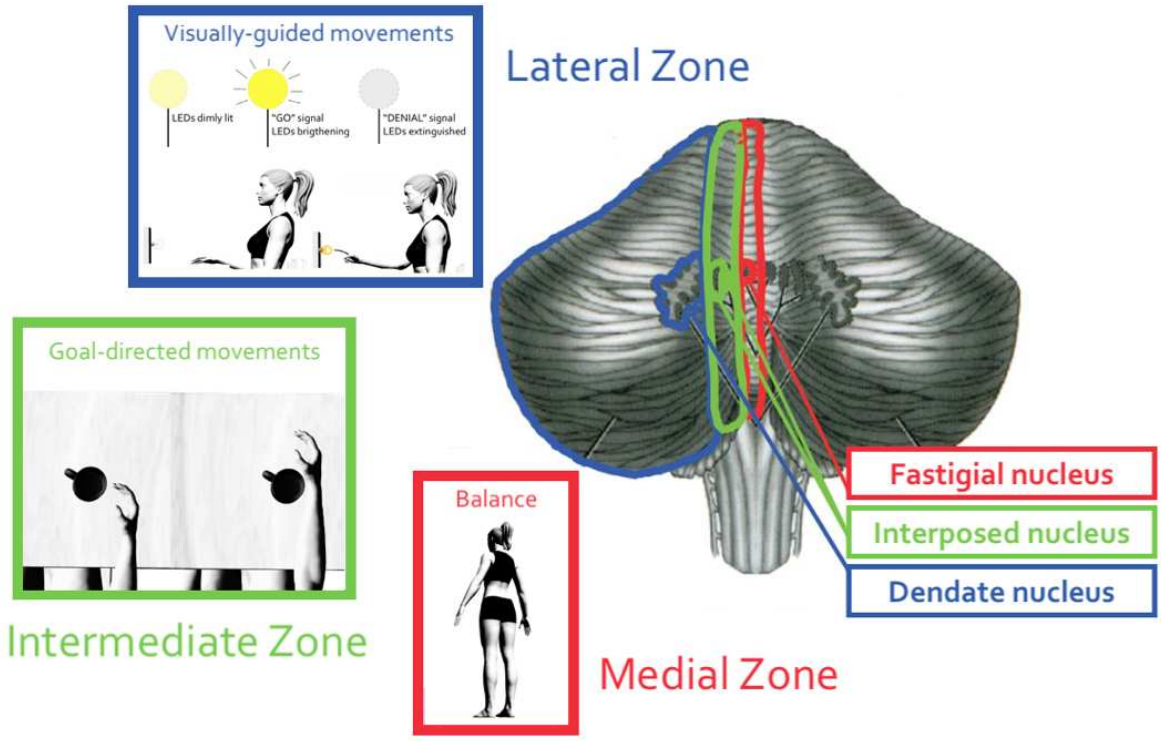
Abbreviations

2MWT	2-min walk test
ABC	Activities-specific Balance Confidence scale
ADLs	Activities of daily living
AP	Anterior-posterior
CA	Cerebellar ataxia
CoT	Cost of transport
CV	Coefficient of variation
DS	Dynamic stability
EC	Eyes closed
EO	Eyes open
EQ-5D	EuroQoL-5 dimension
F	Fastest overground walking speed
F'	120% preferred overground walking speed
FES-I	Falls Efficacy Scale – International
FXTAS	Fragile X-associated tremor and ataxia syndrome
HR	Heart rate
HC	Healthy controls
IDCA	Idiopathic cerebellar ataxia
IPAQ-SF	International Physical Activity Questionnaire short form
LOS	Limits of stability
MCS	Mental component summary
ML	Medio-lateral
Mini-BESTest	Mini Balance Evaluation Systems Test
MVC	Maximum voluntary contraction
P	Preferred overground walking speed
P_t	P_t (preferred overground walking speed measured at the respective timepoint)
p&g	Posture and gait
PCS	Physical component summary
PGI	Patient Global Impression
PROM-Ataxia	Patients Reported Outcome Measure of Ataxia
RAS	Rhythmic auditory stimulation
S	Slow overground walking speed
S'	80% preferred overground walking speed
SampEn	Sample Entropy
SARA	Scale for Assessment and Rating of Ataxia
SCA	Spinocerebellar ataxia
SF-36	Short form Health survey
SSE	Square step exercise
t	Corresponding timepoint
τ	Tau
TUG	Timed up and go
$\dot{V}O_2$	Oxygen uptake

Introduction

Ataxia reflects a poor coordination during movements. Dysfunctional cerebellar circuits may also lead to cerebellar ataxia (CA), a large and multifaced group of disorders, some also genetically inherited, reasonably explained by disturbances in movement accuracy and coordination, which can lead to oculomotor dysfunction, dysarthria, gait and limb ataxia as well as impaired balance control as main clinical features [1–3]. Indeed, the cerebellum can be divided into distinct functional zones according to its afferent and efferent connections (Figure 1).

Figure 1 | Localisation of cerebellar functions in gait control



Functional zones of the cerebellum and their key roles. Adapted from Ilg et al., 2013 [4]

Briefly, the medial region plays a key role in locomotion, upright stance and dynamic balance control. The intermediate zone seems particularly crucial when performing precise limb movements, including limb placement and regulation of agonist and antagonist muscles to control timing and movement amplitude. The lateral zone regulates adjustment of locomotion patterns to novel contexts or when strong guidance is required [4]. Of these functions, the progressive deterioration of gait and balance control ("drunken gait") are reported to be the most disabling conditions of functional (im)mobility, also affecting independence in daily activities throughout the disease progression with a considerable negative impact on quality of life [1–3].

Currently, global epidemiological studies estimate an overall ataxia occurrence rate of 2.7/100,000 and 3.3/100,000 for dominant (e.g. spinocerebellar ataxia [SCA]) and recessive (e.g. Friedreich ataxia) hereditary CA, respectively [2]. X-linked ataxias are even more rare, with fragile X-associated

tremor and ataxia syndrome (FXTAS) dominating the prevalence in this field. Many hereditary CA are caused by trinucleotide repeat expansions, and its length affects the age of symptom onset, clinical severity, and rate of disease progression [2,5]. Notwithstanding current development in understanding aetiology and underlying causes of ataxias, a sizeable proportion of patients remains with unknown pathophysiological cause (idiopathic cerebellar ataxia [IDCA]) [2].

When it comes to the characteristics of CA, compared to healthy controls, the ataxic gait is typically characterised by altered gait spatial-temporal metrics with the most striking and distinctive features that appear to be a high variability of step length, stride length and stride time [6]. In addition, kinematic data such as range of motion, knee flexion at load response, and electromyography co-activations of tibialis anterior and gastrocnemius during the double and single support phases resulted altered compared to healthy controls [7]. To compensate the difficulty in integrating somatosensory, vestibular and visual inputs of the cerebellum for control of balance, people with CA become more dependent upon vision; therefore, postural balance tasks with closed eyes are particularly difficult for individuals with CA [1]. Recently, in addition to classical parameters of balance control as sway path and sway area, Nguyen et al., 2018 evaluated the regularity and complexity of the signal during static stance showing promising correlations with clinical rating scales [8]. Overall, patients with ataxia show inaccurate limb adjustments, lack of neuromuscular precision and control of timing for rapid movements; also, coordination and predictive postural adjustments can be impaired [3,9]. By contrast, muscle strength and tones seem less affected [3]. Overall, these alterations as well as increased postural sway [10–14], lead to a stumbling walking path and a high risk of falling [4].

The assessment of ataxia severity relies on clinical measures such as the Scale for Assessment and Rating of Ataxia (SARA) or the International Cooperative Ataxia Rating Scale (ICARS)[15]. However, the SARA score should be correlated with patient-reported outcomes to evaluate whether meaningful benefits during activities of daily living and in quality of life have been reached (e.g. Patients Reported Outcome Measure of Ataxia [PROM-Ataxia]) [16]. Actually, PROM-Ataxia is the first cerebellar ataxia-specific patient-reported rating scale developed based on patients' experiences. It has been shown valid and reliable and recent consensus recommend its use in patient care and clinical trials, also as marker of disease severity [17]. Also, the EuroQoL-5 dimension (EQ-5D) has been used to measure the impact of ataxia on QoL [1]. Furthermore, since balance and gait impairments are cornerstone clinical conditions reported by patients to be the most disabling features as the disease progresses, these outcomes represent ecological, low-cost and valid markers of diseases progression and treatment response [1]. In fact, variability measures of gait and postural sway in stance have been shown to strongly correlate with ataxia severity in

multiple cross-sectional studies and should be reported alongside clinical measures as objective markers of disease progression [1].

Although research regarding treatment has considerably advanced in the last two decades, no satisfying pharmacological treatment exists, and treatment perspectives involving rehabilitation therapies and prescribed exercise training programmes are used to manage symptoms and prevent secondary complications such as falls [2,5]. Overall, improvements have been shown for ataxia severity, balance (Berg Balance Scale), gait speed, with contradictory results on functional independence measures (i.e. FIM instrument to assess the activities of daily living [ADLs]) [18–20]. Over 20 studies examining rehabilitation or physical exercise for people living with ataxia have been identified by systematic reviews, showing positive outcomes, but of these only seven randomised controlled trials have been conducted (Friedreich ataxia [21,22], SCA [23,24], SCA6 [25], SCA2 preclinical carriers [26,27], SCA2 [27]). Recently, systematic reviews identified coordination, balance, gait and treadmill training, multifaced inpatient rehabilitation, occupational therapy and inspiratory muscle training as the main types of training proposed in an inpatient, supervised outpatient, home based setting or as hybrid model. The duration of sessions varied from 15 to 60 minutes, conducted from once a week to twice daily for about 6 weeks on average [19,20]. Intensity-related parameters were scarcely reported, except for balance exercise challenge in the study by Keller et al., 2014 [28], which directly affected the improvement in walking speed. Indeed, current recommendations suggest including multifaced interventions targeting more than one area of impairment, although the optimal intensity, duration, and type of intervention are yet to be determined. However, due to rising health-care costs, rarity of patients with hereditary CA, and distance as critical factors, clinicians could prescribe life-long home-based programmes, which would be highly convenient for patients and caregivers, also from a cost-saving perspective [29,30].

Nonetheless, the conclusions that can be drawn by current evidence are limited by underpowered sample sizes, an absence of between-group statistical analyses and no long-term follow-up evaluations in many of these studies [5]. Furthermore, to perform such clinical trials, there is a critical need for objective disease severity markers therapeutic outcomes [1].

Therefore, this study aims to provide a self-controlled clinical trial examining a hybrid training intervention model, consisting of a supervised outpatient training intervention, integrated with a home-based multicomponent exercise programme for people living with CA. This study is the first to evaluate such a training model in this population on clinical, functional and patient-related outcomes. Moreover, according to the "Framework to guide the selection and development of digital measures of health" [31], the present study will attempt to provide those measures meaningful for clinical practice integrating i) the areas of patient's life most impacted by the CA, ii)

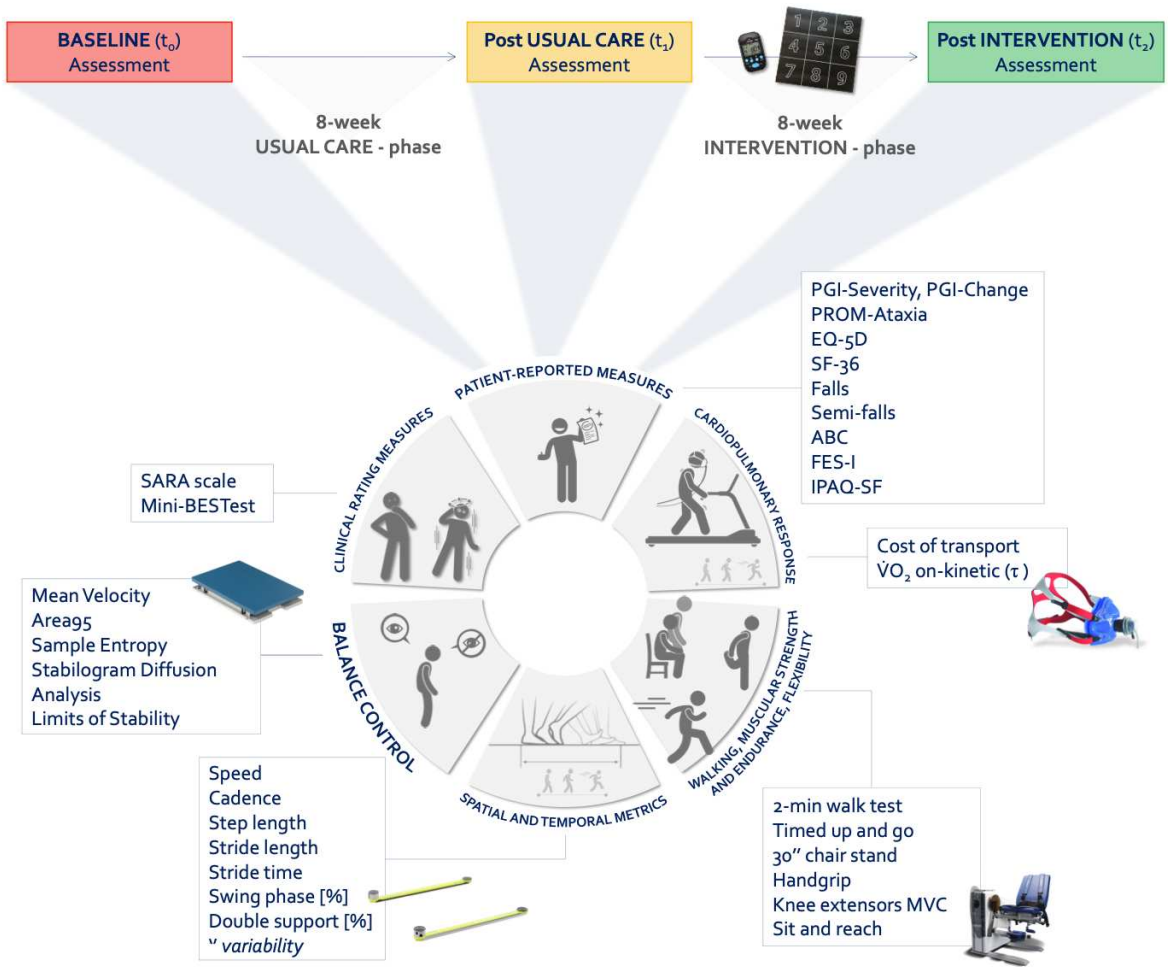
the symptoms that affect these activities, iii) the outcomes that make sense to the patient, and iv) the expected change to see a positive difference in the patient's life.

Materials and Methods

Study design

The ATAEXER trial (i.e. *atax*ia + *exer*cise) was a self-controlled clinical trial, comparing different time windows with and without intervention, within the same group of participants. The study design is shown in Figure 2. The study took place in the Sports and Exercise Medicine Division of the Department of Medicine, University of Padova, and was conducted in accordance with the Declaration of Helsinki. The trial protocol and any subsequent amendments were approved by the local Ethical Committee for Clinical Research (protocol code APO2938). All participants provided their informed consent.

Figure 2 | Study design



Visual representation of the ATAEXER study design, a self-controlled clinical trial consisting in an 8-week phase of usual care as control period ($t_0 - t_1$) and a following 8-week intervention phase with an exercise training programme ($t_1 - t_2$). Assessments and data collection were performed at t_0, t_1, and t_2.
Abbreviations: ABC: Activities-specific Balance Confidence scale; ADLs: Activities of daily living; CA: cerebellar ataxia; HC: healthy controls; EQ-5D: EuroQoL-5 dimension; FES-I: Falls Efficacy Scale – International; IPAQ-SF: International Physical Activity Questionnaire short-form; MCS: mental component summary; Mini-BESTest: Mini Balance Evaluation Systems Test; PCS: physical component summary; PGI: Patient Global Impression; PROM-Ataxia: Patients Reported Outcome Measure of Ataxia; SARA: Scale for Assessment and Rating of Ataxia; SF-36: Short form Health survey.

Participants

Patients with at least a mild CA severity according to the SARA score (≥ 3) were eligible [1]. Severity of ataxia is defined as mild with SARA score from 3 to 7, moderate from 8 to 14, and severe with a SARA score > 14 [32]. Furthermore, CA can be stratified according to the severity of the posture and gait dysfunctions, as assessed by the subscore of the SARA scale ($SARA_{p\&g}$): mild CA, $SARA_{p\&g}$ 0-2; moderate CA, $SARA_{p\&g}$ 3-4; severe CA, $SARA_{p\&g}$ 5-6 [33]. Full eligibility criteria are listed in Box 1.

Box 1 | Eligibility criteria

Inclusion criteria

- Individuals with a molecular diagnosis of inherited cerebellar ataxia or idiopathic cerebellar ataxia.
- Aged over 40 years *.
- A minimum score of 3 according to the SARA score and a maximum score of 3 for question 1 'gait' of the SARA scale (3 = *Considerable staggering, difficulties in half-turn, but without support*) to identify individuals able to walk independently without assistance.
- Ability to walk on a treadmill holding a handrail for at least 10 minutes *.

Exclusion criteria

- Musculoskeletal injury limiting exercise testing/training *.
- Major orthopaedic surgery in the last 6 months *.
- Significant cognitive impairment limiting participation *.
- Other neurological, metabolic, or musculoskeletal conditions affecting balance and gait control *.
- Already completing more than 150 min/week of lower limb/goal-based physical exercise training *.

* Valid also for the enrolment of healthy subjects as baseline control group.

Procedures

The study consisted out of two phases: an 8-week phase of usual care as control period ($t_0 – t_1$) and a following 8-week intervention phase with an exercise training programme ($t_1 – t_2$), consisting in four training sessions per week provided either in a supervised (i.e. outpatient or as synchronous tele-intervention by videoconference), or non-supervised setting (i.e. asynchronous video-based instructions performed at home). The attendance setting was at the participants' choice with strong recommendation for the supervised modality. Session attendance and drop-out were monitored using daily diaries. Measurements and data collection were performed at t_0, t_1, and t_2. Moreover, apparently healthy and age-matched controls (HC) were enrolled at baseline as controls at t_0.

Intervention

The ATAEXER programme is a multicomponent exercise training programme organised in two different sessions: session *A* addressing specifically balance and gait training (indoor + outdoor), and session *B* working on coordination (square step exercise) and resistance training; both *A* and *B* included mobility and flexibility. Each session is structured in 5 levels of progression/difficulty (1-3 weeks for each level) to (i) take into account the different functional capacity of patients at baseline and (ii) keep the overall relative intensity constant with progressive adaptations throughout the intervention period (moderate-vigorous intensity monitored using the Borg Rating of Perceived

Exertion [34] between 13 "*somewhat hard*" and 15 "*hard*"). Each participant was given a metronome and a mat 90 x 90 cm. Briefly, mobility encompassed whole body movements, while flexibility focused mainly on the lower limbs and intrinsic foot muscles. In session *A*, balance training leveraged on the visual, proprioceptive, and vestibular system combining static and dynamic balance using ankle, hip and step strategies as well as reducing the base of support. Gait training was performed for those muscles involved in the gait cycle and metronome was used to control the walking speed and cadence (i.e. preferred, fast or slow) (Box 2). In session *B*, the square step exercise was included for coordination training of lower limbs combined with motor and cognitive dual task (Box 2), while the resistance training targeted trunk, hip, knee, and ankle flexor and extensor muscles as well as intrinsic foot muscles. For the detailed ATAEXER programme see Supplementary Information Table S1, S2.

Box 2 | Key elements of the ATAEXER programme: rhythmic auditory stimulation and square step exercise

Rhythmic auditory stimulation

The outdoor gait training was performed following a rhythmic auditory stimulation (RAS) provided by a metronome set at the participant's individualised cadence. The participant was instructed "to take a big step in time to the beat". RAS has been found to be effective in improving stride time variability, muscle activation pattern, symmetry, and coordination of gait, as well as walking speed and stride length more than walking alone in persons with stroke [35], Parkinson disease[36,37], and multiple sclerosis [38,39].

The sound stimulation and its periodicity affect the limbic and paralimbic regions, as well as the brain regions involved in motor function such as cortical motor areas, cerebellum, and basal ganglia leading to improvement of motor patterns in patients with movement disorders [35,37]. Tempo was changed from the preferred cadence to a slow tempo to counteract shuffling gate (i.e. short stride length with faster cadence) and to a fast tempo to counteract reduction in gait velocity, cadence, stride length with a rhythm of ± 15% of the preferred cadence; this tempo variation was gradually introduced over the 8-week intervention period. Moreover, participants were instructed to think at few prompts while walking such as relaxing shoulders and gently swing arms alternating them to lower limbs, look ahead and not down, land with the heel first and then push off on toes, etc.

Rhythmic auditory stimulation + square step exercise

The coordination training program was performed according to the square step exercise (SSE) developed to improve lower extremity functional fitness and reduce fall risk in older adults. This type of training consists of performing stepping movements in specific patterns that involve steps in multiple directions. The SSE challenges both motor and cognitive function [40], providing beneficial effects on static and dynamic balance, risk of falls, and agility. Key elements of the SSE adopted by the ATAEXER Trial are:

- Increasing RAS tempo;
- Increasing pattern complexity (from short and forward/lateral steps to wider and backward/oblique steps) and length sequences;
- Increasing dual-/multi-task complexity (both motor and cognitive dual task) [41].

Participants were provided with the same metronome for the outdoor gait training and a squared rubber mat (90 x 90 cm) divided into 9 equal squares with a 3 x 3 pattern and numbers from 1 to 9.

Outcome overview

The primary outcome was the change in cost of transport (CoT) or walking efficiency, determined as the ratio of oxygen uptake ($\dot{V}O_2$) relative to body mass at a given walking speed. This outcome was chosen because in response to a gait disability, a patient will adapt by performing compensatory gait mechanisms which affect energy expenditure [42]. The key secondary outcome was the change in the clinical rating measures of ataxia (SARA score and $SARA_{p\&g}$ score). This outcome was chosen since the assessment of ataxia severity by the neurologists relies on clinical measures such as the SARA scale. The Mini Balance Evaluation Systems Test [Mini-BESTest] was administered as an overall assessment for dynamic balance, functional mobility and gait. Globally, $SARA_{Total}$ and Mini-BESTest are semi-quantitative observer administered clinical outcome assessments (COAs). Other outcomes were patient-reported ataxia severity (Patient Global Impression of Severity [PGI-S]),

impairment evaluations of mobility and quality of life (i.e. PROM-Ataxia, EQ-5D, Short form Health survey [SF-36]), patient-reported balance assessments (i.e. numbers of reported falls and semi-falls, Activities-specific Balance Confidence scale [ABC], Falls Efficacy Scale – International [FES-I]), and patient-reported subjective change in ataxia severity (Patient Global Impression of Change [PGI-C]). Moreover, other evaluated outcomes were spatial, temporal, kinematic parameters of gait, as well as body sway, sample entropy [SampEn] and Stabilogram Diffusion Analysis [SDA] (see Sample Entropy and Stabilogram Diffusion Analysis) of the Centre of Pressure (CoP) evaluated in static balance and dynamic stability. Some field tests were also performed assessing dynamic balance (i.e. Timed up and Go), flexibility (i.e. Sit and Reach test), walking capacity (2-min walk test [2MWT]), and strength (handgrip, 30-s chair stand, isometric maximum voluntary contraction (MVC) of the knee extensor muscles). Moreover, the physical activity level was measured using the International Physical Activity Questionnaire short-form (IPAQ-SF). Patients were always assessed by the same exercise physiologist and neurologist, who were not blinded to the study design.

Cardiopulmonary assessment

$\dot{V}O_2$ was determined on a breath-by-breath basis by means of a metabolic unit (Vyntus™ CPX, Vyaire Medical, Mettawa, IL, USA; accuracy: 1.15±1.07 relative percentage errors for $\dot{V}O_2$ [43]) with the system calibrated (i.e. airflow, volume, and both the O_2 and CO_2 analysers) immediately before each evaluation.

Walking efficiency (i.e. oxygen cost per metre or CoT, Eq.1) was measured on a treadmill applying a customised protocol for this study (Supplementary Information Figure S1).

$$\text{(Eq. 1)} \qquad Cost\ of\ Transport = \frac{\dot{V}O_2}{speed}\left[\frac{mL}{kg \times min} \times \frac{s}{m}\right] = \frac{VO_2}{distance}\left[\frac{mL}{kg \times m}\right]$$

Before each evaluation, participants familiarised with the treadmill walking for around 10-min. During the test participants hold the handrail bar and wore a safety harness.

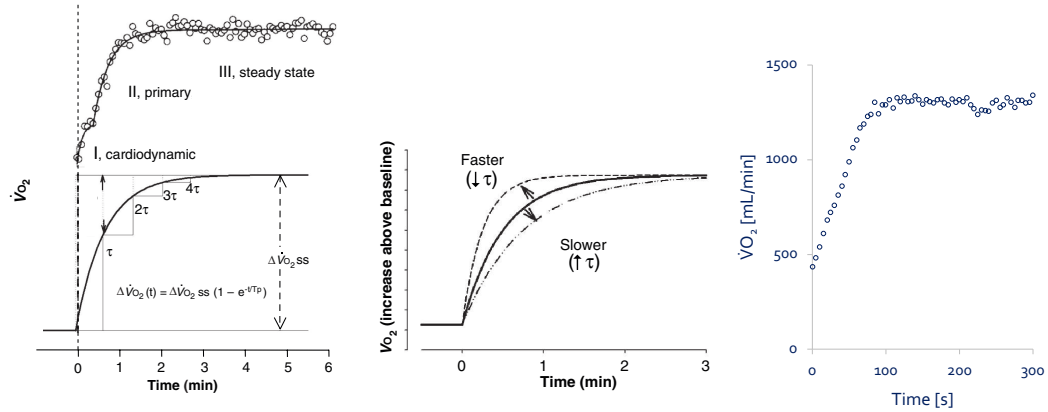
Moreover, $\dot{V}O_2$ at the preferred walking speed of each timepoint P_t (preferred walking speed at t_0, t_1 and t_2, respectively) and at 120% (fast, F') and 80% (slow, S') of the preferred walking speed were measured in the last 30 s of the respective steady state phase. Participants wore a chest-strap heart rate monitor (HRM-Dual, Garmin) during the whole cardiopulmonary assessment.

$\dot{V}O_2$ on-kinetics

The kinetic of $\dot{V}O_2$ is the rate of adjustment of the $\dot{V}O_2$ to a sudden increase in the workload during the transition from rest to a constant moderate intensity exercise (Figure 3) and permits to specifically analyse gas exchange kinetics of peripheral skeletal muscles [44,45]. The faster $\dot{V}O_2$ steady state can be achieved (i.e. the more rapid the $\dot{V}O_2$ kinetics), the better. The evaluation of $\dot{V}O_2$

kinetics can provide information about an exercise intensity domain that is close to that of most ADLs [46].

Figure 3 | $\dot{V}O_2$ on-kinetic



Adapted from Poole et al., 2012 [47]. Left panel: breath-by-breath alveolar $\dot{V}O_2$ response following the onset of moderate intensity exercise and below the schematic demonstrating fundamental properties of the single component exponential response. Central panel: the faster $\dot{V}O_2$ steady state can be achieved the better. Right panel: the related $\dot{V}O_2$ of one of the participants.
Abbreviations: τ: Tau; $\dot{V}O_2$: oxygen uptake.

Therefore, measurements of the $\dot{V}O_2$ kinetics were obtained during the transition from standing to exercise, i.e. within 5-min at the overground preferred walking speed measured at t_0 (P_0) (see Clinical gait assessment); two constant load exercise tests were averaged and used for the determination of the $\dot{V}O_2$ kinetics. The $\dot{V}O_2$ kinetics analyses focused on the fundamental component (phase II) of the response to exercise determining the time constant Tau (τ), which was shown to reflect predominantly gas exchange kinetics of the skeletal muscles. The $\dot{V}O_2$ response averaged every 5-s was firstly interpolated using a specifically developed MATLAB R2023a code (The MathWorks, Inc., MA, USA). Iterative nonlinear regression was used to characterise the primary $\dot{V}O_2$ response after removing the phase I component, known as "cardiodynamic phase" of around 20-s and the time spent to reach the target speed of around 30-s, fitting the resting 5-min in a mono-exponential function according to the equation (Eq. 2):

$$\dot{V}O_2(t) = \dot{V}O_2(baseline) + A \times \left(1 - e^{-\frac{t-TD}{\tau}}\right) \quad \text{(Eq. 2)}$$

where $\dot{V}O_2$ (t) is the $\dot{V}O_2$ at the time *t*; $\dot{V}O_2$ (baseline) is the $\dot{V}O_2$ measured in the 30 s preceding the transition; A, TD and τ are the amplitude, time delay and time constant of the primary response of $\dot{V}O_2$ kinetics, respectively. The beginning of the phase II was determined by visual inspection of gas exchange data [48].

Clinical muscular strength and endurance assessment

For the assessment of the bilateral isometric MVC of knee extensor muscles, participants were seated on a multi-joint evaluation system (Prima Plus, Easytech, Italy) with the backrest angles at

90° to the seat, belts placed across thighs, the pelvis and the shoulders, while legs were extended at a 15° angle from the vertical. Before the beginning of the tests, participants completed the whole test battery for gait and balance assessment and familiarised themselves with the apparatus performing 1 MVC; then, they performed 3 MVCs lasting 5-s with rest intervals of 2-min. The mean of the two best contractions was considered as MVC knee extension strength (Nm). Moreover, maximal handgrip strength was measured with 3 MVCs each hand alternating the dominant and non-dominant hand, considering their average for analyses. For the muscular strength assessment of the upper limbs a Baseline LiTE hydraulic hand dynamometer was used (White Plains, NY, USA).

Clinical gait assessment

Spatial and temporal metrics at the preferred (P) (i.e. comfortable pace), slow (S) (i.e. self-determined 'slow') and fast (F) (i.e. as fast as possible without running and in a safe condition) walking speed were measured walking multiple times (10, 6, and 6 walks for P, S and F speed, respectively) along a 10-m walkway where 4 interconnected 1-m strips of OptoJump Next system were placed to analyse the 4 central meters of steady-state locomotion (1,000 Hz; 96 LEDs per 1-m; Microgate, Bolzano, Italy). Walking capacity was evaluated along a 20-m hallway with the 2MWT, the instructions given were "*Cover as much distance as possible over 2 minutes. The goal is to feel at the end of the test that more ground could not have been covered in 2 minutes*". Moreover, spatiotemporal parameters were obtained also during the 2MWT, as a goal-oriented fast walk. The first walk was removed from data analysis for each condition resulting in overall ~45 steps for the P walking speed as recommended to ensure reliable measures of gait variability [1], ~40 steps for S and ~30 for F speed. Extracted spatial and temporal metrics were mean and variability (i.e. coefficient of variation [CV]) of gait speed (m/s), cadence, stride length (cm), step length (cm), stride time (s), swing phase (%), and double support (%).

During the walks described above, biomechanical kinematic data of five right and five left gait cycles for each speed condition were also collected via a markerless approach; final outcome were the angle [°] of the ankle, knee and hip joint on the sagittal plane during the whole gait cycle. Data analyses were performed according to Yang and Park [49], and Pataky et al. [50].

Clinical balance assessment

Although for pre-ataxic stages more complex stance task assessments are recommended (e.g. foam cushion or tandem position), in the present study static balance control was measured with eyes open and eyes closed over a firm surface with a standardised foot position keeping a 7-cm distance between the heels and a wide-open position of the tips of about 30° between them. Five tests for

the eyes open (EO) condition and 3 tests with eyes closed (EC) lasting 30-s each were performed with 30-s of recovery between them. Limits of stability (LOS) in the antero-posterior direction were measured with three tests performing three voluntary forward and backward alternating sways. For each condition, balance tests were performed on a 60 cm x 40 cm dynamometric platform (AMTI BP400600, Watertown, MA, USA) to measure the CoP trajectory. The signal was recorded with the software Balance Clinic 1.4.2. On the CoP trajectory the following parameters were calculated: Area95 (i.e. the area of the 95th percentile ellipse measured in cm^2), the Path Length and the Mean Velocity (the path length per time unit; i.e. the average velocity in cm/s). For the dynamic stability tests, the ΔCoP trajectory in anterior-posterior direction was extracted, LOS *AP*.

Sample Entropy and Stabilogram Diffusion Analysis

The SampEn [51] and the SDA [52] are two computational non-linear methods to assess the stochastic behaviour and complexity of the CoP, that could be related to the level of automaticity of balance tasks. Regarding neuromuscular control mechanisms, the more regular the CoP displacements (i.e. lower SampEn values), the greater the attention invested in postural balance control [53], the more effective the postural control strategy.

The SampEn was calculated in the frontal and sagittal planes (i.e. SampEn ML and SampEn AP, respectively) for static balance and dynamic stability tests. In the present study, the SampEn computation followed the procedure of Ramdani and colleagues [54], and Rizzato and colleagues [55].

The SDA [52] was calculated for static balance tests in EO condition; the diffusion coefficients were computed from the slopes of the lines fitted to the short-term and long-term regions along the *x* axis (Dfxs [mm^2/s] and Dfxl, respectively), the *y* axis (Dfys and Dfyl, respectively), and the combination of the two (Dfr^{2}s and Dfr^{2}l, respectively). The Critical Point (CP) was defined by the intersection of the lines fitted to the two regions of the plot considering the *x* axis (Δt_{xCP}, $<\Delta x^2>_{CP}$), the *y* axis (Δt_{yCP}, $<\Delta y^2>_{CP}$), and the combination of the two (Δt_{rCP}, $<\Delta r^2>_{CP}$). The SampEn and SDA analysis tool was developed with MATLAB R2022b (The MathWorks, Inc., MA, USA).

Statistical Analysis

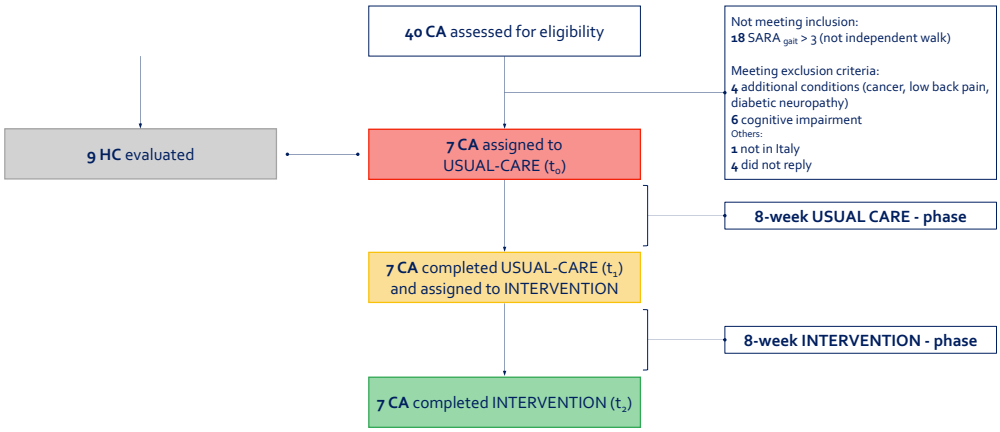
To observe a treatment effect of 0.02 on oxygen cost at the preferred overground walking speed powered to 80% (p = 0.05), the study required a total sample of 18 participants [56]. Sample size were therefore set at 23 participants considering 30% drop-out. Differences between CA and HC were determined using the nonparametric Mann-Whitney U-test for continuous variables and the χ^2 test for categorical variables. Within-group differences of CA over the 8-week usual care – phase and the following 8-week exercise phase were determined using the nonparametric Wilcoxon

signed-rank test for pair-wise comparisons. For kinematic parameters the statistical analysis was performed according to Pataky et al. [50]. Those measures found different between HC and CA at baseline were correlated with clinical assessments of severity of ataxia for concurrent validity evaluations using the Spearman rank correlation. Significance levels of both correlation indexes and differences between and within groups were set as $p\ value < .05$.

Results

Enrolment occurred between 1 January and 26 July, 2024, overall 7 individuals with CA and 9 HC were enrolled, the flow through the study can be seen in Figure 4. Demographic and anthropometric data of participants who completed the study are reported in Table 1; no statistical difference was found between patients and controls at baseline.

Figure 4 | Participant flow through the study



Abbreviations: CA: cerebellar ataxia; HC: healthy controls; SARA: Scale for Assessment and Rating of Ataxia.

Table 1 | Demographic and anthropometric data of participants

	HC	CA			CA t_0 vs. HC	CA [c]		
		Baseline (t_0)	Post usual care (t_1)	Post intervention (t_2)		t_0 vs. t_1	t_1 vs. t_2	t_0 vs. t_2
Number [female/male]	9 [5/4]	7 [4/3]	7 [4/3]	7 [4/3]	1.000 [a]	-	-	-
Age [years]	60.82 [54.83 – 63.63]	56.37 [47.32 – 64.52]	-	-	.606 [b]	-	-	-
Body mass [kg]	64.30 [55.60 – 86.00]	71.80 [69.60 – 82.70]	72.00 [66.00 – 82.70]	66.70 [67.20 – 82.70]	.210 [b]	.833	.916	.462
Body height [m]	1.66 [1.57 – 1.72]	1.70 [1.59 – 1.72]	-	-	.536 [b]	-	-	-
SCA1/IDCA/FXTAS	-	3/3/1	-	-	-	-	-	-
Disease duration [years]	-	11.52 [5.32 – 25.41]	-	-	-	-	-	-

All values are reported as median [1st quartile – 3rd quartile], p < .05.
Abbreviations: CA: cerebellar ataxia; FXTAS: fragile X-associated tremor and ataxia syndrome; HC: healthy controls; IDCA: idiopathic cerebellar ataxia; SCA1: spinocerebellar ataxia – type1.
[a] χ^2 test - Fisher exact test, [b] Mann-Whitney test, [c] Wilcoxon test.

Adherence, attendance, and feasibility

All participants completed the scheduled tests and the entire ATAEXER Trial, with 100% adherence; only one patient found difficulties in closed eyes static balance tests and was thus excluded from these analyses with a pairwise deletion method.

Attendance is reported in Table 2. It is noteworthy reporting that one patient due to strong leg pain before and during the enrolment in the study, completed only part of the scheduled sessions. Nonetheless, total attendance is provided considering for her an attendance rate equal to 50% (by contrast, considering for this patient 16 total sessions instead of 32, the total attendance raises to 93.30%). No adverse events were reported.

Table 2 | Attendance to the exercise programme and perceived intensity/challenge

CA	Session A	Session B	Overall
Attendance			
Scheduled sessions [n]	112	112	224
Completed sessions [%]	87.50	89.29	**88.39**
Attendance setting			
Supervised	-	-	54.55
Outpatient	-	-	38.89
Synchronous tele-intervention	-	-	15.66
Non-supervised	-	-	
Asynchronous video-based instructions	-	-	45.45
Perceived intensity [RPE scale [34]: 6 – 20]			
Overall, 8-week	13.55	13.69	**13.6**
Week 1 - 2	13.00	13.71	**13.3**
Week 3 - 4	13.77	13.59	**13.7**
Week 5 - 6	13.85	14.13	**14.0**
Week 7 - 8	13.54	13.33	**13.4**

Observer administered clinical outcome and patient-reported measures

Regarding clinical measures, recruited patients presented mild CA according to the $SARA_{Total}$ and $SARA_{p\&g}$ scores. Although the mild severity, CA differed from HC in the global evaluation of balance, mobility and gait as assessed by the Mini-BESTest (Table 3) and all patient-reported questionnaires of mobility in ADLs, quality of life and fear of falling; patients and HC were not different for number of falls, but CA risked falling (i.e. semi-falls) significantly more than HC (Table 4). In assessing concurrent validity of those outcomes different between HC and CA with respect to the clinical measure of ataxia severity, the $SARA_{Total}$ score showed strong and significant correlation with the Mini-BESTest, but whereas the former correlated only with the PROM-Ataxia score, the Mini-BESTest strongly correlated with Prom-ATAXIA score as well as with EQ-5D, SF-36 and FES-I (Table 9). In the usual care phase, some outcomes got worse (i.e. $SARA_{stance}$, $SARA_{heel\text{-}shin\ slide}$, $PROM\text{-}Ataxia_{Total}$), while after the training program clinical measures of ataxia and

balance impairment severity, as well as patient-reported ataxia severity and quality of life improved, well established also by improvement in Patient Global Impression of severity and change of severity. No change was reported for EQ-5D $_{Total}$, EQ-5D $_{VAS}$, falls, semi-falls ($p = 0.058$), ABC-score and FES-I, measures of quality of life, balance confidence and fear of falling, respectively.

Table 3 | Clinical rating measures

	HC	CA			CA t_0 vs. HC [b]	CA [c]		
		Baseline (t_0)	Post usual care (t_1)	Post intervention (t_2)		t_0 vs. t_1	t_1 vs. t_2	t_0 vs. t_2
Clinical rating measures								
$SARA_{Total}$	-	6.0 [3.5 – 7.5]	6.5 [4.5 – 10.0]	4.0 [2.5 – 9.0]	-	.203	.017	.141
$SARA_{p\&g}$	-	1.0 [0.7 – 2.0]	1.7 [1.0– 1.7]	0.6 [0.3 – 1.7]	-	.157	.024	.054
$SARA_{gait}$	-	2.0 [1.0 – 4.0]	3.0 [1.0 – 3.0]	2.0 [1.0 – 3.0]	-	1.000	.317	.317
$SARA_{stance}$	-	1.0 [1.0 – 2.0]	2.0 [2.0 – 2.0]	0.0 [0.0 – 2.0]	-	.046	.024	.059
$SARA_{sitting}$	-	0.0 [0.0 – 0.0]	0.0 [0.0 – 0.0]	0.0 [0.0 – 0.0]	-	1.000	.317	.317
$SARA_{speech}$	-	1.0 [0.0 – 1.0]	1.0 [0.0 – 1.0]	0.0 [0.0 – 1.0]	-	.564	.000	.564
$SARA_{finger\ chase}$	-	0.5 [0.5 – 1.0]	1.0 [0.5 – 1.0]	0.5 [0.0 – 1.0]	-	.414	.257	.317
$SARA_{nose\text{-}finger}$	-	0.0 [0.0 – 0.5]	0.0 [0.0 – 0.5]	0.0 [0.0 – 0.5]	-	.317	.317	1.000
$SARA_{hand\ movements}$	-	0.0 [0.0 – 1.0]	0.0 [0.0 – 0.5]	0.5 [0.0 – 0.5]	-	.458	.317	1.000
$SARA_{heel\text{-}shin\ slide}$	-	0.5 [0.0 – 1.0]	1.0 [0.5 – 1.0]	1.0 [0.0 – 1.0]	-	.046	.564	.180
Mini-BESTest$_{Total}$	27.0 [26.5 – 28.0]	15.0 [14.0 – 24.0]	15.0 [12.0 – 23.0]	22.0 [18.0 – 24.0]	.0002	.527	.018	.027
Mini-BESTest$_{Ant}$	6.0 [5.0 – 6.0]	3.0 [2.0 – 4.0]	3.0 [2.0 – 5.0]	4.0 [3.0 – 5.0]	.0003	.157	.059	.020
#3 one leg EO [s]	20.0 [17.0 – 20.0]	0.0 [0.0 – 5.0]	4.0 [1.0 – 6.0]	4.0 [2.0 – 13.0]	.0003	.344	.042	.088
Mini-BESTest$_{RPC}$	6.0 [6.0 – 6.0]	4.0 [3.0 – 4.0]	4.0 [1.0 – 5.0]	6.0 [5.0 – 6.0]	.002	.395	.026	.041
Mini-BESTest$_{SO}$	6.0 [6.0 – 6.0]	4.0 [3.0 – 5.0]	4.0 [3.0 – 5.0]	5.0 [5.0 – 6.0]	.0002	.000	.039	.039
#8 foam EC [s]	30.0 [30.0 – 30.0]	0.0 [0.0 – 10.0]	5.0 [0.0 – 15.0]	20.0 [6.0 – 30.0]	.0002	.131	.018	.018
Mini-BESTest$_{Gait}$	9.0 [9.0 – 10.0]	6.0 [4.0 – 10.0]	6.0 [5.0 – 9.0]	7.0 [6.0 – 9.0]	.142	.705	.336	.490

All values are reported as median [1st quartile – 3rd quartile], p < .05.
Abbreviations: CA: cerebellar ataxia; HC: healthy controls; p&g: posture and gait; Mini-BESTest: Mini Balance Evaluation Systems Test; SARA: Scale for Assessment and Rating of Ataxia.
[b] Mann-Whitney test, [c] Wilcoxon test.

Table 4 | Patient-reported mobility, quality of life and balance impairment

	HC	CA			CA t_0 vs. HC [b]	CA [c]		
		Baseline (t_0)	Post usual care (t_1)	Post intervention (t_2)		t_0 vs. t_1	t_1 vs. t_2	t_0 vs. t_2
Patient-reported impairments in mobility and quality of life								
PGI-Severity	-	4.0 [3.0 – 4.0]	4.0 [4.0 – 5.0]	4.0 [3.0 – 4.0]	-	.157	.046	.317
PGI-Change	-	-	4.0 [3.0 – 4.0]	3.0 [2.0 – 4.0]	-	-	.034	-
PROM-Ataxia$_{Total}$	6.0 [3.5 – 27.0]	67.0 [36.0 – 106.0]	71.0 [38.0 – 115.0]	52.0 [15.0 – 98.0]	.001	.028	.028	.108
PROM-Ataxia$_{Physical}$	4.0 [0.5 – 9.5]	50.0 [25.0 – 64.0]	46.0 [29.0 – 74.0]	35.0 [12.0 – 49.0]	.0002	.204	.018	.027
PROM-Ataxia$_{ADLs}$	0.0 [0.0 – 0.0]	5.0 [0.0 – 8.0]	6.0 [1.0 – 14.0]	5.0 [0.0 – 13.0]	.016	.176	.202	.465
PROM-Ataxia$_{Mental}$	5.0 [2.0 – 15.0]	17.0 [8.0 – 34.0]	21.0 [8.0 – 27.0]	18.0 [3.0 – 36.0]	.042	.167	.462	.832
EQ-5D$_{Total}$	1.0 [1.0 – 1.0]	1.4 [1.8 – 2.0]	1.4 [1.4 – 2.6]	1.2 [1.6 – 2.0]	.0007	.892	.084	.223
EQ-5D$_{VAS}$	95.0 [82.5 – 96.5]	78.0 [50.0 – 85.0]	60.0 [50.0 – 80.0]	80.0 [55.0 – 85.0]	.031	.500	.400	.465
SF-36$_{Total\ [\%]}$	90.26 [85.69 – 94.10]	68.19 [44.58 – 73.47]	53.75 [46.39 – 71.39]	71.25 [52.22 – 80.28]	.0007	.498	.018	.018
SF-36$_{PCS\ [\%]}$	95.24 [88.81 – 96.43]	70.48 [44.76 – 78.58]	47.62 [38.81 – 70.71]	71.43 [45.95 – 83.33]	.0007	.091	.018	.236
SF-36$_{Physical\ functioning}$	100.00 [97.50 – 100.00]	70.00 [65.00 – 85.00]	60.00 [45.00 – 80.00]	65.00 [50.00 – 85.00]	.0003	.840	.096	.680
SF-36$_{Role\ physical}$	100.00 [100.00 – 100.00]	100.00 [0.00 – 100.00]	500.00 [0.00 – 100.00]	100.00 [25.00 – 100.00]	.525	.854	.273	.317
SF-36$_{Bodily\ pain}$	100.00 [83.75 – 100.00]	90.00 [45.00 – 100.00]	55.00 [45.00 – 90.00]	100.00 [45.00 – 100.00]	.142	.058	.042	.194
SF-36$_{General\ health}$	80.00 [67.50 – 87.50]	40.00 [30.00 – 60.00]	35.00 [25.00 – 60.00]	50.00 [25.00 – 75.00]	.0007	.748	.172	.263
SF-36$_{MCS\ [\%]}$	89.64 [79.11 – 92.68]	57.14 [40.00 – 73.57]	65.00 [59.29 – 73.93]	72.50 [64.64 – 77.86]	.005	.027	.028	.028
SF-36$_{Role\ emotional}$	100.00 [100.00 – 100.00]	33.33 [0.00 – 100.00]	100.00 [33.33 – 100.00]	100.00 [66.00 – 100.00]	.091	.414	.102	.102
SF-36$_{Vitality}$	85.00 [60.00 – 87.50]	55.00 [25.00 – 60.00]	50.00 [50.00 – 70.00]	50.00 [45.00 – 70.00]	.008	.121	.892	.121

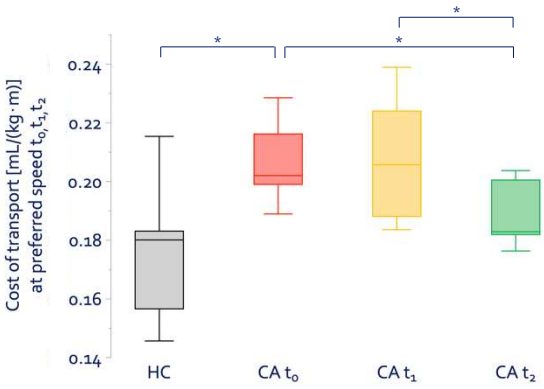
SF-36$_{Emotional\ well\text{-}being}$	84.00 [70.00 –94.00]	72.00 [56.00 –72.00]	64.00 [64.00 –76.00]	72.00 [56.00 – 84.00]	.114	.589	.131	.068
SF-36$_{Social\ functioning}$	100.00 [87.50 – 100.00]	87.50 [62.50 – 100.00]	75.00 [62.50 – 100.00]	87.50 [62.50 – 100.00]	.210	.679	.414	.594
Patient-reported balance impairments								
Falls	0.0 [0.0 – 0.0]	0.0 [0.0 – 2.0]	0.0 [0.0 – 1.0]	0.0 [0.0 – 1.0]	.252	-	.564	-
Semi-falls	0.0 [0.0 – 0.0]	5.0 [1.5 – 15.0]	4.0 [0.0 – 15.0]	1.0 [0.0 – 3.0]	.023	-	.058	-
ABC Score [%]	98.13 [95.94 – 99.38]	74.38 [56.25 – 84.38]	70.63 [56.75 – 90.00]	77.69 [70.00 – 90.00]	.003	.237	.116	.237
FES-I	17.0 [16.0 – 17.5]	28.0 [21.0 – 40.0]	25.0 [21.0 – 37.0]	22.0 [19.0 – 34.0]	.0007	.336	.092	.058
Physical activity level								
IPAQ-SF [min/week]	1620 [1472 – 3030]	720 [528 – 1660]	225 [168 – 1336]	1320 [1290 – 1840]	.114	.237	.063	.128

All values are reported as median [1st quartile – 3rd quartile], p < .05.
Abbreviations: ABC: Activities-specific Balance Confidence scale; ADLs: Activities of daily living; CA: cerebellar ataxia; HC: healthy controls; EQ-5D: EuroQoL-5 dimension; FES-I: Falls Efficacy Scale – International; IPAQ-SF: International Physical Activity Questionnaire short-form; MCS: mental component summary; PCS: physical component summary; PGI: Patient Global Impression; PROM-Ataxia: Patients Reported Outcome Measure of Ataxia; SF-36: Short form Health survey.
[b] Mann-Whitney test, [c] Wilcoxon test.

Cardiopulmonary response

When it comes to the CoT, differences between CA and HC were registered in the oxygen cost per metre at the preferred overground walking speed as well as at slower speed (Figure 5). Moreover, ΔCoT appeared -0.0019, -0.0177, and -0.0163 in t_1-t_0, t_2-t_1, and t_2-t_0 differences, respectively. Also, a difference in the $\dot{V}O_2$ on-kinetic (i.e. τ) has been revealed, which was slower in CA than in HC, but did not improve with training (Table 5). Regarding concurrent validity of clinical measures of ataxia severity, none of the cardiopulmonary parameters showed an association with the $SARA_{Total}$, but the CoT at baseline revealed a strong correlation with the Patient Global Impression of severity (*Rho* = 0.768) (Table 9).

Figure 5 | Cost of transport (the main outcome)



* p < .05. Abbreviations: CA: cerebellar ataxia; HC: healthy controls.

Table 5 | Cardiopulmonary response during exercise testing (treadmill)

	HC	CA			CA t_0 vs. HC [b]	CA [c]		
		Baseline (t_0)	Post usual care (t_1)	Post intervention (t_2)		t_0 vs. t_1	t_1 vs. t_2	t_0 vs. t_2
Rest								
HR [bpm]	72.0 [62.5 – 83.0]	72.0 [64.0 – 72.0]	65.0 [63.0 – 82.0]	64.0 [61.0 – 73.0]	.681	.932	.270	0.497
$\dot{V}O_2$ [mL·(kg·min)$^{-1}$]	3.57 [3.31 – 4.02]	3.09 [2.90 – 4.10]	3.37 [2.88 – 3.68]	3.45 [3.24 – 3.74]	1.000	.612	.735	0.398
Preferred speed								
HR [bpm] P_0	107.5 [97.3 – 117.5]	110 [104.0 – 120.0]	99.0 [94.0 – 117.5]	95.0 [92.0 – 105.5]	.606	.018	.063	.018
$\dot{V}O_2$ [mL·(kg·min)$^{-1}$] P_0	14.41 [11.74 – 16.78]	14.07 [12.68 – 18.21]	13.65 [12.08 – 17.14]	13.36 [12.02 – 15.91]	.758	.612	.091	.018
P_0 [m/s]	1.40 [1.15 – 1.55]	1.18 [1.07 – 1.48]	1.18 [1.07 – 1.48]	1.18 [1.07 – 1.48]	.252	-	-	-
Cost of transport P_0 [mL·(kg·m)$^{-1}$]	0.180 [0.153 – 0.194]	0.202 [0.199 – 0.219]	0.191 [0.181 – 0.233]	0.192 [0.179 – 0.205]	.016	.612	.128	.018
$\dot{V}O_2$ [mL·(kg·min)$^{-1}$] P_t	14.41 [11.74 – 16.78]	14.07 [12.68 – 18.21]	14.76 [13.95 – 16.46]	14.09 [11.88 – 15.49]	.758	.237	.028	.499
P_t [m/s]	1.40 [1.15 – 1.55]	1.18 [1.07 – 1.48]	1.26 [1.03 – 1.49]	1.20 [1.01 – 1.46]	.252	.176	.735	.176
Cost of transport P_t [mL·(kg·m)$^{-1}$]	0.180 [0.153 – 0.194]	0.202 [0.199 – 0.216]	0.206 [0.189 – 0.224]	0.183 [0.182 – 0.201]	.016	1.000	.018	.018
τ	22.69 [18.42 – 26.12]	30.09 [24.46 – 33.40]	30.33 [20.80 – 35.86]	28.87 [19.86 – 32.05]	.038	.612	.128	.310
120% preferred speed								

$\dot{V}O_2$ [mL·(kg·min)$^{-1}$] F'$_t$	17.79 [12.54 – 20.09]	16.46 [15.35 – 19.90]	16.72 [13.47 – 20.21]	15.93 [12.42 – 20.88]	1.000	.612	.046	.463
Cost of transport F'$_t$ [mL·(kg·m)$^{-1}$]	0.166 [0.146 – 0.200]	0.192 [0.187 – 0.202]	0.188 [0.181 – 0.208]	0.184 [0.174 – 0.193]	.114	.176	.046	.116
80% preferred speed								
$\dot{V}O_2$ [mL·(kg·min)$^{-1}$] S'$_t$	12.62 [10.62 – 14.35]	11.98 [11.04 – 15.40]	12.82 [9.97 – 14.59]	12.14 [9.84 – 14.45]	.837	.917	.600	.600
Cost of transport S'$_t$ [mL·(kg·m)$^{-1}$]	0.186 [0.166 – 0.209]	0.223 [0.216 – 0.233]	0.209 [0.175 – 0.221]	0.205 [0.190 – 0.223]	.023	.091	.600	.046

All values are reported as median [1st quartile – 3rd quartile], p < .05. Cost of transport = $\dot{V}O_2$/walking speed = VO_2/distance.
Abbreviations: CA: cerebellar ataxia; F': 120% preferred overground walking speed; HR: heart rate; HC: healthy controls; P: preferred overground walking speed; S': 80% preferred overground walking speed; t: corresponding timepoint; $\dot{V}O_2$: oxygen uptake; τ: Tau (Tau = a time constant that indicates how quickly oxygen uptake stabilises when suddenly moving from a resting state to a constant moderate intensity exercise. It permits to analyse gas exchange kinetics of peripheral skeletal muscles).
[b] Mann-Whitney test, [c] Wilcoxon test.

Field test assessment

With regard to the analyses of functional capacity (Table 6), all components of walking capacity, as well as lower limb muscular endurance and flexibility were different between CA and HC, which improved only after the training period. The muscular strength of the lower and upper limbs did not differ between groups and did not improve in any period. The dynamic balance of CA was different from that of HC and improved both after the usual care and after the training period. Of these variables, only the 2MWT distance and the 30-s chair stand score correlated significantly with both the $SARA_{Total}$ and the Mini-BESTest scores, the latter with slightly better correlation indexes (Table 9).

Table 6 | Functional capacity

	HC	CA			CA t_0 vs. HC [b]	CA [c]		
		Baseline (t_0)	Post usual care (t_1)	Post intervention (t_2)		t_0 vs. t_1	t_1 vs. t_2	t_0 vs. t_2
Walking capacity and dynamic balance								
2MWT [m]	224 [199 – 249]	160 [137 – 190]	158 [135 – 195]	170 [146 – 206]	.002	.149	.034	.028
$2MWT_{HR}$	134 [109 – 140]	95 [85 – 94]	101 [95 – 106]	110 [104 – 111]	.003	.058	.865	.018
$2MWT_{RPE}$	13 [12 – 15]	13 [11 – 15]	13 [12 – 17]	13 [12 – 15]	.681	.596	.552	1.000
TUG [s]	7.23 [6.76 – 7.83]	10.15 [8.54 – 11.99]	9.59 [7.98 – 11.52]	9.28 [7.32 – 10.34]	.0007	.018	.043	.018
Muscular endurance and strength								
30-s chair stand [n]	17 [14 – 22]	10 [8 – 13]	10 [8 – 13]	12 [9 – 16]	.002	.705	.047	.058
Handgrip [kg]	29.17 [24.00 – 45.50]	29.33 [25.33 – 38.50]	28.33 [23.66 – 39.33]	29.67 [21.00 – 34.67]	.758	.528	.612	.499
MVC leg extension [Nm]	265.0 [210.3 – 421.0]	303.5 [229.0 – 334.5]	274.0 [228.5 – 339.5]	284.0 [211.0 – 339.5]	.837	1.000	.893	.398
Normalised MVC leg extension [Nm/kg]	4.24 [3.61 – 5.21]	2.79 [2.89 – 4.23]	3.81 [3.02 – 3.87]	3.52 [2.94 – 4.35]	.210	.866	.917	.612
Lower limbs flexibility								
Sit and Reach [cm]	9.5 [- 0.8 – 11.8]	- 7.0 [-13.5 – 5.0]	- 4.0 [- 15.5 – 4.0]	0.5 [- 7.0 – 10.5]	.031	.933	.042	.051

All values are reported as median [1st quartile – 3rd quartile], p < .05.
Abbreviations: 2MWT: 2-min walk test; CA: cerebellar ataxia; HC: healthy controls; MVC: maximum voluntary contraction; TUG: timed up and go.
[b] Mann-Whitney test, [c] Wilcoxon test.

Gait assessment

Specifically analysing spatiotemporal parameters of walking at different walking speeds (Table 7), at the preferred one only the percentage of the swing and the double support phase, and the step length variability were different between CA and HC; there was no evidence of an improvement in any of these parameters. At slow speed, step length variability was the only value that differed between CA and HC, which however improved only after the usual care phase. The training

program brought benefit to the walking cadence and stride time. In the fast-walking condition, the speed as well as the percentage of swing and double support phases resulted different between groups, but no improvements were registered within the study period. Overall, the ratio preferred-fast and slow-fast speed were different between groups and the latter increased after the training phase. Finally, analysing the spatiotemporal parameters of the 2MWT, a goal-oriented fast walk, almost all analysed parameters were different between CA and HC and improved significantly only after the training period. The percentage of the swing and related double support phase, as well as the variability of the step length at different walking conditions (Table 9) demonstrated the highest concurrent validity with the $SARA_{Total}$ score.

Considering kinematic data of the flexion-extension angle at the ankle, knee and hip joint at the preferred speed, ankle kinematic demonstrated greater plantar flexion in CA than in HC during the mid-stance, terminal stance and the pre-swing, however CA subjects showed improvements both after the usual-care and after the exercise phase. At ~67% of the gait cycle, CA presented a reduced toe-off angle than HC at both t_0 and t_1, which however became comparable after the training period. At knee joint, CA displayed a reduced knee flexion during the pre-swing and initial swing, and a reduced knee extension during the terminal swing when compared with HC, which improved only after the exercise phase. The hip joint behaved like the ankle joint, showing a difference between CA and HC during the terminal stance which improved only after the exercise phase and a reduced hip extension during the initial swing which however improved just after the usual-care phase (Figure 6).

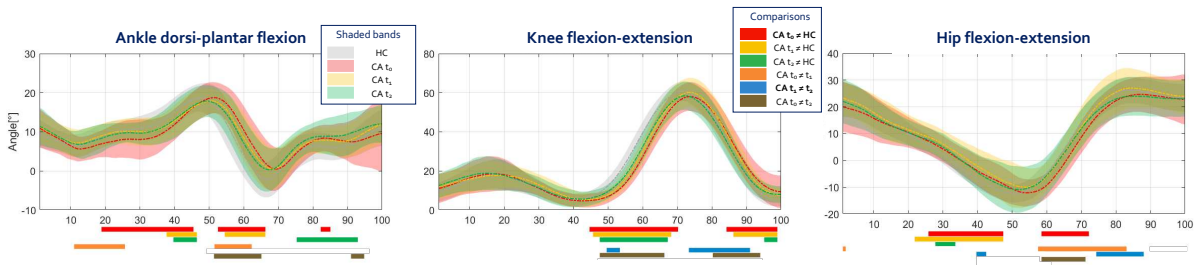
Table 7 | Spatial and temporal metrics at preferred, slow and fast walking speed (overground)

	HC	CA			CA t_0 vs. HC [b]	CA [c]		
		Baseline (t_0)	Post usual care (t_1)	Post intervention (t_2)		t_0 vs. t_1	t_1 vs. t_2	t_0 vs. t_2
Preferred walking speed								
Speed [m/s]	1.40 [1.15 – 1.55]	1.18 [1.07 – 1.48]	1.26 [1.03 – 1.49]	1.20 [1.01 – 1.46]	.252	.176	.735	.176
Cadence [step/min]	113 [109 – 121]	113 [103 – 117]	113 [106 – 116]	108 [104 – 117]	.470	.612	.310	.612
Step length [cm]	72.21 [66.69 – 76.93]	69.21 [52.82 – 75.83]	72.00 [57.00 – 79.20]	69.16 [57.98 – 81.35]	.299	.063	.398	.063
Stride length [cm]	146.20 [133.40 – 153.93]	138.18 [106.00 – 151.70]	144.45 [113.76 – 158.50]	138.31 [116.08 – 162.92]	.299	.043	.310	.063
Stride time [s]	1.06 [0.99 – 1.09]	1.06 [1.02 – 1.16]	1.06 [1.04 – 1.13]	1.11 [1.03 – 1.14]	.470	.398	.398	.735
Swing phase [%]	36.07 [34.97 – 38.12]	34.83 [31.88 – 35.88]	34.52 [33.17 – 36.14]	34.18 [33.74 – 37.68]	.042	.310	.735	.398
Double support [%]	28.25 [24.03 – 30.68]	30.74 [28.72 – 36.50]	31.58 [27.96 – 33.60]	32.08 [25.33 – 33.82]	.042	.237	1.000	.398
Speed CV [%]	3.21 [2.12 – 4.03]	3.08 [2.83 – 3.59]	3.63 [3.09 – 4.47]	3.61 [2.65 – 4.67]	1.000	.735	1.000	.310
Cadence CV [%]	1.64 [1.40 – 2.05]	2.14 [1.45 – 3.35]	2.63 [1.77 – 2.79]	2.02 [1.96 – 3.12]	.351	.866	1.000	.310
Step length CV [%]	2.58 [2.19 – 3.23]	3.58 [2.89 – 5.06]	3.68 [3.31 – 4.65]	4.53 [3.18 – 5.21]	.023	.237	.398	.866
Stride length CV [%]	1.92 [1.49– 2.64]	2.92 [1.75 – 2.93]	2.53 [2.08 – 3.09]	2.31 [1.99 – 3.45]	.536	.237	.866	.398
Stride time CV [%]	2.68 [1.76 – 3.60]	2.89 [1.93 – 3.41]	2.92 [2.35 – 3.48]	3.73 [2.13 – 4.43]	.681	.866	.398	.237
Swing phase % CV [%]	4.15 [3.61 – 4.41]	4.29 [3.07 – 4.75]	4.46 [2.84 – 5.37]	4.66 [3.68 – 5.48]	.918	.499	.612	.128
Double support % CV [%]	6.58 [4.71 – 10.03]	5.24 [4.03 – 6.19]	4.84 [4.21 – 7.50]	4.96 [4.14 – 6.33]	.091	.612	1.000	.612
Slow walking speed								
Speed [m/s]	1.03 [0.74 – 1.09]	0.91 [0.83 – 1.00]	1.02 [0.93 – 1.08]	0.91 [0.64 – 1.07]	.918	.310	.091	1.000

Cadence [step/min]	99 [83 – 101]	97 [91 – 110]	98 [93 – 110]	90 [69 – 101]	.606	.735	.028	.063
Step length [cm]	61.74 [52.91 – 66.14]	56.50 [52.57 – 64.24]	64.54 [50.70 – 66.92]	59.44 [52.75 – 66.56]	.536	.091	.735	.176
Stride length [cm]	123.59 [105.76 – 132.19]	112.00 [105.36 – 127.90]	129.26 [101.20 – 132.85]	118.45 [105.93 – 134.05]	.536	.063	.735	.176
Stride time [s]	1.22 [1.19 – 1.44]	1.24 [1.09 – 1.32]	1.22 [1.10 – 1.29]	1.32 [1.20 – 1.73]	.681	.612	.028	.063
Swing phase [%]	33.22 [31.09 – 35.71]	32.66 [31.12 – 34.12]	32.64 [31.07 – 34.11]	32.05 [30.36 – 32.62]	.408	1.000	.237	.499
Double support [%]	34.25 [29.37 – 38.35]	34.90 [32.44 – 38.18]	34.76 [32.81 – 38.19]	36.72 [35.27 – 39.88]	.470	1.000	.310	.612
Speed CV [%]	3.38 [2.91 – 4.59]	4.38 [3.56 – 6.81]	5.29 [3.15 – 6.41]	5.43 [4.68 – 6.24]	.114	.612	.398	.866
Cadence CV [%]	2.22 [1.89 – 3.11]	2.97 [2.59 – 4.93]	2.57 [2.26 – 3.50]	3.46 [2.76 – 5.31]	.114	.310	.091	.499
Step length CV [%]	3.85 [3.02 – 4.76]	5.66 [4.42 – 7.85]	4.86 [3.34 – 7.15]	5.30 [4.72 – 6.04]	.042	.028	1.000	.499
Stride length CV [%]	2.09 [1.93– 3.13]	3.35 [2.99– 4.04]	3.38 [2.03– 3.99]	2.60 [2.52– 4.42]	.114	.612	.866	.310
Stride time CV [%]	2.87 [2.75 – 3.99]	3.18 [2.75 – 5.60]	3.52 [2.48 – 5.44]	4.83 [3.02 – 5.76]	1.000	.499	.310	.310
Swing phase CV [%]	5.03 [3.71 – 5.77]	7.14 [3.42 – 7.55]	5.69 [4.88 – 6.88]	9.34 [5.66 – 10.01]	.408	.612	.091	.237
Swing phase % CV [%]	4.73 [3.69 – 5.66]	6.80 [3.22 – 7.44]	5.41 [5.04 – 7.34]	6.05 [5.76 – 8.97]	.408	.612	.176	.398
Double support % CV [%]	6.14 [4.59 – 7.64]	6.84 [3.86 – 8.29]	4.78 [4.15 – 7.94]	5.69 [5.14 – 6.65]	.758	.735	.176	.735
Fast walking speed								
Speed [m/s]	2.12 [1.67 – 2.23]	1.53 [1.24 – 1.67]	1.41 [1.24 – 1.87]	1.61 [1.34 – 1.91]	.012	.310	.176	.028
Cadence [step/min]	142 [125 – 159]	123 [117 – 135]	126 [120 – 128]	122 [122 – 131]	.091	.398	.612	1.000
Step length [cm]	83.24 [76.68 – 92.99]	78.05 [55.07 – 81.20]	77.05 [57.74 – 88.24]	79.60 [65.36 – 86.35]	.071	.091	.237	.018
Stride length [cm]	166.25 [153.20 – 185.99]	156.20 [109.80 – 162.67]	153.87 [116.23 – 176.50]	159.60 [130.85 – 173.00]	.071	.043	.237	.018
Stride time [s]	0.84 [0.75 – 0.95]	0.97 [0.88 – 1.03]	0.95 [0.93 – 1.00]	0.98 [0.92 – 0.98]	.071	.499	.612	1.000
Swing phase [%]	40.02 [38.81 – 41.43]	36.27 [33.03 – 37.12]	37.13 [34.02 – 37.80]	36.33 [35.00 – 39.91]	.002	.735	.091	.043
Double support [%]	21.04 [17.96 – 23.12]	27.73 [26.10 – 34.03]	26.28 [24.27 – 32.32]	27.41 [20.12 – 30.37]	.001	.398	.063	.043
Preferred/slow speed	1.42 [1.31 – 1.61]	1.18 [1.09 – 1.32]	1.22 [1.14 – 1.38]	1.31 [1.20 – 1.65]	.055	.612	.063	.176
Preferred/fast speed	0.73 [0.60 – 0.74]	0.80 [0.76 – 0.86]	0.81 [0.72 – 0.92]	0.76 [0.75 – 0.86]	.008	.612	.128	.128
Slow/fast speed	0.52 [0.39 – 0.57]	0.65 [0.60 – 0.80]	0.71 [0.52 – 0.82]	0.57 [0.45 – 0.69]	.016	.612	.028	.128
Fast walking speed *during 2MWT*								
Speed [m/s]	2.12 [1.82 – 2.31]	1.49 [1.25 – 1.79]	1.48 [1.25 – 1.86]	1.62 [1.40 – 1.92]	.003	.176	.063	.028
Cadence [step/min]	143 [134 – 166]	127 [121 – 131]	127 [124 – 129]	130 [123 – 132]	.008	.735	.237	.176
Step length [cm]	81.82 [77.47 – 92.89]	78.26 [58.64 – 79.18]	77.92 [58.08 – 85.80]	80.03 [63.22 – 86.72]	.031	.128	.018	.028
Stride length [cm]	164.00 [155.92 – 186.19]	156.87 [117.56 – 162.68]	157.46 [116.63 – 172.63]	161.48 [126.79 – 173.82]	.055	.128	.018	.028
Stride time [s]	0.83 [0.72 – 0.88]	0.95 [0.92 – 0.97]	0.94 [0.93 – 0.97]	0.92 [0.91 – 0.97]	.008	.176	.176	.128
Swing phase [%]	39.50 [38.47 – 41.64]	36.29 [34.95 – 37.85]	37.11 [34.38 – 37.56]	37.55 [34.99 – 39.24]	.005	1.000	.018	.063
Double support [%]	21.42 [17.16 – 23.56]	28.08 [24.95 – 30.26]	26.43 [25.25 – 31.40]	25.35 [22.31 – 30.52]	.002	.612	.028	.063

All values are reported as median [1st quartile – 3rd quartile], p < .05.
Abbreviations: 2MWT: 2-min walk test; CA: cerebellar ataxia; CV: coefficient of variation; HC: healthy controls.
[b] Mann-Whitney test, [c] Wilcoxon test.

Figure 6 | Kinematic gait analysis



Kinematic data of the flexion-extension angle at the ankle, knee and hip joint at the preferred overground walking speed.
Abbreviations: CA: cerebellar ataxia; HC: healthy controls.

Balance assessment

Looking at balance performance and its control mechanisms (Table 8), Area95 was different between CA and HC in both EO and EC conditions. Almost all parameters of the SDA, as well as SampEn in the anterior-posterior direction with EC and during dynamic balance and LOS showed to be different comparing CA and HC. The CP of the SDA could not be well defined for many subjects, therefore comparisons between and within groups were not performed. In the concurrent validity analyses only the LOS as a measure of dynamic stability correlated with both $SARA_{Total}$, Mini-BESTest and PROM-Ataxia scores. LOS improved in the usual care phase, while Area95 and the planar long-term diffusion coefficient with EC significantly decreased in the training period (-61.7% and - 72.1%, respectively).

Table 8 | Clinical balance assessment

	HC	CA			CA t_0 vs. HC [b]	CA [c]		
		Baseline (t_0)	Post usual care (t_1)	Post intervention (t_2)		t_0 vs. t_1	t_1 vs. t_2	t_0 vs. t_2
Eyes open								
Mean velocity EO [cm/s]	6.29 [4.99 – 7.10]	6.99 [5.56 – 7.95]	6.50 [5.31 – 7.12]	6.62 [5.20 – 7.92]	.408	.735	.310	.499
Area95 EO [cm²]	1.19 [0.65 – 1.62]	6.05 [2.41 – 11.54]	5.75 [2.57 – 9.45]	3.25 [2.18 – 8.77]	.002	.866	.612	.735
SampEn *ML* EO	1.30 [1.29 – 1.31]	1.32 [1.30 – 1.35]	1.34 [1.31 – 1.35]	1.32 [1.29 – 1.34]	.091	.612	.866	.499
SampEn *AP* EO	1.36 [1.31 – 1.37]	1.30 [1.02 – 1.35]	1.34 [1.161 – 1.36]	1.31 [1.09 – 1.38]	.142	.612	.866	.398
Dfxs EO [mm²/s]	0.48 [0.35 – 0.89]	2.77 [1.56 – 14.31]	2.58 [1.78 – 7.17]	2.43 [1.34 – 9.74]	.016	.866	.612	.735
Dfxl EO [mm²/s]	0.14 [0.07 – 0.35]	2.11 [0.13 – 2.33]	1.59 [0.19 – 3.81]	0.77 [0.24 – 2.19]	.055	.735	.176	.499
Dfys EO [mm²/s]	2.35 [1.54 – 3.84]	9.81 [5.93 – 75.31]	9.66 [4.91 – 47.69]	7.18 [7.08 – 67.26]	.016	.499	1.000	.398
Dfyl EO [mm²/s]	0.68 [0.48 – 1.48]	2.23 [1.25 – 5.69]	1.26 [0.80 – 6.54]	2.05 [0.40 – 5.26]	.091	.499	.612	.499
Df_{r^2s} EO [mm²/s]	3.09 [1.92 – 4.68]	12.32 [7.62 – 89.63]	12.24 [6.63 – 54.86]	8.80 [8.34 – 76.99]	.016	.612	.866	.499
Df_{r^2l} EO [mm²/s]	0.84 [0.61 – 1.76]	4.35 [1.58 – 8.02]	2.85 [0.99 – 11.13]	3.12 [1.18 – 6.06]	.008	.499	.398	.499
Eyes closed *								
Mean velocity EC [cm/s]	6.47 [5.29 – 7.41]	7.02 [5.94 – 9.18]	6.78 [5.97 – 9.40]	6.96 [5.61 – 8.93]	.328	.600	.600	.600
Area95 EC [cm²]	1.27 [0.66 – 2.11]	13.27 [2.75 – 28.93]	10.76 [3.97– 19.18]	4.12 [2.92 – 11.64]	.003	.753	.028	.116
SampEn *ML* EC	1.31 [1.29 – 1.34]	1.34 [1.28 – 1.36]	1.34 [1.30 – 1.37]	1.34 [1.31 – 1.36]	.272	.173	.917	.600
SampEn *AP* EC	1.34 [1.32 – 1.37]	1.21 [0.84 – 1.31]	1.26 [0.89 – 1.31]	1.27 [1.03 – 1.35]	.008	.463	.173	.075
Dfxs EC [mm²/s]	0.82 [0.47 – 1,14]	7.66 [2.67 – 32.03]	5.30 [3.55 – 19.44]	3.07 [2.63 – 14.38]	.0004	.345	.075	.116
Dfxl EC [mm²/s]	0.09 [0.05 – 0.21]	3.71 [0.18 – 12.23]	2.40 [0.22 – 6.33]	0.25 [-0.01 – 0.70]	.008	.463	.075	.116
Dfys EC [mm²/s]	5.22 [2.54 – 6.52]	42.20 [15.35 – 206.70]	27.36 [18.27 – 228.79]	21.57 [13.79 – 121.10]	.0004	.753	.345	.249
Dfyl EC [mm²/s]	0.68 [0.14 – 1.71]	4.37 [1.55 – 5.60]	4.14 [1.88 – 6.86]	1.69 [0.79 – 3.74]	.026	.600	.116	.249
Df_{r^2s} EC [mm²/s]	5.90 [3.07– 7.94]	51.70 [19.18 – 232.35]	32.05 [22.12 – 248.24]	24.18 [17.06 – 135.48]	.0004	.753	.249	.116
Df_{r^2l} EC [mm²/s]	0.79 [0.20 – 1.88]	8.08 [1.66 – 17.83]	7.32 [2.11– 12.03]	2.04 [0.89 – 5.01]	.008	.917	.046	.173
Dynamic stability								
LOS *AP*	17.20 [14.15 – 18.46]	12.83 [11.45 – 16.74]	16.10 [13.22 – 18.57]	17.16 [13.57 – 18.46]	.023	.028	.237	.018
SampEn *ML* DS	1.35 [1.29 – 1.37]	1.31 [1.17 – 1.34]	1.26 [1.11 – 1.33]	1.30 [1.27 – 1.32]	.174	.116	.310	.866
SampEn *AP* DS	0.99 [0.91 – 1.07]	0.60 [0.29 – 0.85]	0.60 [0.56 – 0.93]	0.61 [0.44 – 0.64]	.003	.116	.128	.735

All values are reported as median [1st quartile – 3rd quartile], $p < .05$. *: analyses conducted in 6 out of 7 patients.
Abbreviations: AP: anterior-posterior; CA: cerebellar ataxia; DS: dynamic stability; EC: eyes closed; EO: eyes open; HC: healthy controls; LOS: limits of stability; ML: medio-lateral; SampEn: Sample Entropy.
[b] Mann-Whitney test, [c] Wilcoxon test.

Table 9 | Concurrent validity with clinical rating measures

Clinical rating measures

	$SARA_{Total}$	$SARA_{p\&g}$	Mini-$BESTest_{Total}$	Mini-$BESTest_{Ant}$	Mini-BESTest #3 one leg EO	Mini-$BESTest_{RPC}$	Mini-$BESTest_{SO}$	Mini-BESTest #8 foam EC	Mini-$BESTest_{Gait}$
$SARA_{Total}$	/	/	- 0.873	- 0.982	- 0.757	- 0.617	- 0.748	- 0.394	- 0.829
$SARA_{p\&g}$	/	/	- 0.833	- 0.880	- 0.794	- 0.727	- 0.600	- 0.241	- 0.826
PROM-$Ataxia_{Total}$	0.857	0.800	- 0.982	- 0.873	- 0.802	- 0.810	- 0.875	- 0.611	- 0.775

Patient reported impairment in mobility, QoL and mobility

	PGI-Severity	PROM-$Ataxia_{Total}$	PROM-$Ataxia_{Physical}$	PROM-$Ataxia_{ADLs}$	PROM-$Ataxia_{Mental}$	EQ-$5D_{Total}$	EQ-$5D_{VAS}$	SF-36_{Total}	SF-36_{PCS}	SF-36_{MCS}	Semi-falls	ABC Score	FES-I
$SARA_{Total}$	0.571	0.857	0.857	0.727	0.786	0.691	0.000	- 0.643	- 0.429	- 0.739	- 0.342	- 0.321	- 0.473
Mini-$BESTest_{Total}$	- 0.451	- 0.982	- 0.982	0.898	- 0.927	- 0.861	0.000	0.891	0.636	0.954	0.037	0.655	- 0.787
PROM-$Ataxia_{Total}$	0.512	/	/	/	/	0.855	- 0.073	- 0.893	- 0.607	- 0.955	0.018	- 0.679	0.782

Cardiopulmonary assessment

	Preferred		Slow
	$CoT\ P_0$	τ	$CoT\ S'_0$
$SARA_{Total}$	0.286	- 0.393	0.393
Mini-$BESTest_{Total}$	- 0.127	0.400	- 0.218
PROM-$Ataxia_{Total}$	0.107	- 0.321	0.250
PGI - Severity	0.768	- 0.079	0.374

Functional capacity

	2MWT	TUG	30-s chair stand	Sit and Reach
$SARA_{Total}$	- 0.786	0.500	- 0.775	- 0.286
Mini-$BESTest_{Total}$	0.818	- 0.455	0.881	- 0.073
PROM-$Ataxia_{Total}$	- 0.750	0.321	- 0.883	0.000

Clinical gait assessment

	Preferred			Slow	Fast			Preferred Slow Fast		Fast during 2mwt					
	Swing phase [%]	Double support [%]	Step length CV [%]	Step length CV [%]	Speed	Swing phase [%]	Double support [%]	Preferred/fast speed	Slow/fast speed	Speed	Cadence	Step length	Stride time	Swing phase [%]	Double support [%]
$SARA_{Total}$	- 0.786	0.786	0.929	0.279	- 0.571	- 0.857	0.857	- 0.036	0.179	-0.714	- 0.071	- 0.857	0.071	- 0.857	0.857
Mini-$BESTest_{Total}$	0.673	-0.673	- 0.818	- 0.145	0.618	0.764	- 0.764	- 0.127	- 0.182	0.727	- 0.073	0.873	0.073	0.764	- 0.764
PROM-$Ataxia_{Total}$	- 0.607	0.607	0.750	0.121	- 0.500	- 0.714	0.714	0.143	0.250	- 0.643	0.071	- 0.786	- 0.071	- 0.714	0.714

Clinical balance assessment

	Area95 EO	Df_{ss} EO	Df_{fs} EO	Df^2_{fs} EO	Df^2/EO	Area95 EC *	SampEn *AP* EC *	Df_{ss} EC	Df_{sd} EC	Df_{fs} EC	Df_{fd} EC	Df^2_{fd} EC	Df^2/EC	ΔCoP-*AP*	SampEn *AP* DS
$SARA_{Total}$	0.071	0.464	0.536	0.571	- 0.143	- 0.200	- 0.200	0.086	-0.486	0.314	- 0.143	0.200	-0.314	- 0.857	0.179
Mini-$BESTest_{Total}$	- 0.036	- 0.346	- 0.455	- 0.509	0.236	- 0.087	0.464	- 0.348	0.145	- 0.522	- 0.174	- 0.464	0.000	0.818	- 0.346
PROM-$Ataxia_{Total}$	0.214	0.500	0.571	0.643	- 0.107	0.200	- 0.486	0.429	-0.029	0.543	0.314	0.486	-0.143	- 0.821	0.357

All values are Spearman's rank correlation coefficients, $p < .05$. *: analyses conducted in 6 out of 7 patients.
Abbreviations: 2MWT: 2-min walk test; ABC: Activities-specific Balance Confidence scale; AP: anterior-posterior; CV: coefficient of variation; EC: eyes closed; EO: eyes open; EQ-5D: EuroQoL-5 dimension; FES-I: Falls Efficacy Scale – International; IPAQ-SF: International Physical Activity Questionnaire short-form; MCS: mental component summary; P: preferred overground walking speed; Mini-BESTest: Mini Balance Evaluation Systems Test; p&g: posture and gait; PCS: physical component summary; PGI: Patient Global Impression; PROM-Ataxia: Patients Reported Outcome Measure of Ataxia; O_2: oxygen uptake; S': 80% preferred overground walking speed; SampEn: Sample Entropy; SARA: Scale for Assessment and Rating of Ataxia; SF-36: Short form Health survey; TUG: timed up and go.

Discussion

This clinical trial focused on short-term effects of a multicomponent exercise training programme for patients with CA, evaluating a set of outcomes from different perspectives. Due to rising health-care costs and rarity of patients with hereditary CA, clinicians could prescribe home-based programmes, which are less expensive, require less travel, and are more convenient for patients who do not have access to a clinic [28–30], the ATEAXER programme aimed to follow this direction.

Key points

- A first key message is that the ATAEXER programme is feasible; indeed, patients completed ~90% of training sessions and such a high attendance rate is rare to be found in literature [28].
- As a second key message, the results revealed a significant reduction of impact of disease, particularly related to balance and gait control, as assessed by clinical rating scales, instrumental measures and patient-reported outcomes. Indeed, patients reported a reduced ataxia severity (PGI-S) and a significant improvement of signs and symptoms (PGI-C).

- A third key message of the study is related to the limited recruitment capacity because many patients were at an already too advanced stage of the disease and therefore dependent on walking aids (~50% of patients considered for eligibility did not meet inclusion criterium of being able to walk independently without assistance) and 0% of patients met exclusion criteria of "Already completing greater than 150 min/week of lower limb/goal-based physical exercise programme".

In this study neurologists, exercise physiologists and CA patients were involved, with corresponding semi-quantitative measures of $SARA_{Total}$, Mini-BESTest, and PROM-Ataxia, respectively, which demonstrated strong association between each other, therefore highly recommended in clinical practice. Interestingly, the Mini-BESTest correlated with patient-reported and filed-test measures even better than the $SARA_{Total}$. Moreover, the Mini-BEST results highly reliability [57] and able to improve significantly and clinically, +7.0 vs. 4.1 of Minimal Detectable Change [58], and ~4.0 of Minimal Clinically Important Difference [59,60]. Hence, these easily accessible scales might be recommended for testing mild CA.

Brief overview on what differentiate CA from HC

Functional scores such as the Mini-BESTest, as well as questionnaires for ataxia severity, quality of life and balance confidence, have proved useful in differentiating mild CA from HC. CoT at preferred and slow speed, accompanied by measure of walking capacity like the 2MW distance, the muscular endurance (i.e. 30-s chair stand), as well as flexibility, and the dynamic balance (i.e. TUG) also demonstrated differentiability. During walking, mainly the step length variability, percentage of swing, double support and fast speed discriminated between the two groups, while during static stance the discriminating parameters are recognisable in the Area95 (both with EO and EC) and the stabilogram diffusion coefficients (particularly with EC). Also, the LOS was different at baseline between CA and HC. However, both the LOS and the TUG (although showing high ICCs elsewhere [28]) seemed to be affected by a usual care period, making the familiarisation process and/or the considerable day-to-day fluctuation possible confounding factors on these parameters [61]. Therefore, it might be in line not to consider these parameters for the assessment of baseline and disease progression.

What was the impact of the ATAEXER programme between timepoints in CA

Overall, the usual care phase before the intervention period does not seem to influence the latter as no improvements were observed during the former, with the exception of LOS and TUS as explained above. Furthermore, the mental component of the quality of life also appeared to improve after the usual care, but this might be explained by the patient's feeling of "being part of something" or "having a change to feel better" for the first time.

Walking ability

In terms of walking ability, the primary outcome of CoT assessed on a treadmill provided interesting results for its strong concurrent validity at baseline with the self-reported severity, also demonstrating significant change only after the intervention phase. Indeed, the median changes in both the $\dot{V}O_2$ of -1.33 mL·(kg·min)$^{-1}$ and the CoT of -0.018 mL·(kg·m)$^{-1}$ over the intervention phase exceed the % error for the $\dot{V}O_2$ (i.e. 1.15±1.07%) and the reported Minimal Detectable Change for CoT of 0.01 mL·(kg·m)$^{-1}$ [62], thus the change in CoT represents a real change in walking efficiency. Conversely, the change of -0.002 mL·(kg·m)$^{-1}$ during the usual care phase did not exceed the above value. In terms of gait efficiency, by comparing energy cost with reference values according to Waters et al., 1999 [42], HC presented a +8.9% CoT than predicted, while CA displayed +24.5%, +26.3% and +15.4% of CoT at t_0, t_1, and t_2, respectively. In fact, the CoT is determined by the total energy required to perform the task of walking and may be elevated by either an increased $\dot{V}O_2$ or by a low walking speed with a normal $\dot{V}O_2$ [42].

However, in our sample, neither the walking speed nor the relative $\dot{V}O_2$ resulted different between CA of mild ataxia severity and HC. However, the combination of these components resulted significant different and even improved after the exercise programme, also correlating with the self-reported ataxia severity. Therefore, the CoT might also reflect the patient's perceived global walking ability. Overall, this result strengthens the combined evaluation of $\dot{V}O_2$ and preferred walking speed, instead of drawing conclusions by keeping these values separate. Furthermore, it is important to emphasise that the preferred speed should always be considered, as walking efficiency at a controlled speed, as well as at a controlled cadence, forces participants to ambulate in a more energy costly range [42].

The mechanics represent the other side of the same coin of the energy cost, which is fundamental to understand the latter [63]. Hence, after the determination of the energy cost, a further analysis of mechanical work performed during gait was done analysing gait kinematics parameters. Considerable differences between CA and HC at all joint levels throughout the whole gait cycle were highlighted, especially during the stance period and initial swing for the ankle and hip, and the whole swing phase for the knee, with no alterations detected at the loading response and at the mid-swing. Interestingly, the toe-off angle as a well-recognised parameter discriminating CA from HC [1], showed discriminability also between mild CA and HC, and improved with the training program. Overall, the pattern suggests a delay in joint control as reported also by Palliyath et al. [64]. However, the training programme provided little benefits to gait kinematics (mostly knee), and data appeared to improve even within the usual-care phase (mainly at the hip and ankle), making the results rather weak. It is likely that the large variability also reported for kinematic data gives these parameters less reliability and validity in mild CA [64].

In addition, the τ was evaluated as a measure of gas exchange kinetics [44], reflecting indirectly an overall efficiency of muscle contraction [65] (i.e. recruitment of motor units and mechanical coupling efficiency [66]) at an exercise intensity domain close to that of most ADLs. It could be of particular interest in CA, as cerebellum regulates the timing of agonist/antagonist muscles, as well as of synergic muscles that are automatically activated during voluntary movements [9]. Well-recognised gait abnormalities include lack of intra-limb, inter-limb and inter-segmental coordination in patients with CA [67]. This analysis has been previously performed overground in individuals with Parkinson Disease [48], demonstrating improvement in τ after an overground locomotor training. Despite a differentiability of τ between CA and HC, our results did not detect improvement after the training programme.

When coming to the global functional capacity in terms of walking, dynamic balance, muscular strength, endurance and flexibility, a field-based test battery has been rarely administered in patients with cerebellar ataxia. Of all these categories, muscular endurance appeared different between groups and improved significantly with the ATAEXER programme. Furthermore, the walking capacity assessed by the 2MWT appeared a useful marker of functional capacity, showing (i) discriminability between CA and HC, (ii) strong concurrent validity and (iii) responsiveness to an exercise training programme. The 2MWT can be considered as a practical replacement for the 6MWT in multiple sclerosis [68], thus, this easily accessible and rapid test might be recommended also for testing mild CA. Moreover, this simple test becomes even more interesting when the synchronous spatiotemporal metrics are evaluated, especially the step length and the percentage of the swing/double support.

Actually, by looking at spatiotemporal gait parameters, the swing phase and the double support at fast speed, and surprisingly only the variability of the step length at comfortable and slow speed were able to distinguish CA from HC. However, they did not improve with the exercise programme, probably because our patients had only mild gait impairments. Nonetheless, step length variability at preferred walking speed strongly correlated with the clinical severity of ataxia. We found no differences between groups in preferred and slow speed, while maximum walking speed was reduced comparing CA and HC. Similarly, also Schniepp et al., 2012 [69] and Stolze et al., 2002 [70] found no significant reduction in preferred and slow walking speed in CA patients compared to HC, and Schniepp et al., 2012 also found, as in the present study, a concomitant higher ratio of preferred to maximal speed than HC, mainly because of a decrease in maximal speed while preferred walking speed maintained stable. Patients often reported "*Its easier to walk a bit faster, slowly is more difficult*", which is in contrast with some studies reporting "slowing down should make the balance problem less severe" [64,70], assuming that CA walk slower in order to improve their dynamic stability. Conversely, the present results in accordance with other studies, providing no

difference in the preferred walking speed between CA and HC might suggest that these patients utilise more speed potential in order to improve dynamic stability [69], therefore it is less likely that differences and thus improvements are observed. Moreover, when patients were asked to walk as fast as possible, gait fluctuation magnitude stressed cerebellar-specific impairments of limb control and intra-limb coordination, which were primarily indicative of the clinical severity of ataxia symptoms (even at a mild disease stage) [71].

Overall, our findings regarding the walking ability indicate the importance of a clinical and quantitative assessment of ataxia gait disorders at a non-preferred fast walking speed (stressed-walk), especially during a goal-driven test as the 2MWT. Indeed, the 2MW distance and related spatiotemporal parameters showed discriminability between CA and HC, strong concurrent validity with clinical severity of ataxia and responsiveness to the ATAEXER programme; therefore, this may be a useful measure in the clinical evaluation of patients with CA.

Balance control

Regarding posture, our findings showed greater Area95, Mean Velocity, and overall instability in motor control in CA than HC, as reported elsewhere [1,14]. Particularly, eye closure that typically worsens the ataxia of stance [9] increased the discriminability in the balance assessment, both in classical (i.e Area95) and unconventional postural parameters (i.e. SampEn and SDA; these parameters do not ignore the dynamic characteristics of the stabilogram as Area95 and Mean Velocity do [52]). Indeed, further than the capacity to distinguish CA from HC, only Area95 and the long-term region planar diffusion coefficient with eyes closed improved with training, demonstrating a better balance performance and motor control in standing without the vision support.

Although there is a general consensus that tandem stance is particularly sensitive to detect ataxia [1,9], this condition was too challenging for all mild CA enrolled in the study, with one subject even not being able to perform the stance-task with closed eyes on the force platform. On the other hand, postural control with both feet slightly apart and eyes open as well as tandem stance resulted not useful in our sample, because either too easy or too challenging for mild CA, respectively. The timed one leg stance resulted associated with clinical severity and improved with exercise, but it is likely that the tandem stance time or the semi-tandem time (not evaluated) would have provided better association because of an intermediate progression of difficulty, although a "floor effect" is detectable even in mild CA.

Regarding the SDA analysis, it had never been performed in subjects with CA. The ATAEXER trial observed an increased instability in CA compared to HC, with an improvement in planar balance control after an 8-week period of specific and non-specific training; therefore,

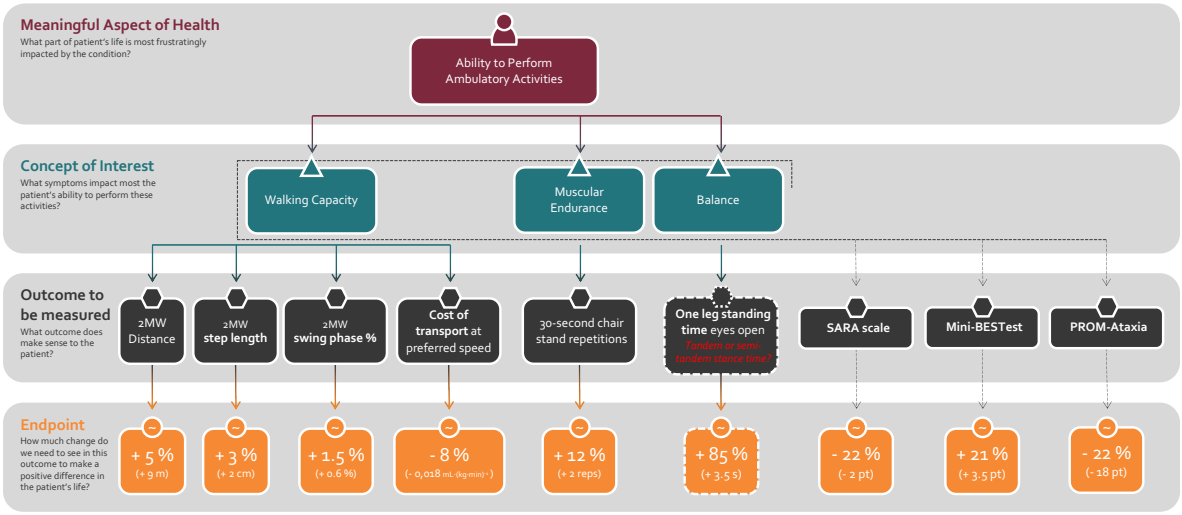
this promising analysis might be implemented in future studies. Indeed, the closed-loop control mechanism improved, which may imply a "less random" postural motor control in long-term region. In this phase corrective feedback mechanisms are called into play after a short-term region where small fluctuations at various joints of the body are left unchecked by the postural control system [52].

Surprisingly, all stabilogram parameters were not associated with clinical rating measures and patient-reported ataxia severity, but this corroborate previous evidence which used force platforms not supporting that postural balance are related to clinical scores [14]. Conversely, Liu X et al. [13] found significant strong correlations (*Rho* = 0.723) between SARA score and sway area with EO in a group of mild to moderate patients with SCA3, also showing a marked difference of all postural parameters between mild and moderate stage groups. The ATAEXER programme significantly improved postural stability, whereas Keller et al. [28] implementing a balance-focused 6-week home-based programme in moderate CA patients did not find positive results.

According to the ATAEXER training programme, the added value of the RAS and SSE which leverage the capacity of the cerebellum circuits to generate and adapt motor sequences, as well as a specific balance and resistance training programme exploiting several control systems appeared effective. In line with the "Framework to guide the selection and development of digital measures of health" [31], an important study finding is considering which measures are meaningful for clinical practice considering the patients' meaningful aspect of health, the concept of interest, the outcome to be measured and endpoint. Therefore, from our results, Figure 7 represents this four-level framework showing parameters that (i) were able to identify mild CA patients from HC, (ii) demonstrated also good concurrent validity with clinical ataxia severity and patient-reported severity, and (iii) have improved with the ATAEXER training programme; results corroborating the framework are visually represented in Supplementary Information Figure S2.

The ATAEXER programme has proven to be clinically useful, and it might be implemented in clinical practise as a standard procedure for patients with mild CA. The lesson learned is to think about physical exercise when caring for a patient with CA, especially from the mildest stages of the disease, keeping in mind to "Be timely in prescribing, administering and performing exercise". This topic deserves attention from clinicians, exercise physiologists and the population with CA.

Figure 7 | Functional evaluation test battery for developing patient-relevant measures



Proposal of a framework to guide the selection and development of digital measures of health in patients with mild cerebella ataxia considering which measures are meaningful for clinical practice. This considers the patients' meaningful aspect of health, the concept of interest, the outcome to be measured and endpoint, specifically looking at (i) discriminability between healthy and cerebellar ataxic individuals, (ii) association with ataxia severity and (iii) responsiveness to an exercise training programme. Model adapted from Ilg et al. [1], and Manta et al. [31]

Limitations and future perspectives

Despite the interesting new findings revealed in this clinical trial, some potential limitations should be considered.

The study is largely underpowered due to the small sample size, undermining the internal and external validity of the study and limiting its generalisability substantially. These recruitment issues in rare diseases are also typical of the clinical picture internationally, but a possible solution is to adopt a concurrent control design in which participants serve as their own control [72]. Internationally, sample sizes vary from 7 to 42 participants (i.e. sample size mean±SD of RCTs, intraindividual control design, one group pre-post-intervention, and case series = 28±13, 15±5, 15±1, and 13±6, respectively) [19,20]. However, although the concurrent control design was adopted in the ATAEXER trial, the sample size remained low; accordingly, more participants should be evaluated before generalising the results.

Moreover, the study enrolled patients who were still able to walk independently, which reflects mild CA. Therefore, the results of the present study might not be transferable to patients with moderate or even severe CA.

Furthermore, walking efficiency was assessed on a treadmill which may not fully reflect the impact of the training programme performed while walking on the ground. Therefore, a portable metabolimeter could have provided findings closer reflecting the training programme and ADLs.

Finally, our findings accounted only for the effect in the short-term, while a follow-up analysis could have provided further insights into the long-term effects of the programme. Further research with a more prolonged exposure is warranted.

Conclusions

Our findings provided evidence that a multicomponent exercise programme, with basic equipment and the possibility to be performed autonomously at home, is feasible and effective for people living with mild cerebellar ataxia. Therefore, the ATAEXER project provided a model for a clinical care pathway and real-life exercise prescription and a framework was presented to guide the selection of measures of health for patients with cerebellar ataxia. These parameters are identifiable in some spatiotemporal variables during the 2-min walk test, its distance as well, accompanied by the Cost of transport at the preferred overground walking speed, the repetitions performed during the 30-s chair stand, and the single-leg time. These variables overall describe patients' walking ability, dynamic balance, and lower limb muscular endurance and are thus recommended as parameters to evaluate functional capacity in patients with mild cerebellar ataxia, as well as simultaneously administering semi-quantitative clinical scales and patient-reported measures as the SARA scale, the Mini-BESTest and the PROM-Ataxia. Furthermore, although not specifically analysed, it is likely that other movement disorders could also benefit from the ATAEXER programme with appropriate adaptations. For implementation into clinical care, clinicians, exercise physiologists and patients should work synergistically keeping in mind to "Be timely in prescribing, administering and performing exercise".

Contributions

Sara Faggian conceived and designed research; Sara Faggian, Miryam Carecchio, Giulia Bonato participated in the patients' recruitment; Sara Faggian, Giulia Bonato and Adalberto Codognola contributed to data collection with contributions from Elisa Agostini, Silvia Romito, Daniel Neunhaeuserer, Fabiola Spolaor, Annamaria Guiotto and Giulio Rigoni; Sara Faggian, Elisa Agostini and Silvia Romito contributed to the practical conduction of the intervention periods; Sara Faggian performed the analyses and subsequent interpretation of data, prepared the figures and wrote the manuscript. Daniel Neunhaeuserer and Andrea Ermolao revised the manuscript. Andrea Ermolao, Giuseppe Marcolin and Zimi Sawacha contributed materials.

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Supplementary Information

Table S1 | ATAEXER Programme – Session *A*

Mobility training (5-min: 10 reps x 2 sets completed in a circuit mode)

No level of progression (Level 1 – 5)

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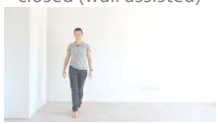
Ankle circles	Hip flexion – external rotation	Stand up child pose	Shoulder internal-external rotation and trunk flexion-extension
			

Balance training (15-min: 60-s/10 reps x 2 sets completed in a circuit mode)

Level 1	Level 2	Level 3	Level 4	Level 5
Feet closed, eyes open	Feet closed, eyes closed	Feet closed, eyes closed, foam pad	Feet closed, eyes closed, foam pad, heat rotations	Feet closed on toes, eyes closed
				
				Alternative in progression: feet closed on toes, eyes closed, head rotations
				
Semi-tandem, eyes open	Semi-tandem, eyes closed	Tandem, eyes open	Toe-heel tandem, eyes open (wall assisted)	One leg, eyes open
				
		Alternative in progression: tandem, eyes closed (wall assisted)		Alternative in progression: one leg, eyes closed
				
Feet apart, ankle strategy anterior-posterior LOS	Feet closed, ankle strategy anterior-posterior LOS	Feet closed, ankle strategy anterior-lateral-posterior-medio LOS (cross)	Feet closed, ankle strategy anterior-lateral-posterior-medio LOS (circumduction)	Feet closed, ankle strategy anterior-lateral-posterior-medio LOS (circumduction), eyes closed
				

Feet apart, ankle strategy medio-lateral LOS

Feet apart, hip strategy anterior-posterior LOS

Feet apart, hip strategy medio-lateral LOS

Feet closed, ankle strategy medio-lateral LOS

Feet closed, hip strategy anterior-posterior LOS

Feet closed, hip strategy medio-lateral LOS

Feet closed, hip strategy anterior-lateral-posterior-medio LOS (cross)

Step strategy anterior-lateral-posterior-medio

Feet closed, hip strategy anterior-lateral-posterior-medio LOS (circumduction)

Step strategy anterior-lateral-posterior-medio

Feet closed, hip strategy anterior-lateral-posterior-medio LOS (circumduction), eyes closed

Indoor gait training (15-min: around 20 steps x 2 sets completed in a circuit mode)

Level 1

Toe walk (wall assisted)

Heel walk (wall assisted)

Stance phase (load acceptance – push off) (wall assisted)

High-knee walk (wall assisted)

Level 2

Toe walk, wide base of support

Heel walk, wide base of support

Stance phase (load acceptance – push off)

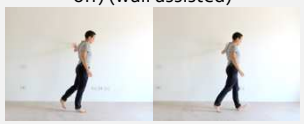
High-knee walk

Level 3

Toe walk

Heel walk with high body perturbation

Stance phase walk (load acceptance – push off) (wall assisted)



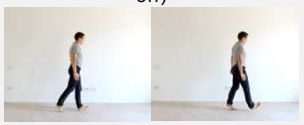
High-knee slow walk (3-s iso)

Level 4

Toe slow walk, low obstacles

Heel slow walk with high body perturbation

Stance phase walk (load acceptance – push off)



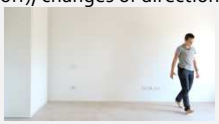
High-knee slow walk (3-s iso), low obstacles

Level 5

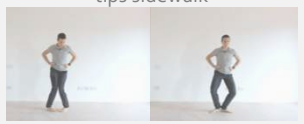
Toe walk, arm crossed to the chest, changes of direction

Heel walk, arm crossed to the chest, changes of direction

Stance phase walk (load acceptance – push off), changes of direction



High-knee slow walk (3-s iso), high obstacles

Sidewalk	Sidewalk, low obstacles	Crossed sidewalk	Crossed sidewalk with high obstacles	Crossed sidewalk with changes of direction
				 Alternative in progression: open-closed tips sidewalk 

Outdoor gait training (15-min)

Level 1	Level 2	Level 3	Level 4	Level 5 (x 3 sets)
15-min: bpm 100% preferred cadence	5-min: bpm 100% preferred cadence 5-min: bpm 120% preferred cadence 5-min: bpm 80% preferred cadence	5-min: bpm 80% preferred cadence 5-min: bpm 120% preferred cadence 5-min: bpm 80% preferred cadence	4-min: bpm 100% preferred cadence 4-min: bpm 120% preferred cadence 4-min: bpm 100% preferred cadence 4-min: bpm 80% preferred cadence	2-min: bpm 100% preferred cadence 2-min: bpm 120% preferred cadence 2-min: bpm 80% preferred cadence

Flexibility training (3-min: 30-s reps x 2 sets completed in a circuit mode)

No level of progression (Level 1 – 5)

Posterior kinetic chain	Calf
	

Table S2 | ATAEXER Programme – Session *B*

Mobility training (5-min: 10 reps x 2 sets completed in a circuit mode)

No level of progression (Level 1 – 5)

Ankle circles

Anterior-posterior pelvic tilt

Hand to opposite foot

Cat-cow

SCAN ME
for asynchronous
video-based instructions

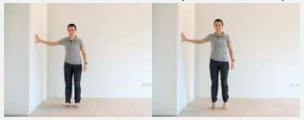
Coordination training – square step exercise (20-min: 3/4 sequences x 10 sets)

Level 1 (week 1)	Level 2 (week 2)	Level 3 (week 3)	Level 4 (week 4)	Level 5 (week 5)
Right foot (both feet start @5) 2-3-6 2-6-9 8-3-6 8-6-2 3-5-9 3-2-6	**Right foot (both feet start @5)** 2-3-6-9 2-6-9-2 8-3-6-5 8-6-2-6 3-5-9-2 3-2-6-8	**Right foot (both feet start @5)** 2-9-3-6 2-5-6-2 2-4-6-7 3-6-9-2 3-9-2-8 9-8-3-2 9-5-6-2	**Right foot (both feet start @8)** 5-3-6-9-2 5-6-9-2-3 2-3-6-5-2	**Right foot (both feet start @8)** 5-3-6-9-2-5 5-6-9-2-3-6 2-3-6-5-2-8
96 bpm	**98 bpm**	**100 bpm**	**102 bpm**	**104 bpm**
Dual task None	**Dual task** None	**Dual task** None	**Dual task** Balance a magazine on the head	**Dual task** Clap hands in front and behind the back
Left foot (both feet start @5) 2-1-4 2-4-7 8-1-4 8-4-2 1-5-7 1-2-4	**Left foot (both feet start @5)** 2-1-4-7 2-4-7-2 8-1-4-5 8-4-2-4 1-5-7-2 1-2-4-8	**Left foot (both feet start @5)** 2-7-1-4 2-5-4-2 1-4-7-2 8-5-2-7 1-7-2-8 7-8-1-2 7-5-4-2	**Left foot (both feet start @8)** 5-1-4-7-2 5-4-7-2-1 2-1-4-5-2	**Left foot (both feet start @8)** 5-1-4-7-2-5 5-4-7-2-1-4 2-1-4-5-2-8
96 bpm	**98 bpm**	**100 bpm**	**102 bpm**	**104 bpm**
Dual task None	**Dual task** None	**Dual task** None	**Dual task** Balance a magazine on the head	**Dual task** Clap hands in front and behind the back
Both feet (both feet start @5, right foot starts) 6-4-3 6-8-2 2-1-6 2-4-6 3-2-6 3-1-2 9-7-8 8-4-6	**Both feet (both feet start @5, start right foot starts)** 6-4-3-2 6-8-2-2 2-1-6-7 2-4-6-2 3-2-6-1 3-1-2-4 9-7-8-4 8-4-6-2	**Both feet (both feet start @5, start right foot starts)** 2-4-6-2 2-1-6-7 3-2-6-4 3-4-8-7 6-4-3-2 6-8-5-4 9-7-8-4 8-4-5-2	**Both feet (both feet start @8, start right foot starts)** 6-4-2-7-9 6-7-2-4-9 2-1-4-7-3 2-4-6-7-2	**Both feet (both feet start @8, start right foot starts)** 6-4-3-1-2-7 6-7-5-2-9-5 2-1-4-7-9-5 2-4-6-2-5-7
84 bpm	88 bpm	90 bpm	92 bpm	94 bpm
Dual task	**Dual task**	**Dual task**	**Dual task**	**Dual task**

None	None	None	Clap hands in front and behind the back	Balance a magazine on the head
Level 6 (week 6) **Right foot (both feet start @8)** 2-9-3-6-5-3 2-5-6-2-3-9 3-9-2-8-3-5 **106 bpm** **Dual task** Passing an object around the trunk from one hand to the other **Left foot (both feet start @8)** 2-7-1-4-5-1 2-5-4-2-1-7 1-7-2-8-1-5 **106 bpm** **Dual task** Passing an object around the trunk from one hand to the other **Both feet (both feet start @8, start right foot starts)** 2-1-7-4-9-5 3-1-9-2-6-5 6-7-3-2-9-7 6-7-3-1-9-5 96 bpm **Dual task** Spelling of words	**Level 7 (week 7)** **Right foot (both feet start @5)** 2-3-6-7-9-5-8 2-6-9-1-5-2-3 8-3-6-2-8-1-9 **108 bpm** **Dual task** Passing an object around the trunk from one hand to the other **Left foot (both feet start @5)** 2-1-4-9-7-5-8 2-4-7-3-5-2-1 8-1-4-2-8-3-7 **108 bpm** **Dual task** Passing an object around the trunk from one hand to the other **Both feet (both feet start @5, start right foot starts)** 6-4-3-9-1-7-6 6-8-5-2-7-4-9 2-6-3-7-8-6-3 2-9-6-4-5-9-6 98 bpm **Dual task** Clap hands in front and behind the back	**Level 8 (week 8)** **Right foot (both feet start @5)** 2-3-6-7-9-5-8-2 2-8-6-3-5-7-9-3 **110 bpm** **Dual task** Counting backward 2 by 2 **Left foot (both feet start @5)** 2-1-4-9-7-5-8-2 2-8-4-1-5-9-7-1 **110 bpm** **Dual task** Counting backward 2 by 2 **Both feet (both feet start @5, start right foot starts)** 6-4-7-3-8-5-1-4 6-8-4-2-3-7-9-2 2-1-4-2-8-3-9-4 3-9-1-7-8-3-6-4 100 bpm **Dual task** Clap hands in front and on thighs Alternative in progression: clap hands once in front and twice behind the back		

Resistance training (20-min: around 10 reps x 2 sets completed in a circuit mode)

NB: a Time Under Tension focused on a slow eccentric and explosive concentric phase was adopted for many exercises.

Level 1	Level 2	Level 3	Level 4	Level 5
Calf and tibialis raise (wall assisted) 	Calf and tibialis raise 	Step calf raise 	Monopodalic calf and tibialis raise (wall assisted) 	Bounced calf 

Thigh extension and external rotation (face to the wall)

Sit to stand

Opposite arm-knee push

Hip hinge

Toe-grasp of easy-soft objects

Thigh extension and external rotation (chair assisted)

Squat box

Mountain climber (chair assisted)

Hip Hinge

Stand bird dog (chair assisted)

Toe-grasp of tiny-hard objects

Isometric thigh extension and external rotation (chair assisted)

Squat

Quadrupedal knee raise (5-s iso)

Bird dog

Toe-grasp of objects in a standing position

Glute bridge

Squat on toes

Quadrupedal knee raise lifting one foot (5-s iso)

Alternative in progression: quadrupedal knee raise lifting one hand (5-s iso)

Kneeling hip hinge with feet off the ground

Toe-grasp of objects in a standing position

Monopodalic glute bridge

Squat jump

Quadrupedal knee raise lifting opposite hand-foot (5-s iso)

Alternative in progression: quadrupedal knee raise walk

Kneeling hip hinge with feet off the ground (5-s iso)

"Taste the water", toe-grasp of distant objects in a standing position

Flexibility (15-min: 30-s reps x 2 sets completed in a circuit mode)

No level of progression (Level 1 – 5)

Posterior kinetic chain

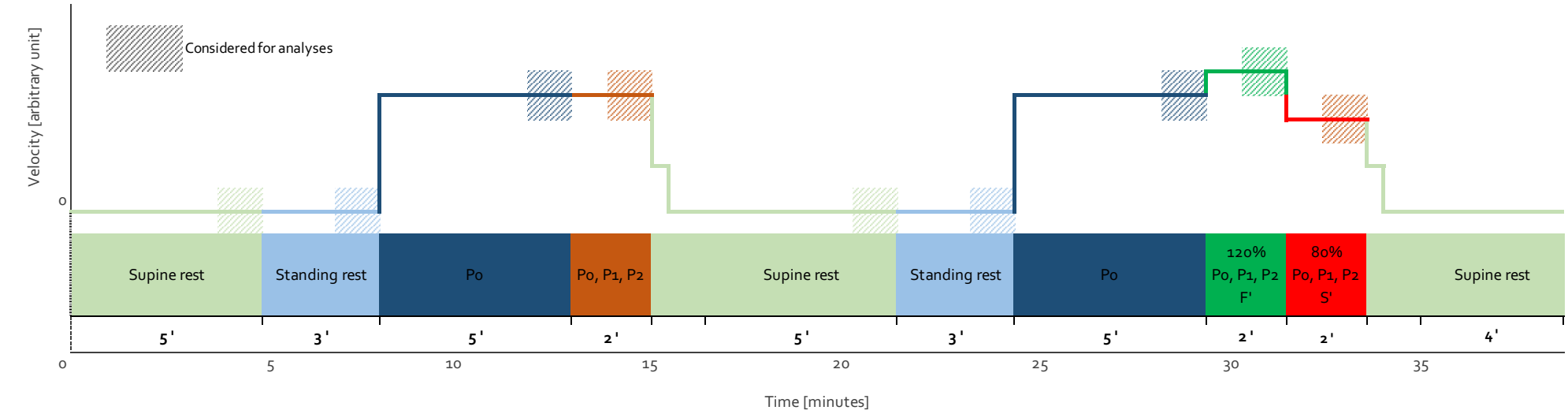
Lateral trunk flexion

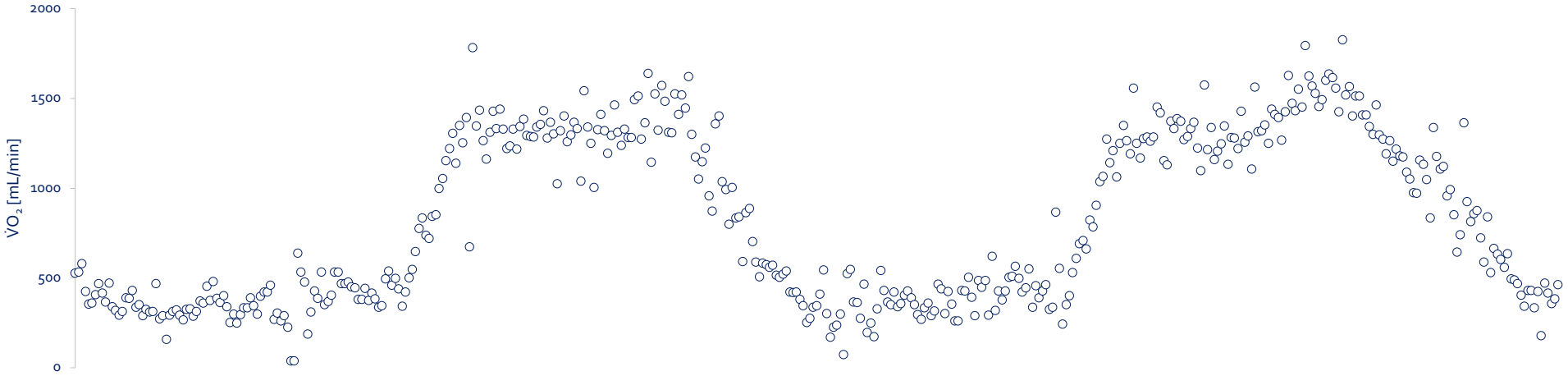
Passive toe spread

Dorsiflexors stretch

Plantar flexors stretch

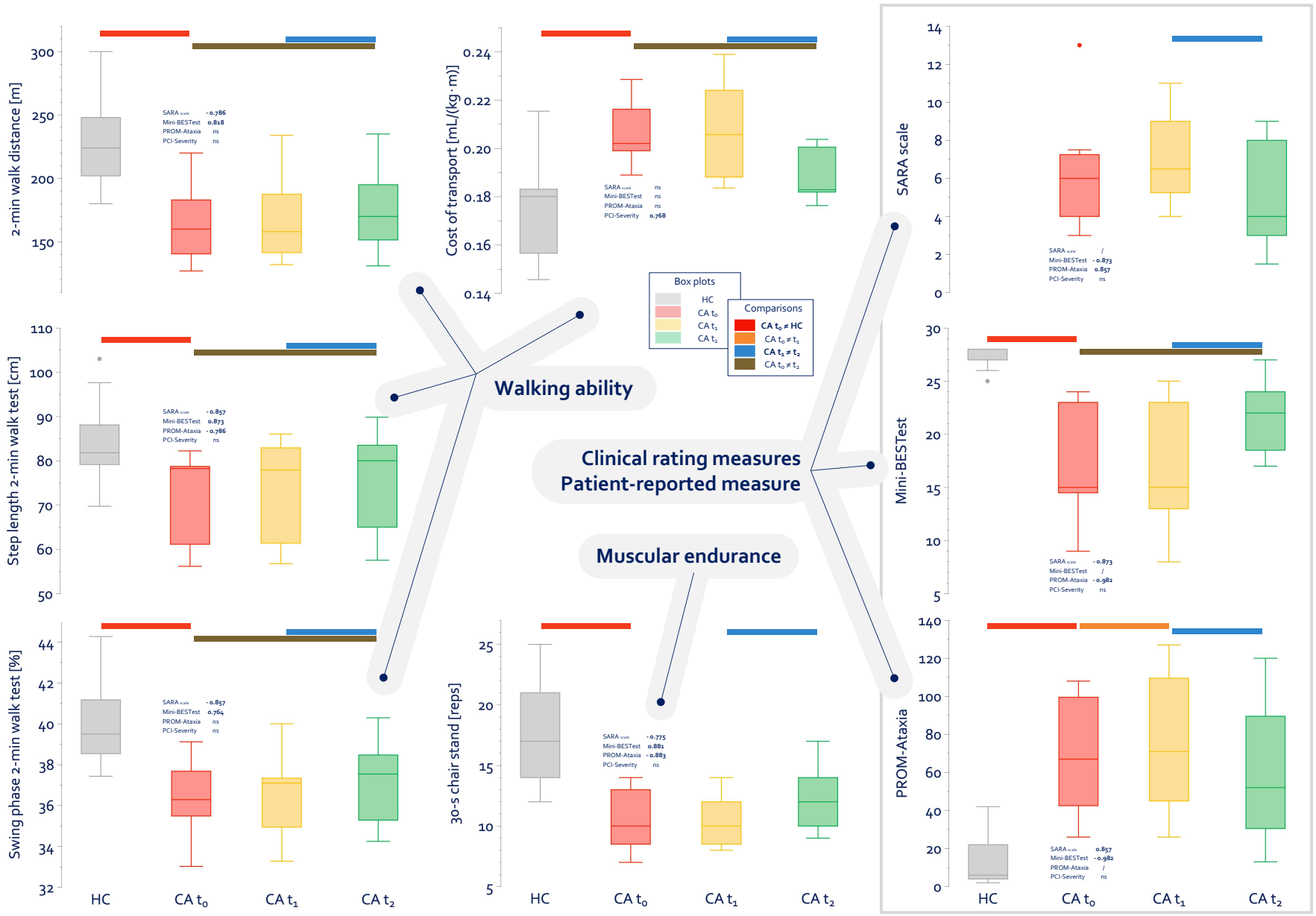
Figure S1 | Treadmill protocol for CPET evaluation





Above: customised treadmill protocol for the assessment of cardiopulmonary response. Below: the related oxygen uptake of one of the participants.
Abbreviations: Po: preferred walking speed t_0; P1: preferred walking speed t_1; P2: preferred walking speed t_2.

Figure S2 | Graphical representations of results corroborating the "Framework to guide the selection and development of digital measures of health" [31]



Results of the ATAEXER Trial supporting the development of the "Framework to guide the selection and development of digital measures of health" in patients with mild cerebellar ataxia.
Abbreviations: CA: cerebellar ataxia; HC: healthy controls; Mini-BESTest: Mini Balance Evaluation Systems Test; PROM-Ataxia: Patients Reported Outcome Measure of Ataxia; SARA: Scale for Assessment and Rating of Ataxia.

Publications [27.11.2024]

- [Under review] Rizzato A.*, **Faggian S.***, Paoli A., Marcolin G. Transfer of balance performance and neuromuscular control mechanisms depend on the specificity of balance training. *Journal of Applied Physiology*.
- [Under review] **Faggian S.**, Battista F., Vecchiato M., Casaburi R., Emtner M., Borasio N., Studnicka M., Ermolao A., Niebauer J., Neunhaeuserer D. Supplemental oxygen during exercise training in chronic obstructive pulmonary disease. *Exercise and Sport Sciences Reviews*.
- [Under review] Vecchiato M., Duregon F., Borasio N., **Faggian S.**, Bassanello V., Aghi A., Palermi S., Degano G., Battista F., Ermolao A., Neunhaeuserer D. Cardiopulmonary exercise response in high altitude for patients with congenital heart disease: a systematic review and meta-analysis. *Frontiers in Cardiovascular Medicine, section Pediatric Cardiology*.
- [Under review] Quinto G., Duregon F., Vecchiato M., Battista F., **Faggian S.**, Fabris M., Gasperetti A., Ermolao A., Neunhaeuserer D. From theory into practice: insights from a real-world implementation model for tailored exercise prescription in chronic diseases. *BMC Public Health*.
- [Pre-proof] **Faggian S.**, Borasio N., Vecchiato M., Gatterer H., Burtscher M., Battista F., Brunner H., Quinto G., Duregon F., Ermolao A., Neunhaeuserer D. (2024). Sport climbing performance determinants and functional testing methods: A systematic review. Advance online publication. *Journal of Sport and Health Science*.
- **Faggian S.**, Centanini A., Quinto G., Vecchiato M., Ermolao A., Battista F., Neunhaeuserer D. (2024). The many faces of exercise intensity: a call to agree on definitions and provide standardized prescriptions. *European Journal of Preventive Cardiology*.
- Bezerra A., Boppre G., Freitas L., Battista F., **Faggian S.**, Busetto L., Ermolao A., Fonseca H. (2023). Body Composition Changes in Adolescents Who Underwent Bariatric Surgery: A Systematic Review and Meta-analysis. *Current Obesity Reports*.
- Battista, F., Sarri C., Foccardi G., Quinto G., **Faggian S.**, Vecchiato M., Durego F., Neunhaeuserer D. (2023). "Exercise in Medicine: From Functional Evaluation to Adapted Exercise Training": a Massive Open Online Course to Respond to the Burning Need for Exercise Prescription to Combat Chronic Diseases. 74: 193-196. *German Journal of Sports Medicine*.
- Vecchiato M., **Faggian S.**, Quinto G., Battista F., Foletto M., Di Vincenzo A., Bettini S., Gasperetti A., Busetto L., Ermolao A., Neunhaeuserer D. (2023). Analysis of Walking Economy after Sleeve Gastrectomy in Patients with Severe Obesity. 12(5):746. *Biology (Basel)*.

Oral presentations [27.11.2024]

- Moderate poster "Validity of 'range-based methods' compared to the 'ventilatory thresholds-based method' for exercise intensity prescription in patients after bariatric surgery", American College of Sports Medicine 2024 Annual Meeting, May 28 – 31, 2024, Boston.
- Invited speaker "Impariamo a conoscere e a prenderci cura della nostra circolazione – L'esercizio fisico come prevenzione e terapia", Dì Salute, Pillole di salute, Department of Medicine, May 23, 2024, Padova (PD).
- Invited speaker "Valutazione funzionale nell'arrampicata sportiva: determinanti della performance", Convegno del 30° Corso di Perfezionamento in Medicina di Montagna, September 16, 2023, Sesto (BZ).
- Oral presentation "Sport climbing performance determinants and functional testing methods: a systematic review" accepted for oral presentation in the 28th Annual Congress of the European College of Sport Science, July 04th - 07th, 2023, Paris.
- Invited speaker "Dall'ambulatorio alla palestra: percorsi di attività motoria adattata", Il tumore della mammella: recupero funzionale e qualità di vita dopo l'intervento chirurgico, May 12th, 2023, Piazzola sul Brenta (PD).
- Poster "Roux-en-Y gastric bypass effect on body composition in adolescents: a systematic review and meta-analysis" accepted for poster presentation in 10th Europe Initiative for Exercise in Medicine Congress, October 27th - 29th, 2022, Padova.
- Invited speaker 'Attività pratica-interattiva sull'esercizio fisico' in the meeting 'Corso sugli stili di vita attivi' April 21st, 2022, Casa Sacro Cuore di Saccolongo (Padova), ECM training, Provider: University of Torino, coordinator Dr. Enrica Favaro.