

FATIG'AGE: Co-Creation And Validation Of An Ecologically Informed Daily-Activity Protocol To Assess Fatigability In Ageing Populations With Diverse Functional Profiles

Reinhard Claeys

Vrije Universiteit Brussel

Juha Carlon

KU Leuven

Mahyar Firouzi

Vrije Universiteit Brussel

Sylvie De Raedt

Universitair Ziekenhuis Brussel

Siddhartha Lieten

Universitair Ziekenhuis Brussel

Tom Verstraten

Vrije Universiteit Brussel

Benjamin Filtjens

Delft University of Technology

Eva Swinnen

Vrije Universiteit Brussel

David Beckwée

David.Beckwee@vub.be

Vrije Universiteit Brussel

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Abstract

Fatigue is a highly prevalent and relevant clinical parameter, and is recognized as a key determinant of vitality capacity within the Healthy Ageing framework. Within its construct, fatigability refers to fatigue that develops in response to a specific activity, which impacts performance in daily life. However, current fatigability assessments predominantly rely on isolated or single-modality tasks, which insufficiently capture the complex and cumulative demands of everyday functioning. In this study, we developed and validated FATIG'AGE, the first standardized, ecologically valid, multi-task protocol to assess fatigability in ageing and clinical populations with varying functional abilities. Using a human-centred, iterative design approach, FATIG'AGE was co-created through repeated participant testing and structured feedback, with the aim of inducing progressive increases in perceived fatigability within the one-hour timeframe. Overall the protocol was found to be safe and realistic, and during validation, it consistently elicited increasing perceived exertion across participants. Differences in perceived exertion trajectories and total task execution demonstrated discriminative potential, with lower fatigability observed in older adults without mobility impairments compared to older adults with sarcopenia and stroke survivors. Overall, FATIG'AGE provides a structured and meaningful approach to evaluate fatigability as a component of vitality capacity in both research and clinical settings.

Introduction

Fatigue in its various forms is a highly prevalent and clinically relevant health construct across a wide range of populations. Within the World Health Organization's (WHO) *Healthy Ageing* framework, fatigue is recognized as a key determinant of *vitality capacity*, the physiological determinant of one's intrinsic capacity [1]. Intrinsic capacity, defined as the composite of an individual's physical and mental capacities, interacts with environmental factors to shape functional ability and, ultimately, well-being in older age [2]. In an ageing population, fatigue affects up to 42.6% of older adults [3], and is associated with age-related musculoskeletal conditions such as primary sarcopenia [4] and osteoarthritis [5]. Beyond ageing, fatigue is also highly prevalent in neurological populations, including individuals with stroke, multiple sclerosis, Parkinson's disease, traumatic brain injury, myasthenia gravis, amyotrophic lateral sclerosis, and post-polio syndrome [6]. For instance, post-stroke fatigue affects nearly half (48%) of the stroke survivors [7] and is associated with reduced mobility [8], diminished functioning and participation in daily life [9], and an increased likelihood of dependency in activities of daily living (ADL) [10]. In older adults, fatigue predicts a range of adverse health outcomes, including mortality, physical disability, hospitalisation, physical decline [11], and falls [12,13]. Across these populations, fatigue represents a major barrier to sustained engagement in everyday activities.

To appropriately assess fatigue in clinical and research settings, it is important to consider its multidimensional and complex nature. According to the taxonomy proposed by Van Geel et al. (2020), it can be categorized into trait and state fatigue, the latter also referred to as activity-based fatigue or *fatigability* [14]. Trait fatigue reflects a persistent experience of fatigue over time, whereas fatigability refers to fatigue that develops in response to a specific activity or task. Both forms comprise motor and

cognitive components, have different underlying causes, and are influenced by multiple internal and external factors [14]. Trait fatigue is most commonly assessed using self-report questionnaires covering longer time periods, such as the Fatigue Severity Scale [15]. In contrast, fatigability is assessed by examining changes that occur during or in response to a predefined activity [14]. These changes can be expressed as *perceived fatigability*, reflecting subjective exertion (e.g., Borg Rating of Perceived Exertion [16]), or as *performance fatigability*, reflecting objective changes in task performance such as increased task completion time or reduced distance covered [14,17,18]. Perceived fatigability captures the integrated physical and cognitive experience of effort during task performance, making it particularly relevant for capturing a comprehensive view on fatigue [19].

Insights from our prior qualitative research provide a real-life perspective on how fatigability manifests in clinical populations. In focus group discussions with older adults and stroke survivors with mobility limitations, fatigue was consistently described as a prominent and limiting factor in daily life [20,21]. Participants reported that fatigue most often emerged during the performance of functional, daily activities, such as negotiating stairs and carrying objects, and developed progressively over time as activities accumulate throughout the day [20,21]. These findings underscore that in order to understand and evaluate real-world fatigue, fatigability assessments that capture the complex, variable, and cumulative demands of everyday life are of prime importance.

Nevertheless, although a variety of protocols are currently used to assess fatigability, these predominantly rely on repeated isolated tasks (e.g., sit-to-stand tests), overground walking, treadmill walking, or cycling-based protocols [17,18,22]. While these protocols can successfully induce fatigue, they insufficiently reflect the diversity and sequencing nature of daily-life activities that are central to healthy ageing, such as household tasks, community mobility, and grocery shopping [2]. Consequently, performance on these assessments may not fully represent an individual's capacity to cope with the cumulative and variable demands encountered in real-world situations. This limitation aligns with the call to action to develop fatigability measures that explicitly account for individual impairments, environmental context, and task-specific demands under which fatigue is experienced [23].

To date, no standardized fatigability protocol exists that integrates the broad range of real-life functional demands relevant to ageing populations within a controlled laboratory setting. Such a protocol could serve as an important bridge between the laboratory-based assessments, offering safety, experimental control, and precise measurement, and real-world relevance, reflecting ecological validity. One key application lies in the evaluation of interventions aimed at reducing fatigability in daily life, such as assistive technologies including lower-limb exoskeletons (LLEs). Beyond assistive technologies, a multi-task fatigability protocol could also be applied to evaluate exercise-based [24] and pharmacological interventions [25,26], and to support fundamental research on fatigue as part of one's vitality capacity, including fatigue mechanisms [6], the interaction between trait and state fatigue [27], and the impact of fatigue on everyday movement and function [28].

Therefore, the aim of this study was to develop and validate a novel, standardized, ecologically valid lab-based protocol (i.e., FATIG'AGE) that reliably induces meaningful activity-based fatigue, in close collaboration with the population of interest. First, the development of the FATIG'AGE protocol focused on establishing an initial, theoretical protocol version (based on qualitative research [20,21]), which was then iteratively optimised toward a final protocol version (i.e., *optimization phase*). Unlike conventional approaches in which protocols are designed solely by researchers and directly implemented in experimental testing, this study adopted co-creation principles to develop an ecologically valid protocol that explicitly incorporates participant needs and experiences. Subsequently, the finalised protocol was validated in a larger cohort to assess whether the predefined success criteria were consistently achieved across individuals with varying functional abilities (i.e., *validation phase*). Specifically, FATIG'AGE aims to induce a progressive increase in perceived fatigability within a one-hour time frame, establishing feasibility and consistency across individuals with differing mobility levels. The protocol was designed to reflect the sequencing and cumulative demands of functional activities encountered in daily life, while maintaining experimental control. To ensure clinical relevance, the human-centred protocol was developed and evaluated in older adults and stroke survivors representing a wide range of functional abilities.

Results

In total, 40 subjects participated across the iterative optimization and validation phase of this study. Five participants (one older adult without mobility impairments, one older adult with sarcopenia, and three stroke survivors) took part in both phases, based on their availability and continued eligibility. Participant demographics and clinical characteristics for each phase are summarised in Table 1. The group of older adults with mobility impairments comprised a heterogeneous range of (combined) conditions affecting mobility, including arthritis, probable sarcopenia, osteoporosis, partial paralysis, arthrodesis, and/or use of a lower-limb prosthesis.

Table 1
Characteristics of the study population across both the optimization and validation phase.

	Optimisation Phase			Validation Phase		
	OA w/o mob. imp. (n = 5)	Stroke survivors (n = 5)	OA w. mob. imp. (n = 5)	OA w/o mob. imp. (n = 10)	Stroke survivors (n = 10)	OA w. sarcopenia (n = 10)
Age (years)	71.6 (± 10.0)	58.8 (± 13.5)	80.2 (± 8.2)	71.9 (± 6.4)	56.9 (± 10.1)	84.2 (± 4.2)
Sex (male/female)	1M/4F	4M/1F	3M/2F	5M/5F	5M/5F	5M/5F
Time post-stroke (months)	-	35.6 (± 19.4)	-	-	58.8 (± 33.6)	-
MoCA (0–30)	26.2 (± 2.8)	25.4 (± 2.9)	25.2 (± 3.3)	24.9 (± 2.9)	26.1 (± 2.5)*	20.8 (± 4.3)
TUG (sec)	6.5 (± 1.6)	11.7 (± 4.2)	10.2 (± 2.5)	7.8 (± 2.0)	15.4 (± 9.3)	17.4 (± 5.5)
Maximal handgrip strength (kPa)	60.6 (± 21.9)	-	43.4 (± 15.5)	62.9 (± 16.7)	-	40.5 (± 12.2)
5STS (sec)	12.04 (± 3.74)	-	17.05 (± 5.45)	10.62 (± 2.14)	-	24.25 (± 7.20)**
FAC levels (n)	-	3(2), 4(2), 5(1)	-	-	3(5), 4(5)	-
IPAQ-SF (low/moderate/high)	1/1/3	1/1/3	2/0/3	0/3/7	1/5/4	3/4/3
FSS (9–63)	30.0 (± 5.3)	44.8 (± 11.2)	33.6 (± 8.7)	25.3 (± 8.5)	42.3 (± 11.1)	32.4 (± 13.3)

Data is presented for older adults without mobility impairments (OA w/o mob. imp.), stroke survivors, older adults with mobility impairments (OA w. mob. imp.) and older adults with sarcopenia (OA w. Sarcopenia). Values are reported as mean ± standard deviation unless otherwise stated; MoCA = Montreal Cognitive Assessment; TUG = Timed Up and Go; 5STS = Five-Times Sit-to-Stand test; FAC = Functional Ambulation Categories; IPAQ-SF = International Physical Activity Questionnaire–Short Form; FSS = Fatigue Severity Scale; PSQI = Pittsburgh Sleep Quality Index; VAS = Visual Analogue Scale. *one subject was unable to complete the questionnaire due to upper limb paralysis (mean calculated across the other 9 subjects); ** two subjects were unable to execute 5 sit-to-stands (mean calculated across the other 8 subjects).

	Optimisation Phase			Validation Phase		
	OA w/o mob. imp. (n = 5)	Stroke survivors (n = 5)	OA w. mob. imp. (n = 5)	OA w/o mob. imp. (n = 10)	Stroke survivors (n = 10)	OA w. sarcopenia (n = 10)
PSQI (0–21)	6.4 (± 4.6)	7.0 (± 4.1)	5.0 (± 3.7)	5.7 (± 3.7)	4.0 (± 1.7)	5.4 (± 3.2)
# of fallers (≥ 1 self-reported fall in the last 12 months)	1	3	2	3	5	5
VAS Pain Score (0–100):						
During daily life	24.0 (± 21.9)	12.0 (± 13.0)	29.0 (± 28.8)	18.5 (± 17.0)	29.5 (± 28.9)	20.5 (± 19.2)
Walking specific	18.0 (± 24.9)	26.0 (± 28.0)	17.0 (± 24.9)	15.0 (± 20.1)	28.0 (± 21.6)	20.5 (± 20.9)
Mobility aid users:	-	2	3	-	5	5
Use during daily life (n, frequency)	-	Walking cane (1, daily; 1, weekly), tricycle (1, daily), key walker (1, weekly), wheelchair (1, yearly)	Walking cane (1, daily; 1, yearly), key walker (1, daily), orthosis (1, daily)	-	Walking cane (3, daily; 2, weekly), orthosis (1, daily), mobility scooter (1, daily), key walker (1, weekly), wheelchair (1, monthly; 1, yearly)	Walking cane (4, daily), key walker (4, daily), wheelchair (1, weekly)

Data is presented for older adults without mobility impairments (OA w/o mob. imp.), stroke survivors, older adults with mobility impairments (OA w. mob. imp.) and older adults with sarcopenia (OA w. Sarcopenia). Values are reported as mean ± standard deviation unless otherwise stated; MoCA = Montreal Cognitive Assessment; TUG = Timed Up and Go; 5STS = Five-Times Sit-to-Stand test; FAC = Functional Ambulation Categories; IPAQ-SF = International Physical Activity Questionnaire–Short Form; FSS = Fatigue Severity Scale; PSQI = Pittsburgh Sleep Quality Index; VAS = Visual Analogue Scale. *one subject was unable to complete the questionnaire due to upper limb paralysis (mean calculated across the other 9 subjects); ** two subjects were unable to execute 5 sit-to-stands (mean calculated across the other 8 subjects).

	Optimisation Phase			Validation Phase		
	OA w/o mob. imp. (n = 5)	Stroke survivors (n = 5)	OA w. mob. imp. (n = 5)	OA w/o mob. imp. (n = 10)	Stroke survivors (n = 10)	OA w. sarcopenia (n = 10)
Use during protocol (n)	-	Walking cane (1)	Orthosis (1), walking cane (1)	-	Walking cane (2), orthosis (1)	Walking cane (1)
Data is presented for older adults without mobility impairments (OA w/o mob. imp.), stroke survivors, older adults with mobility impairments (OA w. mob. imp.) and older adults with sarcopenia (OA w. Sarcopenia). Values are reported as mean $\pm$ standard deviation unless otherwise stated; MoCA = Montreal Cognitive Assessment; TUG = Timed Up and Go; 5STS = Five-Times Sit-to-Stand test; FAC = Functional Ambulation Categories; IPAQ-SF = International Physical Activity Questionnaire–Short Form; FSS = Fatigue Severity Scale; PSQI = Pittsburgh Sleep Quality Index; VAS = Visual Analogue Scale. *one subject was unable to complete the questionnaire due to upper limb paralysis (mean calculated across the other 9 subjects); ** two subjects were unable to execute 5 sit-to-stands (mean calculated across the other 8 subjects).						

Findings during the optimisation phase

Iterative refinements

During protocol co-creation, FATIG'AGE was iteratively refined across three optimisation cycles based on structured subject input, resulting in four protocol versions (FATIG'AGE versions 1–4). Table 2 provides an overview of each protocol version, including the modifications implemented in each cycle. All refinements aimed at improving safety, clarity, ecological validity, and the protocol's ability to induce progressive fatigability within the one-hour timeframe.

Table 2

Overview of the iterative protocol refinements across the different FATIG'AGE protocol versions.

Overview of tasks:	Version 1 (n = 2)	Version 2 (n = 1)	Version 3 (n = 5)	Version 4 (n = 7)
	1. TUG 2. STS + straight walk 3. Stair ascent 4. Slope descent 5. Grass walking + obstacle avoidance 6. Uneven surface walking 7. Slalom + carry task (6kg) 8. Standing still (1min) 9. 4MWT + cognitive dual task 10. Slope ascend 11. Stair descend 12. Fast walking + sit down	1. TUG 2. Incremental STS + straight walk 3. Stair ascent 4. Slope descent 5. Grass walking + obstacle avoidance 6. Uneven surface walking 7. Slalom + carry task (6kg) 8. 4MWT + cognitive dual task 9. Slope ascend 10. Stair descend 11. Fast walking + sit down	1. TUG 2. Incremental STS + straight walk 3. Stair ascent 4. Slope descent 5. Grass walking + obstacle avoidance 6. Uneven surface walking 7. Slalom + carry task (6kg) 8. 4MWT + cognitive dual task 9. Slope ascend 10. Stair descend 11. Fast walking + sit down	1. TUG 2. Incremental STS + straight walk 3. Stair ascent 4. Slope descent 5. Grass walking + obstacle avoidance 6. Uneven surface walking 7. Slalom + carry task (6kg (man) or 4kg (woman)) 8. 4MWT + cognitive dual task 9. Slope ascend 10. Stair descend 11. Fast walking + sit down
Subject input:	- Small cones are difficult to detect while carrying the basket during the slalom	- The arrows on the ground during the slalom task were perceived too directive on the turning radius	- The weight was perceived too high for women (also reflected in RPE scores)	-No need for modifications-
<i>TUG = Timed Up and Go test; STS = Sit-to-Stand task; Incremental STS = Sit-to-Stand task with gradually increasing workload; Slalom + carry task = walking through a slalom course while carrying a basket with weight; 4MWT + cognitive dual task = four-meter walk test while counting backwards; RPE = Rating of Perceived Exertion; The success criteria are defined as the protocol's ability to induce progressive increase in perceived fatigability within the one-hour time frame; X = protocol version did not meet success criteria; OK = protocol version met success criteria. Bold and underlined tasks underwent modifications based on subject input.</i>				

	- The standing still task allowed recovery	- The uneven surface task was too close to the protocol edge to support the subject		
Success criteria:	X	OK	OK	OK
Protocol modifications:	- Replacement of small cones with chest-height poles during the slalom task - Leave out the standing still task - Implement incremental workload during the sit-to-stand task	- Leave out the arrows during the turns of the slalom task - Leave more space besides the irregular surface walking task and the edge of the protocol	- Decrease the weight of the carry task for women from 6kg to 4kg	- <i>Final-</i>
<i>TUG = Timed Up and Go test; STS = Sit-to-Stand task; Incremental STS = Sit-to-Stand task with gradually increasing workload; Slalom + carry task = walking through a slalom course while carrying a basket with weight; 4MWT + cognitive dual task = four-meter walk test while counting backwards; RPE = Rating of Perceived Exertion; The success criteria are defined as the protocol's ability to induce progressive increase in perceived fatigability within the one-hour time frame; X = protocol version did not meet success criteria; OK = protocol version met success criteria. Bold and underlined tasks underwent modifications based on subject input.</i>				

Fatigue progression

Table 3 presents individual-level results indicating whether participants met the predefined success criteria, defined as a progressive increase in perceived fatigability achieved within the one-hour time frame, across the different FATIG'AGE protocol versions.

In the first protocol version, two older adults were tested—one with and one without mobility impairments. The participant with mobility impairments met the criteria, showing a positive regression slope ($B = 0.053$) and high coefficient of determination ($R^2 = 0.953$) over 30:56 min. The participant without mobility impairments did not meet the criteria, displaying a low slope ($B = 0.009$) and $R^2 = 0.226$, with perceived exertion plateauing despite continued task execution until the maximum protocol duration of one hour.

In the second version, one older adult with mobility impairments was evaluated and met the criteria ($B = 0.059$; $R^2 = 0.877$; completion time = 38:25). This subject voluntarily terminated protocol execution due to exhaustion which caused her discomfort to continue.

The third version involved five stroke survivors, all of whom met the criteria (mean $R^2 = 0.936 \pm 0.047$; mean $B = 0.077 \pm 0.049$; mean completion time = 23:24 $\pm$ 8:06). One participant stopped voluntarily due to knee pain, which was stated to be associated with a pre-existing prosthesis and unrelated to the protocol itself.

The fourth version was tested by seven older adults (three with and four without mobility impairments), all meeting the criteria (mean $R^2 = 0.844 \pm 0.104$; mean $B = 0.046 \pm 0.043$; mean completion time = 31:42 $\pm$ 11:44). All terminated upon reaching a Rating of Perceived Exertion (RPE) score $\geq 8/10$.

Table 3

Summary of results on fatigue progression during the iterative refinement of the FATIG'AGE protocol.

Protocol Version:	Group	Slope (B)	R^2	Completion Time (min:sec)
1	OA w. mob. imp.	0.053	0.953	30:56
	OA w/o mob. imp.	0.009	0.226	60:00
2	OA w. mob. imp.	0.059	0.877	38:25
3	Stroke	0.038	0.957	29:21
	Stroke	0.059	0.959	20:11
	Stroke	0.129	0.952	26:02
	Stroke	0.130	0.962	10:50
	Stroke	0.031	0.852	30:35
4	OA w/o mob. imp.	0.024	0.832	29:51
	OA w/o mob. imp.	0.031	0.840	26:37
	OA w. mob. imp.	0.025	0.826	51:41
	OA w/o mob. imp.	0.026	0.643	32:38
	OA w/o mob. imp.	0.040	0.898	24:59
	OA w. mob. imp.	0.142	0.979	15:19
	OA w. mob. imp.	0.033	0.893	40:46
Data is presented for older adults without mobility impairments (OA w/o mob. imp.), stroke survivors, and older adults with mobility impairments (OA w. mob. imp.); Each row represents one participant; B = unstandardized regression slope; R^2 = the coefficient of determination.				

Safety

Across all FATIG'AGE protocol versions, all participants reported that the protocol felt safe. Participants consistently indicated that they felt secure during execution, with statements such as *"I had no fear"* and

"I did not feel unsafe." This sense of safety was partly attributed to the continuous presence of the researcher alongside the participant during protocol execution, as reflected in comments such as *"it was good that you were always beside me."*

As task adaptations within FATIG'AGE were permitted to ensure safety, two individuals modified the slalom task which involved carrying a weighted basket. One older woman with mobility impairments reduced the basket weight from 7 kg to 2 kg because she was precautious about her balance while walking with her ankle orthosis. Additionally, one stroke survivor was unable to carry a basket due to the constant use of a walking cane, and therefore executed the slalom without carrying the basket.

Ecological validity

All fifteen participants reported that the tasks included in the FATIG'AGE protocol were representative of activities encountered in daily life and did not identify any tasks as unfamiliar or irrelevant to their routines (e.g. *"I don't see tasks that I never do"*). Participants related the protocol tasks to both indoor activities, such as household chores, and outdoor mobility, such as negotiating changes in level (e.g. *"like when you step up the sidewalk"*).

Description of the final FATIG'AGE protocol

Figure 1 provides a visual overview of the finalized FATIG'AGE protocol after the iterative modifications during the optimisation phase took place. All tasks are performed continuously, in a fixed order, at a self-selected pace, and in a manner that reflects how participants would typically perform these activities in daily life. Usual walking speed is defined as the participant's normal everyday pace, excluding both hurried and overly leisurely walking.

The final protocol comprises the following tasks, executed sequentially:

1. Timed Up and Go (TUG): rise from a chair without armrests (height = 47 cm), walk 3 m, perform a 180° turn with both feet behind a taped line, walk back, and sit down as quickly as possible [29].
2. Incremental sit-to-stand (STS) followed by straight walking: stand from a chair and walk 7 m forward at a usual walking pace. This task incorporates an incremental workload principle, whereby the number of sit-to-stand repetitions increases by one with each protocol round (e.g., in round 3, 3 repetitions of sit-to-stand before continuing).
3. Stair ascent: ascend five standard stairs (height = 18 cm, width = 90 cm, depth = 28 cm) at a usual walking pace; handrails (height = 90 cm) at both sides may be used.
4. Slope descent: descend a 10° slope (5.2 m in length) at a usual pace; handrails (height = 90 cm) at both sides may be used.
5. Grass walking with obstacle avoidance: walk 5 m at a usual pace over an artificial grass surface (2 cm leaf length [30]) while stepping over three obstacles. An obstacle consists of two side-by-side

half-round, foam bolsters (height = 10 cm, length = 20 cm, width = 50 cm) which are spaced out equally across the 5 m grass surface.

6. Uneven surface walking: walk 4 m at a usual pace over an uneven surface created by shock-absorbing 2 x 8 relief, polyurethane panels (length = 50 cm, width = 50 cm, max. vertical variation = $\pm 4,5$ cm) (Sensory floor, Artzt Thepro, Germany), which has been shown to influence gait stability and adaptability [31,32].
7. Slalom with carry task: lift a basket (6 kg for men & 4 kg for women; height = 24 cm, length = 49 cm, width = 36 cm) using both hands from a small stool (height = 45 cm), and perform, at a usual pace, four slalom turns around poles (height = 120 cm) spaced 2 m apart, walk back through the centre of the slalom course, and place the basket back down. The load represents the weight of a full basket of laundry.
8. Four-meter walk test (4MWT) with cognitive dual task: walks 4 m at a usual pace while counting backwards aloud from a randomly provided three-digit number (derived from www.random.org) [33]. Task difficulty (counting by sevens, fives, or threes) is individually titrated beforehand to achieve approximately 80% accuracy [34].
9. Slope ascent: ascend the same 10° slope at a usual pace; handrails (height = 90 cm) at both sides may be used.
10. Stair descent: descend the same five standard stairs at a usual pace; handrails (height = 90 cm) at both sides may be used.
11. Fast walking followed by sitting down: walks 7 m back to the chair as fast as possible and sit down.

This fixed sequence of activities is repeated continuously until one of the predefined stopping criteria are met (i.e., an RPE score equal to or greater than 8 out of 10, a maximum protocol duration of one hour, or voluntary termination). Individual task adjustments are permitted when participants are unable to safely or confidently perform specific tasks (e.g., participants using a walking cane complete the slalom task without carrying the basket). Borg CR10 scales are present after each task to promote correct RPE score anchoring (format: A3; font: Aptos 33; black lettering on a white background). For safety reasons, anti-slip strips were applied to both the stair and slope surfaces to minimise slipping risk. A floorplan with the detailed task positions and dimensions can be found on Figure S1 in the Supplementary Information.

Results on the validation of the FATIG'AGE protocol

The finalized version of the FATIG'AGE protocol was evaluated in 30 participants, all of whom demonstrated a progressive increase in perceived exertion throughout protocol execution (Fig. 2). Across participants, fatigue progression was characterised by a positive regression slope and a high proportion of explained variance (mean $B = 0.148 \pm 0.176$; mean $R^2 = 0.911 \pm 0.070$). Fatigue was induced well within the predefined one-hour timeframe, with a mean protocol duration of $23:48 \pm 13:22$ minutes (Table 4).

On average, participants executed 90.4 ± 65.0 (range: 8–278) individual tasks and completed 8.2 ± 5.9 (range: 0.7–25.3) protocol rounds before terminating execution. One stroke survivor reached the

maximum protocol duration of one hour and was stopped according to the predefined stopping criteria. Although this participant did not reach the RPE stopping threshold, a clear progressive increase in perceived exertion was observed ($B = 0.056$, $R^2 = 0.857$), with a final RPE score of 7/10 after completing 83 tasks and 7.5 protocol rounds. Two participants chose to voluntarily stop protocol execution: one older adult without mobility impairments due to muscle cramps, and one older adult with sarcopenia due to respiratory difficulties. These participants still reached RPE scores of 7 and 6, respectively. All remaining 27 participants continued execution until reaching the predefined RPE cut-off score (≥ 8).

As task adaptations were permitted within the FATIG'AGE protocol to ensure safe execution, four participants (two with stroke and two with sarcopenia) completed the slalom task without carrying the weighted basket, as they required continuous walking support (walking cane users). No task adaptations were required for the remaining 26 participants.

Notably, the older adult without mobility impairments who did not meet the success criteria during execution of the first version of the protocol during the optimisation phase (see Section 'Findings during the optimisation phase – Fatigue progression'), was reinvited to execute the final protocol version and now demonstrated a clear progressive increase in perceived exertion ($B = 0.096$, $R^2 = 0.964$) within the one-hour time limit (protocol duration: 17:30 minutes).

Linear mixed-effects modelling revealed a significant group $\times$ protocol exposure interaction ($p = 0.029$), indicating that the rate of increase in perceived exertion with cumulative task exposure differed between groups. A significant main effect of protocol exposure ($p < 0.001$) and a non-significant main effect of group ($p = 0.217$) were also observed, though both are of limited interpretive value in the presence of this interaction.

Further explorative group-level comparisons showed that the slope of RPE increase differed significantly between older adults without mobility impairments and those with sarcopenia ($p < 0.001$). The mean slope of RPE increase was lowest in older adults without mobility impairments ($B = 0.048 \pm 0.032$), intermediate in stroke survivors ($B = 0.160 \pm 0.238$), and highest in older adults with sarcopenia ($B = 0.238 \pm 0.150$). In addition, the number of executed protocol rounds was significantly higher in older adults without mobility impairments compared to both clinical groups ($p < 0.001$) (Table 4).

Table 4

Summary of results on fatigue progression during the validation of the final FATIG'AGE protocol.

Group	Slope (B)	R ²	Completion Time (min:sec)	NET	Amount of protocol rounds
OA w/o mob. imp.	0.096	0.964	17:30	69	6.3
	0.039	0.785	33:14	165	15.0
	0.034	0.919	28:59	167	15.2
	0.025	0.952	47:51	278	25.3
	0.041	0.932	34:51	146	13.3
	0.116	0.948	13:16	68	6.2
	0.039	0.937	31:13	157	14.3
	0.037	0.867	27:04	146	13.3
	0.027	0.901	36:16	212	19.3
	0.024	0.697	26:11	162	14.7
Stroke	0.115	0.964	14:26	63	5.7
	0.083	0.975	16:47	95	8.6
	0.055	0.851	27:30	88	8.0
	0.101	0.962	18:37	85	7.7
	0.118	0.951	20:01	58	5.3
	0.833	0.947	05:29	8	0.7
	0.050	0.934	42:41	145	13.2
	0.093	0.961	16:00	81	7.4
	0.097	0.732	17:10	51	4.6
	0.056	0.857	60:00	83	7.5
OA w. sarcopenia	0.145	0.961	10:48	54	4.9
	0.275	0.921	13:09	23	2.1
	0.111	0.829	07:53	22	2.0

**# Significant differences between groups $p < 0.001$; Data is presented for older adults without mobility impairments (OA w/o mob. imp.), stroke survivors, and older adults with sarcopenia (OA w. sarcopenia.); B = unstandardized regression slope; R² = the coefficient of determination; NET = Number of Executed Tasks; Mean values are followed by the standard deviations ($\pm$).*

Group	Slope (B)	R ²	Completion Time (min:sec)	NET	Amount of protocol rounds
	0.410	0.953	16:22	21	1.9
	0.079	0.945	40:30	80	7.3
	0.180	0.955	13:17	41	3.7
	0.125	0.888	39:58	62	5.6
	0.453	0.944	09:20	17	1.5
	0.458	0.951	09:43	19	1.7
	0.139	0.934	17:46	47	4.3
Mean (all groups):	0.148 ± 0.176	0.911 ± 0.070	23:48 ± 13:22	90.4 ± 65.0	8.2 ± 5.9
Mean (OA w/o mob. imp.):	0.048 ± 0.032*	0.890 ± 0.086	29:39 ± 9:44	157.0 ± 61.2*[#]	14.3 ± 5.6*[#]
Mean (stroke):	0.160 ± 0.238	0.913 ± 0.077	23:52 ± 15:59	75.7 ± 35.2[#]	6.9 ± 3.2[#]
Mean (OA w. sarcopenia):	0.238 ± 0.150*	0.928 ± 0.041	17:52 ± 12:11	38.6 ± 21.7*	3.5 ± 2.0*
[#] Significant differences between groups $p < 0.001$; Data is presented for older adults without mobility impairments (OA w/o mob. imp.), stroke survivors, and older adults with sarcopenia (OA w. sarcopenia.); B = unstandardized regression slope; R ² = the coefficient of determination; NET = Number of Executed Tasks; Mean values are followed by the standard deviations (±).					

Discussion

In this study, we implemented a human-centred, iterative approach to develop and validate FATIG'AGE, a standardized, multi-task protocol designed to assess fatigability in older adults and clinical populations with varying functional abilities. By integrating demanding activities of daily living, the protocol aims to capture fatigability under ecologically relevant, real-world-like conditions that are central to healthy ageing. Overall, FATIG'AGE was found to be safe, as indicated by the absence of falls and by participant feedback, and the tasks were perceived as representative of everyday activities. Importantly, the protocol consistently induced a progressive increase in perceived fatigability across individuals with a broad range of functional capabilities.

A major strength of this study lies in the continuous involvement of participants throughout the entire development process, from initial focus groups informing task selection [20,21], through iterative testing and refinement, to the final validation in the target populations. Such subject involvement is known to enhance the relevance, credibility, and applicability of healthcare research [35]. Beyond improving safety

and clarity, subject feedback directly informed several key protocol adaptations, including the introduction of an incremental workload principle, removal of a standing still task, and sex-specific adjustment of carried load. The incremental workload approach was selected to align with established fatigue-induction paradigms, such as progressively increasing walking incline [36] or cycling workload [37]. The standing still task was removed because, although potentially challenging for certain populations (e.g. balance impairments in people with osteoarthritis [38]), it allowed partial recovery rather than promoting cumulative fatigability. Sex-specific load adjustments are supported by evidence demonstrating differences in acceptable manual handling loads between older men and women [39]. While individual strength capacities may vary independently of sex, this differentiation provides a pragmatic starting point for a task that remains adaptable to individual abilities. Importantly, subject involvement continued beyond meeting the predefined success criteria, ensuring that the final protocol was not only feasible but also aligned with subjects' real-life experiences and needs.

During protocol validation, the majority of participants (27 out of 30) completed the protocol until reaching the predefined RPE stopping score, corresponding to exceeding severe perceived exertion. One stroke survivor reached the maximum protocol duration of 60 minutes, likely due to markedly reduced execution speed associated with hemiplegia [40]. Despite being stopped by the time limit rather than volitional exhaustion, this participant still achieved severe exertion after completing 83 tasks across 7.5 rounds. Two older adults terminated the protocol voluntarily due to physical complaints but nonetheless progressively reached (severe) perceived exertion prior to stopping. Such early termination is not unexpected in older populations, given the high prevalence of reduced functional capacity and comorbidities [41,42], which may limit tolerance to prolonged workloads. Overall, these findings demonstrate that the FATIG'AGE protocol is feasible and reliable for inducing perceived fatigability across a heterogeneous population.

To our knowledge, FATIG'AGE is the first standardized fatigability protocol that integrates a broad range of real-world functional tasks and is applicable across multiple clinical populations. Existing fatigability assessments typically rely on isolated or single-modality tasks, such as overground or treadmill walking performed over a fixed distance or time [14,18]. While these tests are reliable and valid, they provide limited insight into fatigability as experienced during everyday activities, where fatigue is associated with reduced quality of ADL performance, dependence, and life-space mobility [43,44], all of which negatively impact healthy ageing. Although previous work has acknowledged the value of incorporating functional tasks into assessment protocols, such as multi-context gait assessments [45] and obstacle-based mobility courses [46,47], these approaches target mobility outcomes and involve single task executions rather than the repeated, cumulative performance required to elicit progressive fatigability.

Within the WHO framework for measuring Healthy Ageing [48], executing the FATIG'AGE protocol can be conceptualised as a stress test to evaluate 'vitality capacity' with respect to fatigability during daily life. Stress tests are critical for revealing reserve capacity and are commonly operationalised in fatigability assessments through maximal walking tasks (e.g. "as fast" or "as far" as possible) [14]. In contrast, the stress component of FATIG'AGE emerges from the sustained and cumulative execution of diverse

everyday tasks until high levels of exertion are reached, thereby more closely mirroring the real-life physical demands. This approach enables the capture of individual trajectories of fatigability capacity across the course of the protocol. Such trajectory-based assessments are particularly relevant in the context of Healthy ageing, as early deviations from expected capacity trajectories are central to inform preventive health services aimed at mitigating functional decline [2]. As fatigability has been proposed as an early indicator of declining functional ability and the onset of disease burden [49,50], the FATIG'AGE protocol may represent an ecologically valid screening tool for identifying ageing-related functional vulnerability. In line with this, given the growing need for simple and reliable biomarkers of Healthy ageing [51], we explored whether FATIG'AGE-derived fatigability trajectories could discriminate between individuals with varying physical capacities at the group level. We found that the rate of increase in perceived exertion was significantly higher in older adults with sarcopenia compared to those without mobility impairments, and that the total number of executed tasks was significantly higher in older adults without mobility impairments compared to both older adults with sarcopenia and stroke survivors. While more supporting evidence is needed, even with the study's relatively small sample size, visualisation and modelling of perceived exertion progression across FATIG'AGE already indicate discriminative potential across groups with varying physical capacities. This is consistent with previous findings of greater fatigability in older cancer survivors compared with healthy controls [52]. Establishing population-level reference values in future studies would enable individual fatigability trajectories to be interpreted relative to expected ageing/clinical patterns and could inform the need for capacity-enhancing interventions.

Beyond assessment, the FATIG'AGE protocol may provide a valuable framework for evaluating interventions aimed at reducing fatigability in daily life. One such intervention is the use of assistive LLEs, which have shown promising effects on fatigability-related outcomes, including energy cost [53–55], walking distance [56], and walking speed [55–57]. However, evaluation of LLEs remains largely restricted to single-task laboratory assessments, most commonly level walking [58], limiting translation to real-world functioning and comparison across devices and populations. As a result, research and industry have repeatedly emphasised the need for a standardised, reproducible evaluation framework that allows comparison of LLEs under comparable conditions [59,60]. FATIG'AGE may therefore offer a standardized and reproducible evaluation protocol that better captures the functional benefits of LLEs under realistic conditions, thereby supporting more meaningful comparisons and informing device development.

Another promising application of the FATIG'AGE protocol lies in the development of fatigue prediction models for real-world applications. Combining protocol execution with multimodal sensor data (e.g. inertial measurement units, electromyography, electrocardiogram, galvanic skin response, respiratory rate) may enable the development of algorithms capable of detecting and predicting perceived exertion based on objective physiological signals [19,61,62], which could further support personalised interventions for Healthy ageing.

Several limitations of this study should be acknowledged. The relatively small sample size limits the strength of between-group comparisons in fatigability metrics. While the protocol consistently induced progressive fatigability across groups, larger cross-sectional cohorts are required to robustly evaluate its discriminatory capacity. Additionally, because FATIG'AGE incorporates a range of functional daily-life tasks, individuals who were fully dependent on a walker or mobility scooter were excluded. As such, the protocol may not be applicable to this subgroup, which nevertheless represents a substantial proportion of the older population (11.6% using a walker and 2.3% using a mobility scooter in the United States [63]). Future adaptations may be needed to extend applicability to individuals with more severe mobility limitations.

In conclusion, FATIG'AGE represents a safe standardized, ecologically valid, multi-task protocol for assessing fatigability across older adults and clinical populations. Situated within the WHO Healthy Ageing framework, the protocol provides a structured approach to evaluate fatigability as a key component of vitality capacity during everyday functioning. FATIG'AGE offers a practical tool for research and clinical contexts aiming to characterise individual fatigability profiles or to evaluate interventions targeting fatigue and functional resilience in daily life.

Methods

Ethical approval was obtained from the University Hospital Brussels Ethics Committee (BUN: 1432024000164), and the study was preregistered on ClinicalTrials.gov (NTC Number: NCT06513377; first registered on 25/06/2024). Participants were purposively recruited via the University Hospital Brussels (Departments of Geriatrics and Neurology) and through the research group's network. All participants received detailed verbal and written study information and provided written informed consent prior to participation. All study procedures were conducted in accordance with the current good clinical practice (GCP) guidelines and ethical principles outlined in the Declaration of Helsinki.

Development of the FATIG'AGE protocol

The FATIG'AGE protocol was developed using a human-centred, co-creation approach that involved participants throughout the entire development process. An initial theoretical version (*FATIG'AGE version 1*) was first established as the starting point for further optimisation and was informed by input from the target population. The protocol was then refined through an iterative optimisation phase, during which successive protocol versions were tested by different subjects of interest. After each testing round, structured subject feedback was collected and informed targeted protocol modifications, resulting in updated versions. This iterative process continued until a finalised FATIG'AGE version was achieved that was safe, realistic, and capable of inducing progressive fatigability within a predefined one-hour time frame.

FATIG'AGE version 1

The first version of the FATIG'AGE protocol was informed by prior focus group discussions, in which older adults and stroke survivors with mobility limitations identified everyday activities they perceived as

fatiguing and/or challenging [20,21]. Across both groups, these activities included stair negotiation, walking on inclines, sit-to-stand transitions and crouching, prolonged standing, reaching and lifting objects, carrying loads, longer-distance walking, uneven surface negotiation, and tasks requiring simultaneous physical and cognitive engagement. These subject-reported activities formed the conceptual basis of the protocol and were translated into standardized laboratory-based tasks, resulting in the first draft of the FATIG'AGE protocol (see summary of included tasks in Table 2).

Based on this list of activities, we created the FATIG'AGE protocol as a fixed, continuous sequence of functional tasks designed to reflect the cumulative demands of daily-life mobility. In doing so, it captures the five key components of real-world walking: variation in walking speed, incline and stair negotiation, different path geometries, varying walking surfaces, and cognitive demand [45]. It also takes into account the neural control model of functional walking, which states that purposeful locomotion consists of stepping, balance control and walking adaptability [64].

The goal of the FATIG'AGE protocol was to induce a progressive increase in perceived fatigability within a predefined one-hour time frame. The maximum duration of one hour was selected to accommodate feasibility in clinical and research settings, given the time-intensive and technically demanding nature of such assessments. Progressive fatigue induction further allows evaluation of fatigue development across a series of daily-life activities, as well as the potential effects of relevant interventions.

Accordingly, perceived fatigability was assessed throughout the protocol using the RPE, which was verbally reported after completion of each individual task. Perceived fatigability was selected as the primary outcome measure because it captures the integrated physical and cognitive demands of task performance within a single metric [19]. To support standardized assessment, CR10 Borg scales [65], ranging from 0 (no exertion) to 10 (maximal exertion), were displayed at each task location. Assessing RPE after each task provides fixed temporal reference points [61,62], enabling comparison of individual fatigue progression rates across participants with different execution speeds.

Participants were instructed to perform the protocol continuously until one of the following stopping criteria was met: (1) an RPE score equal or greater than 8 out of 10, (2) a maximum protocol duration of one hour, or (3) voluntary termination by the participant. The RPE threshold of $\geq 8/10$ was based on prior studies using a cutoff of 17/20 on the original Borg scale [61,62], exceeding “very hard” exertion [65]. For safety reasons, particularly in clinical populations with an increased fall risk [66], the protocol was deliberately not continued until maximal exertion (i.e., RPE score = 10/10). Voluntary termination accounts for individual factors (e.g. pain or discomfort) that may prevent participants from continuing despite not reaching the predefined RPE threshold.

To ensure applicability across a wide range of movement laboratories, the FATIG'AGE protocol dimensions (length: 10 m, width: 7 m, height: 1.8 m; see Figure S1 in Supplementary Information) were based on the GAMMA recommendations for standardized clinical movement analysis laboratories [67]. According to these recommendations, optimal facility requirements for walking assessments include a room length of 16 m, a width of 8 m, and a height of 3.5 m [67]. Our protocol length of 10 m was selected

to fit within standard laboratory spaces while allowing sufficient space for technical setups (e.g. desks, computers, and measurement equipment). The protocol height of 1.8 m results from the inclusion of stairs and a ramp (height: 0.90 m) with handrails (height: 0.90 m), meaning that laboratories adhering to the recommended ceiling height of 3.5 m retain approximately 2.6 m of clearance for people to navigate, comfortably exceeding the average height of adults worldwide [68]. Thus, gait laboratories established according to GAMMA recommendations should be able to accommodate the FATIG'AGE setup without major structural modifications.

All walking tasks within the protocol exceed the minimal distance of 3.5 m required to capture at least two consecutive strides per leg [45], with walking distances ranging from 4 m (i.e., uneven surface and cognitive dual-task walking) to 7 m (i.e., level walking at usual and high pace).

Furthermore, the FATIG'AGE protocol was designed to allow evaluation of multiple fatigability-related performance metrics [14], including execution time, number of executed tasks, and the slope of perceived exertion over time. These metrics enable comparison of fatigue progression between individuals and between interventions, supporting future applications of the protocol in both clinical and research contexts.

Optimisation phase: towards the final FATIG'AGE protocol

Study sample

To support the iterative refinement of the FATIG'AGE protocol fifteen participants were recruited to take part in the iterative optimization phase: five older adults without mobility impairments, five independent chronic stroke survivors, and five older adults with mobility impairments. Six subjects (three stroke survivors and three older adults with mobility impairments) were reinvited from the prior focus group discussions that informed the first version of FATIG'AGE [20,21], supporting the step-by-step human-centred development process. Participants were selected to capture a diverse range of functional abilities and clinically relevant mobility profiles. To define whether subjects suffered from mobility impairments we followed the International Classification of Functioning, Disability and Health (ICF) framework [69]. In addition to the group-specific inclusion and exclusion criteria (Supplementary Information - Table S1), all participants were required to be able to navigate their life-space environment independently, with or without mobility aids. However, individuals fully dependent on wheeled walkers or mobility scooters were excluded, as these individuals are unable to safely navigate the challenging ADL that were recognized by the community-dwelling population (e.g., stairs, crossing obstacles and uneven surfaces). No exclusions were made based on a low cognitive test score, however participants needed to be capable of understanding instructions and providing informed consent.

Subject testing

An iterative, co-creation approach was implemented to optimize the FATIG'AGE protocol through subject testing. Participants were invited to perform the most recent version of the protocol, in no predefined group order, and to provide structured feedback. If the success criteria were not met (i.e., induction of

progressive fatigability within one hour) or if the protocol version was deemed suboptimal in terms of realism, safety or clarity, refinements on the FATIG'AGE protocol were made. This process was repeated until a finalized and reliable protocol was achieved.

At the start of each measurement session, participants received standardized instructions, a demonstration of all tasks, and an opportunity to familiarize themselves with the protocol to ensure they felt comfortable and safe. When introducing the Borg CR10 scale, participants were instructed to report their 'overall' levels of exhaustion, and were informed that changes in perceived exertion are expected to occur during protocol execution, so that open and honest communication on this was very important. To reduce performance-related bias, the stopping criteria were not disclosed, and no external encouragement was provided during task execution.

During the protocol execution, RPE was reported verbally by participants in real time using the Borg CR10 scale presented after each activity, and total protocol duration, including execution time and number of executed tasks, was recorded. A researcher remained alongside each participant to ensure safety, provide assistance when necessary (primarily for maintaining balance; no physical support), and remind participants of the task order if needed. If a participant did not spontaneously report their RPE after a task, they were prompted to do so after the subsequent activity without interrupting task execution.

Following completion of the protocol, participants provided structured, verbal feedback regarding task realism (e.g., representativeness of daily-life activities), perceived fatigability (intensity and suggestions to increase or decrease task challenge), safety, and potential general improvements.

Data analysis

Fatigue progression at the individual level was assessed using separate linear regression models for each participant, with RPE as the dependent variable and protocol exposure, defined as the cumulative Number of Executed Tasks (NET), as the independent variable. NET was selected as the exposure variable to account for inter-individual differences in execution speed and protocol duration. For each participant, the unstandardized regression slope (B) and the coefficient of determination (R^2) were extracted. The slope reflects the rate of increase in perceived exertion, while the R^2 value represents the proportion of variance in RPE explained by the fitted linear relationship with protocol exposure, providing an indication of how closely the participant's RPE followed a linear increase over time. Total protocol duration and number of completed protocol rounds were also analysed.

Data analysis was performed using IBM SPSS Statistics (29.0.2.0).

Validation Phase using the final FATIG'AGE protocol

Following completion of the iterative optimisation phase, the final human-centred version of the FATIG'AGE protocol was established. The study subsequently progressed to a validation phase, aimed at evaluating whether the final protocol could consistently induce progressive perceived fatigability across individuals with a broad range of functional capabilities.

Study sample

Thirty participants were recruited to validate the finalized FATIG'AGE protocol, consisting of 10 older adults without mobility impairments, 10 chronic stroke survivors, and 10 older adults with (probable) sarcopenia. Participants from the optimization phase were reinvited if they met the eligibility criteria. These groups were selected to provide a focused, clinically well-defined validation sample, while retaining a reference group of older adults without mobility impairments. Group-specific inclusion and exclusion criteria are listed in Supplementary Information - Table S1. Stroke survivors with Functional Ambulation Categories (FAC) levels 3 (dependent on verbal supervision or presence of another person during walking) to 4 (able to walk independently on level surfaces) were selected based on the prevalence and functional impact of motor impairments post-stroke [70,71]. Older adults with probable sarcopenia were selected according to the guidelines of the European Working Group on Sarcopenia in Older People (EWGSOP) based on reduced muscle strength, reflecting clinical relevance [72]. Specifically, subjects were required to score above the cut-off for lower-limb strength (i.e., five-times sit-to-stand test [72]), and below the cut-off for maximal handgrip strength of the dominant hand (cut-off values established by the sarcopenia guidelines of the Belgian Society for Gerontology and Geriatrics [73]). All participants were required to navigate their life-space independently; those fully dependent on wheeled walkers or mobility scooters were excluded. A low cognitive test score was not an exclusion criteria, as long as the participants were able to understand instructions and provide informed consent.

Subject testing

All participants performed the finalized FATIG'AGE protocol following the same standardized procedures used during the optimisation phase (see Section: 'Optimisation phase: towards the final FATIG'AGE protocol – Subject testing'). RPE was recorded at baseline in seated position and after completion of each task. Protocol execution was terminated when participants reported two consecutive RPE scores equal to or greater than 8, after one-hour or if subjects stopped voluntarily.

The primary aim of the validation phase was to evaluate whether all subjects, regardless of their functional capabilities, were able to meet the predefined success criteria of experiencing a progressive increase in perceived fatigability within the one-hour time frame.

Data analysis

Fatigue progression was analysed using the same individual-level analysis used in the optimisation phase (see Section 'Optimisation phase: towards the final FATIG'AGE protocol – Data analysis').

To evaluate whether the FATIG'AGE protocol had a significant effect on the perceived exertion scores, changes over the course of the protocol were analysed using a linear mixed-effects model, including all participants. RPE was specified as the dependent variable, with protocol exposure expressed as the NET included as a continuous fixed effect. Participant identity was included as a random intercept to account for repeated measurements within individuals and inter-individual differences in baseline perceived exertion. In addition, participant-specific random slopes for NET were included to accommodate inter-

individual variability in fatigue progression, which improved model fit as indicated by a lower Akaike Information Criterion. Unequal numbers of observations per participant were handled naturally by the model due to variable protocol duration. Model assumptions (linearity, homoscedasticity, normality of residuals) were evaluated via residual plots.

Given the need for reliable healthy ageing biomarkers that can identify healthy and accelerated ageing [51], an explorative analysis was performed to evaluate whether the performance metrics captured during the FATIG'AGE protocol were able to discriminate between the different population groups in our study. Within the mixed-effect model, 'Group' and the 'Group x NET' interactions were included to assess differences in fatigue progression across groups. Furthermore, groups were compared based on their regression slopes (B), R^2 , completion time, NET, and total rounds completed. Normality was tested using the Shapiro-Wilk test. For normally distributed variables, one-way ANOVAs were performed with Group as the factor. If the ANOVA was significant and homogeneity of variances was met, Tukey's post hoc tests were used for pairwise comparisons. For variables violating normality assumptions, Kruskal-Wallis tests were applied, followed by pairwise Dunn's tests with Bonferroni correction.

To visualise fatigue progression and inter-individual variability, raw perceived exertion trajectories were plotted for each participant alongside group-level linear mixed-effects model predictions. For visualisation purposes, separate models were fitted within each group, with task number as a continuous predictor and participant-specific random intercepts and slopes. Subject-specific predicted trajectories were summarised by their median to represent a typical participant within each group, providing robustness against extreme values. Between-participant variability was shown using the interquartile range (25th–75th percentile) of the subject-specific predictions. To avoid extrapolation beyond supported data, predictions were displayed only up to the highest task number for which data from at least three participants were available.

Data analysis was performed using IBM SPSS Statistics (29.0.2.0).

Declarations

Competing Interests Statement

The authors declare no competing interests.

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Reviewing and editing of the manuscript were performed by R.C., J.C., M.F., S.D.R., S.L., T.V., B.F., E.S., and D.B. All authors reviewed and approved the manuscript.

Author Contribution

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Data Availability

The dataset collected and analysed in the current study is not publicly available due to ethical restrictions and ongoing studies within the research consortium. Data may be made available upon reasonable request to the corresponding author, subject to approval by the Medical Ethics Committee of the University Hospital Brussels and in accordance with applicable ethical and data protection regulations.

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Figures

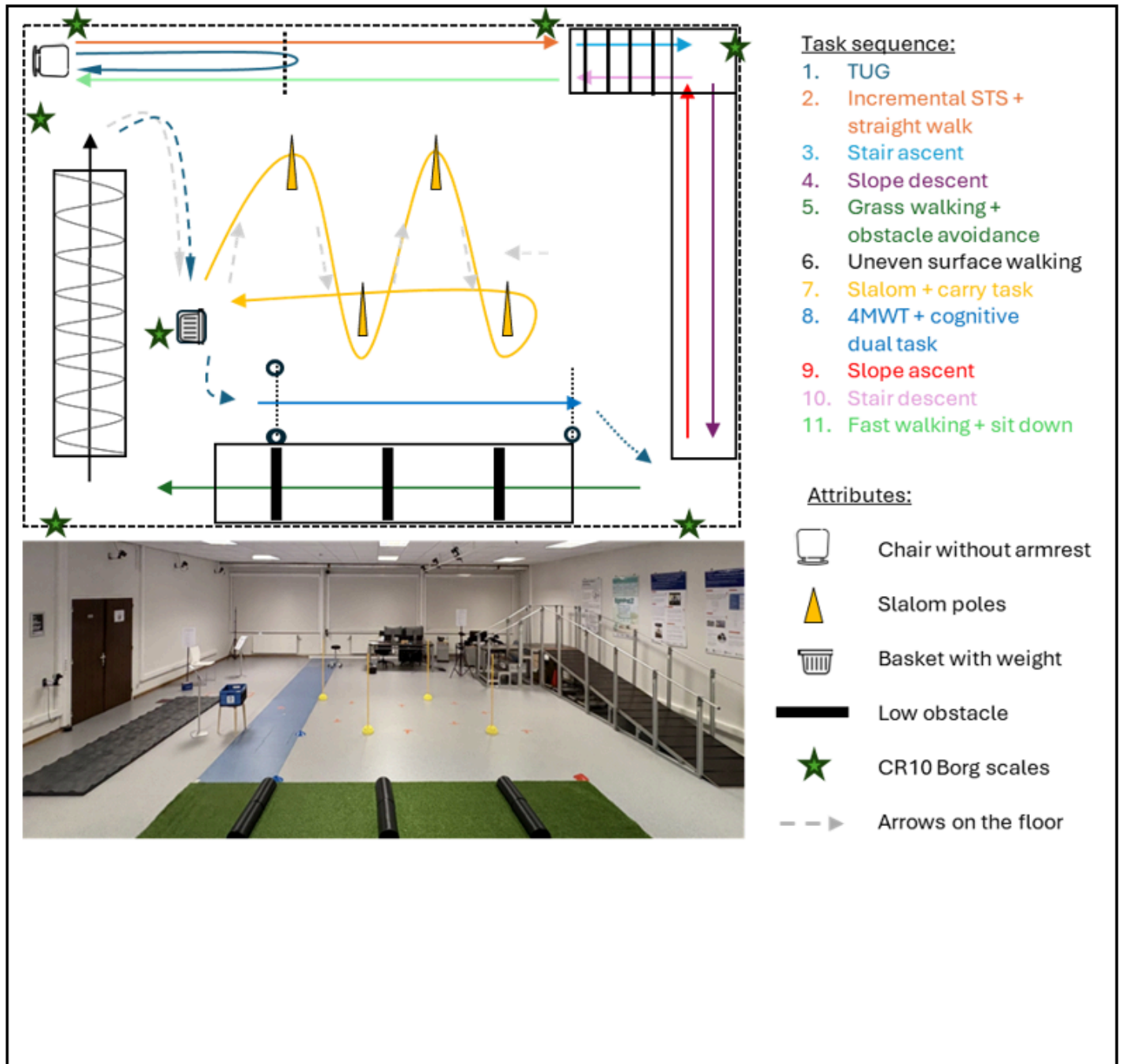


Figure 1

Visual representation of the final FATIG'AGE protocol. Dashed blue arrows in the schematic represent transitions between individual tasks. TUG = Timed Up and Go test; Incremental STS = Sit-to-Stand task with gradually increasing workload; Slalom + carry task = walking through a slalom course while carrying a basket with weight; 4MWT + cognitive dual task = four-meter walk test while counting backwards.

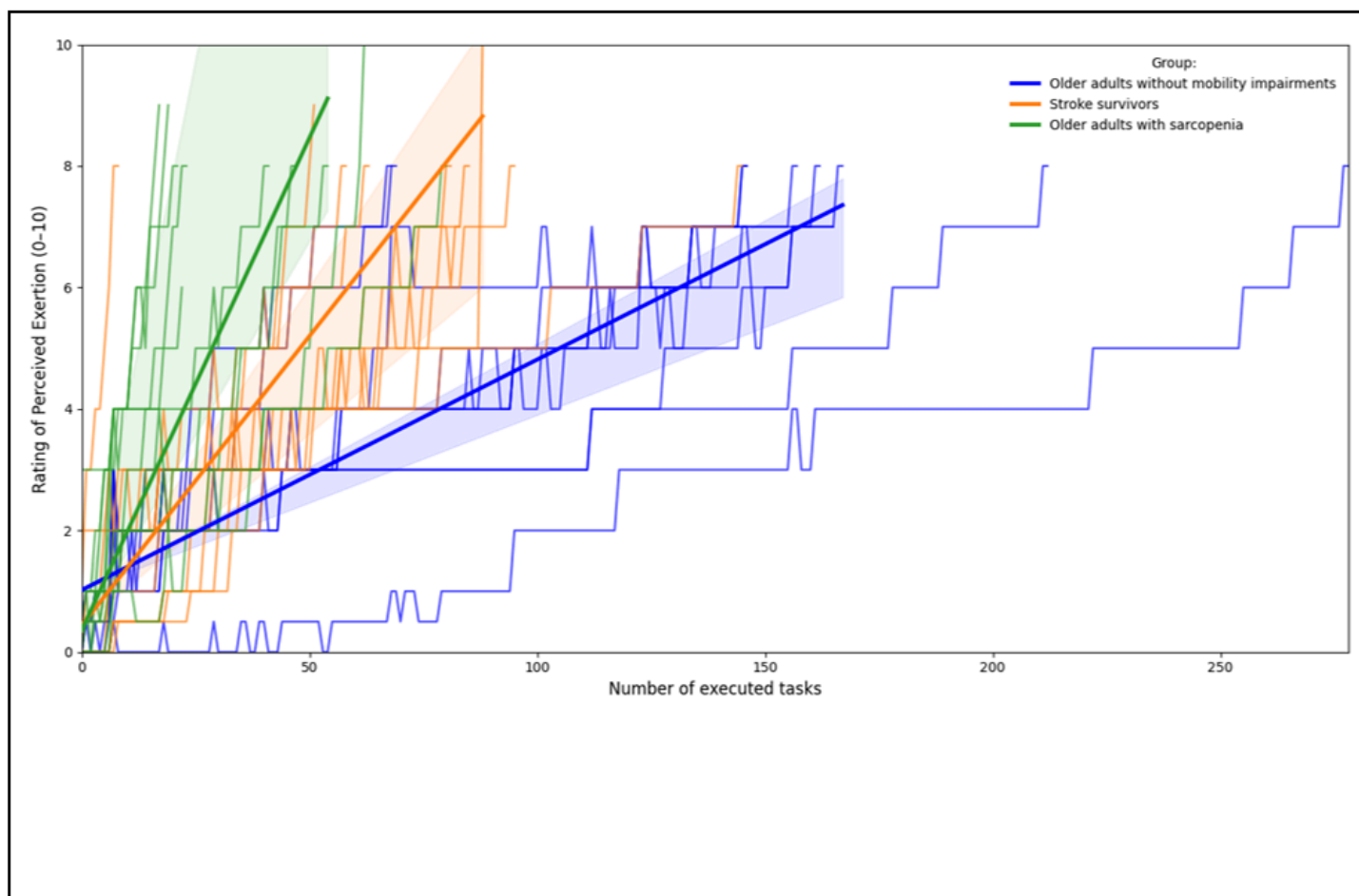


Figure 2

Fatigue progression across the FATIG'AGE protocol for each participant and by group during the validation phase. Thin lines represent individual perceived exertion trajectories across the executed tasks for each participant. Thick lines show the median predicted fatigue trajectory representing a typical participant within each group, derived from subject-specific model predictions. Shaded areas indicate the interquartile range of the subject-specific predictions (25th–75th percentile), reflecting between-participant variability. Predictions are shown only up to the highest task number supported by data from at least three participants.

Supplementary Files

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