



HAL
open science

Are females getting more fatigable as they age?

Mathilde Fiona Bertrand, Giorgio Varesco, Guillaume Y Millet, Léonard Féasson, Thomas Lapole, Vianney Rozand

► **To cite this version:**

Mathilde Fiona Bertrand, Giorgio Varesco, Guillaume Y Millet, Léonard Féasson, Thomas Lapole, et al.. Are females getting more fatigable as they age?. *European Journal of Applied Physiology*, 2024, 10.1007/s00421-024-05637-6 . hal-04843916

HAL Id: hal-04843916

<https://hal.science/hal-04843916v1>

Submitted on 17 Dec 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Copyright



Are females getting more fatigable as they age?

Mathilde Fiona Bertrand¹ · Giorgio Varesco^{2,3,4} · Guillaume Y. Millet^{1,5} · Léonard Féasson^{1,6} · Thomas Lapole^{1,5} · Vianney Rozand⁷

Received: 1 August 2024 / Accepted: 4 October 2024

© The Author(s), under exclusive licence to Springer-Verlag GmbH Germany, part of Springer Nature 2024

Abstract

Purpose The aim of this study was to compare performance fatigability between young ($n = 13$; 18–35 yr.; 23.5 ± 3.3 yr.), old ($n = 13$; 60–79 yr.; 68.2 ± 4.3 yr.), and very old ($n = 11$; ≥ 80 yr.; 85.6 ± 1.8 yr.) females during single-limb isometric (ISO) vs. isokinetic concentric (CON) vs. cycling (BIKE) fatiguing tasks.

Methods Participants randomly performed three incremental fatiguing tasks where increments were set as percentage of body weight to better reflect the daily life: (1) ISO and (2) CON consisted of stages of 75 contractions (120 s, 0.8 s on/0.8 s off) on an isokinetic dynamometer and (3) BIKE consisted of stages of 120 s at 37.5 rpm with similar duty cycle. Knee extensors maximal force, voluntary activation and potentiated twitch amplitude were measured at baseline, after each stage and at exhaustion.

Results Compared to young, exercise performance was 20% and 53% lower in old and very old females in ISO, 46% and 76% lower in CON and 32% and 62% lower in BIKE (all $p < 0.01$). For a given workload (*i.e.* common stages), performance fatigability (*i.e.* force loss) was greater for very old compared to young females in CON only ($p = 0.018$). At exhaustion, performance fatigability was similar across groups and conditions ($\sim 30\%$; all $p > 0.05$), with similar impairments in both voluntary activation and twitch amplitude.

Conclusion These results emphasize the importance of the kind of fatiguing task and modalities of evaluation when investigating the effects of aging on performance fatigability.

Keywords Aging · Fatiguing tasks · Knee extensors · Performance fatigability

Communicated by Paul David Chantler.

✉ Vianney Rozand
vianney.rozand@u-bourgogne.fr

- ¹ Laboratoire Interuniversitaire de Biologie de la Motricité, Université Jean Monnet Saint-Etienne, Lyon 1, Université Savoie Mont-Blanc, 42023 Saint-Etienne, France
- ² Department of Medicine, Faculty of Medicine, Université de Montréal, Montréal, QC, Canada
- ³ Center for Advanced Research in Sleep Medicine (CEAMS), Hôpital du Sacré-Coeur de Montréal, CIUSSS du Nord de l'Île-de-Montréal, Montréal, QC, Canada
- ⁴ Institut National du Sport du Québec, Montréal, QC, Canada
- ⁵ IUF, Institut Universitaire de France, Paris, France
- ⁶ Unité de Myologie, Service de Physiologie Clinique et de l'Exercice, Centre Référent Maladies Neuromusculaires Euro-NmD, CHU de Saint-Etienne, Saint-Etienne, France
- ⁷ CAPS, Inserm UMR1093, UFR des Sciences du Sport, Faculté des Sciences du Sport, Université de Bourgogne, BP 27877, 21078 Dijon, France

Abbreviations

6MWT	Six-minute walk test
ANOVA	Analysis of variance
BIKE	Cycling fatiguing task
CON	Concentric fatiguing task
ISO	Isometric fatiguing task
MVCC	Maximal voluntary concentric contraction
MVIC	Maximal voluntary isometric contraction
NME	Neuromuscular evaluation
QIF test	Quadriceps intermittent fatigue test
RPE	Rating of perceived exertion
TUG	Timed up and go test
Tw	Potentiated twitch
VA	Voluntary activation

Introduction

Aging is associated with a decline in functional capacities in old adults (> 60 years) and this decline is exacerbated at very old (> 80 years) age (Doherty 2003). These age-related alterations threaten autonomy, especially for females whose maximal strength is on average lower than males, and are thus at higher risk of autonomy loss (Varesco et al. 2022). The decline in maximal force production capacities is due to alterations in the neuromuscular system, that involves phenomena such as a decrease in the estimated number of motor units (Campbell et al. 1973), and a decrease in muscle mass (Janssen et al. 2000). This age-related decrease in force production depends on contraction mode, with greater deficits in concentric than isometric contractions (Rozand et al. 2017). In addition, the completion of the activities of daily living can be limited by the ability to repeat muscle contractions. Indeed, the repeated solicitation of the neuromuscular function with exercise is known to cause performance fatigability, which is defined as an exercise-induced decrease in maximal force or power (Bigland-Ritchie & Woods 1984).

Contraction mode has also an impact on age-related alterations in performance fatigability (Krüger et al. 2018). In a meta-analysis, Krüger et al. (2018) evidenced that maximal isometric force loss was higher for young than for old adults after isometric fatiguing tasks, whereas there was no difference when fatigue is induced by dynamic tasks. However, this greater fatigue resistance of old adults to isometric tasks is not maintained in very old adults, who show similar performance fatigability than young adults (Varesco et al. 2022). Moreover, isotonic dynamic tasks (i.e. with unconstrained velocity) induce a higher performance fatigability in old adults (Paris et al. 2022). Similarly, when performance fatigability is quantified as a decrease in maximal power, older adults show greater power reduction than young adults after a high velocity concentric fatiguing task (Krüger et al. 2018; Sundberg et al. 2018).

Age-related alterations in performance fatigability are also influenced by the type of workload (Hunter 2016). Most of the studies set the workload as percentage of maximal force production capacities (Hunter et al. 2004; Justice et al. 2014; Kent-Braun et al. 2002; Varesco et al. 2022; Weavil et al. 2018). More recently, more ecologically valid methods have been proposed, such as setting the workload relatively to body weight (Brownstein et al. 2022; Coates et al. 2020; Hureau et al. 2021; Royer et al. 2023). This approach is thought to better reflect activities of daily living that require moving its own body weight (e.g., walking, climbing stairs) rather than producing a percentage of maximal capacities.

In addition to the contraction mode and the workload, the timing of the measurement must be considered when

evaluating performance fatigability. Indeed, as exhaustion is rarely reached by healthy elderly during activities of daily living, which rather involve submaximal contractions, it may be more relevant to focus on performance fatigability at submaximal levels. Recently, Varesco et al. (2023) found no age-related difference in performance fatigability during a single-limb concentric task at a given submaximal workload, but greater fatigability for very old compared to young males in a single-limb isometric task and a cycling task. It appears that, even when more ecologically valid approaches are implemented, the age-related differences depend on the kind of task performed and the muscle mass involved, at least in males.

Indeed, performance fatigability also depends on sex. In a review, Hunter (2016) reported that females are less fatigable during isometric fatiguing tasks with workload set as percentage of maximal force production capacities. This difference is generally reduced with aging but the mechanisms are still unclear (Hunter 2009). Moreover, the lower number of studies evaluating performance fatigability in females limits our understanding of their age-related differences relative to different task demands (Hunter 2016). As a result, there is a lack of literature for exercise performance and performance fatigability in females during isometric and dynamic (concentric or cycling) tasks with the workload set as percentage of body weight, better representing the activities of daily living.

The present study aimed to compare performance fatigability (i.e. exercise-induced decrease in maximal force) in young, old, and very old females during single-limb isometric, isokinetic concentric and cycling fatiguing tasks, involving different muscle masses, with workloads set as percentage of body weight. We hypothesized that performance fatigability at common stages would be greater in very old females compared to young and old females independent of the task. At exhaustion, we hypothesized that old and very old females would present lower performance fatigability than young females after the isometric task but similar for all groups after the concentric and cycling tasks.

Methods

Participants

Thirty-seven females took part in the study including 13 young (18–35 yr.; 23.5 ± 3.3 yr.), 13 old (60–79 yr.; 68.2 ± 4.3 yr.) and 11 very old (≥ 80 yr.; 85.6 ± 1.8 yr.) adults. They were informed of the procedures and gave their written informed consent before the beginning of the study. All of them were free from neurological, mental, or physical disorders and the old and very old females presented a Mini-Mental State Examination score above 20 (29.5 ± 0.7 ;

maximal score = 30) (Folstein et al. 1975). They were asked to refrain from intense physical exercise, caffeine or alcohol consumption 24 h before each session. All the procedures were approved by the Comité de Protection des Personnes and were performed in accordance with the declaration of Helsinki (ClinicalTrials.gov, Identifier: NCT04516538). The University Hospital of Saint-Etienne was the sponsor of the present study.

Experimental protocol

Participants visited the laboratory on four different occasions, separated by at least 48 h. During the first session they were informed and familiarized with the different testing procedures used to assess neuromuscular capacities and performance fatigability. Old and very old females performed a six-minute walk test (6MWT) during which they had to walk as far as possible for six minutes in a 30-m corridor with standardized encouragements. They also performed the Timed Up and Go test (TUG) that consisted of getting up from a chair, walking 3 m to a mark on the floor and then walking back to the chair. Time recording started when they moved their back from the chair and ended when the back of the participants was back on the chair. All the participants were finally given an accelerometer (wGT3X-BT; ACTIGRAPH, Pensacola, FL) to wear on the non-dominant wrist for 7 days to assess their physical activity level.

Sessions 2, 3 and 4 were similar and corresponded to the three intermittent incremental tests performed in a randomized order: isometric (ISO), concentric (CON) or cycling (BIKE) condition. A schematic representation of the experimental conditions is presented on Fig. 1. ISO and CON were

derived from the quadriceps intermittent fatigue (QIF) test developed in isometric (Bachasson et al. 2013) and concentric (Varesco et al. 2021) modes. BIKE was also adapted from the QIF test to have a similar duty cycle and stage duration across the three conditions (Varesco et al. 2023).

Neuromuscular evaluation

Participants reported to the laboratory and first performed a standardized warm-up consisting of 5-s isometric contractions at 30, 50 and 70% of their perceived maximal voluntary isometric contraction (MVIC), with three repetitions at each intensity. Following the warm-up, their neuromuscular capacity was assessed. First, participants performed two 5-s MVICs during which they had to push “as hard as possible”, which were followed by two maximal voluntary concentric contraction [MVCC, range of motion = 60° (90–150°, knee fully extended = 180°), velocity: 120°·s⁻¹] during which they had to “push as hard and as fast as possible”. Participants then underwent two neuromuscular evaluations (NME) consisting of a 5-s MVIC with a superimposed electrical stimulation (superimposed twitch) and a stimulation at rest 2 s after the MVIC (potentiated twitch, Tw). One minute of rest was allowed between each maximal contraction and one additional contraction was performed if the difference between the two maximal contractions (isometric or concentric) was greater than 5%. Visual feedback of the force (BIKE) or torque (ISO and CON) was provided on a large screen in front of the participants. Participants received vigorous verbal encouragements during all their maximal contractions to ensure a maximal motivation. At least 1 min

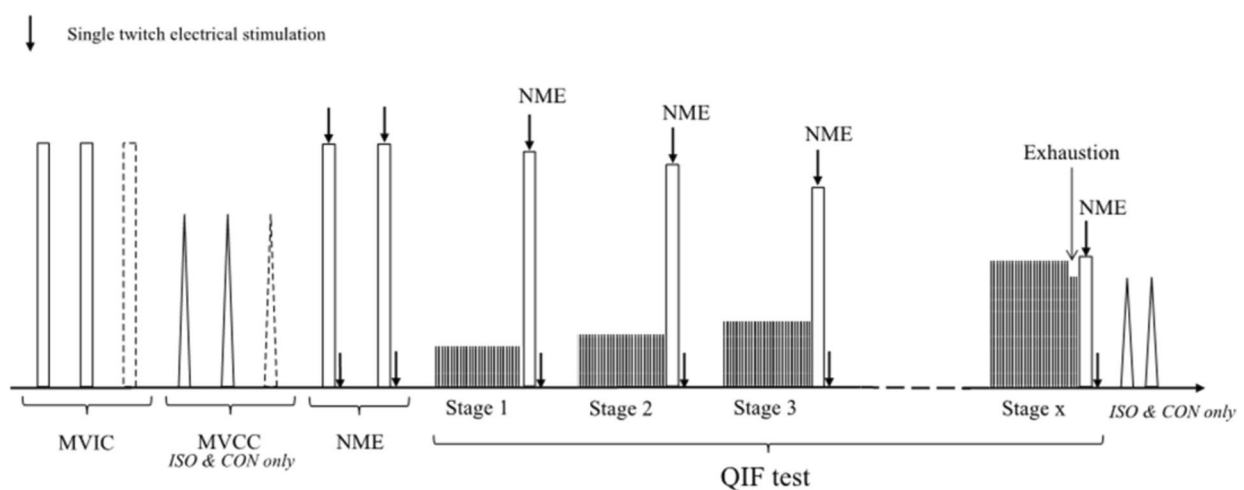


Fig. 1 Experimental procedures for the three body-mass based quadriceps intermittent fatigue (QIF) tests. *MVIC* maximal voluntary isometric contraction, *MVCC* maximal voluntary concentric contraction, *NME* neuromuscular evaluation, *ISO* isometric body-weight

based QIF test, *CON* concentric body-weight based QIF test, Dotted contractions were performed only if the difference between peak force values of the previous two contractions was > 5%

after the last NME, participants started the fatiguing task (QIF test).

QIF tests

ISO and CON were performed on an isokinetic ergometer and consisted of 75-contractions stages (0.8 s ON–0.8 s OFF, stage duration = 120 s). Contraction and rest times were defined to match duration of isokinetic concentric contractions at $120^{\circ} \cdot s^{-1}$. Workload was calculated as a percentage of body weight and increased by 5% at each stage until exhaustion. The first stage workload was defined as 10% of body weight with the following formula (Varesco et al. 2023):

$$\text{Workload first stage (Nm)} = [(body\ mass(kg) \times 9.81) \times lever\ arm\ (m)] * 0.1$$

The target load was displayed on the screen with guidelines (1 Nm above and 1 Nm below). Contraction-relaxation pacing was ensured with a soundtrack of 75 bpm for ISO and participants were instructed to push immediately after the passive return of their leg (90° knee flexion) for CON. Immediately (~ 2 s) after the end of a stage and at task failure, participants performed one NME. Stages were separated by 1 min. Task failure was defined as 5 contractions that did not reach the target load within the same stage.

BIKE was performed on a custom-made cycle-ergometer that allows to lock the pedals to perform NME on the cycle-ergometer (Doyle-Baker et al. 2018). Stage duration was set at 120 s at a cadence of 37.5 rpm that leads to 75 pedal strokes to obtain the same duty-cycle as ISO and CON. Due to different contraction conditions, workload was defined differently according to pilot studies, in order to reach a similar duration than during ISO and CON. Despite the same duty cycle used for ISO, CON and BIKE, workload was differently set for BIKE and elicited different movement coordination and muscle mass involved. Consequently, the three different conditions could not be directly compared. The workload of the first stage was set at $0.6\ W \cdot kg^{-1}$ and increments were set at $0.3\ W \cdot kg^{-1}$ (Varesco et al. 2023). Heart rate was recorded using two electrodes placed under the right clavicle and on the 10th rib. The skin was shaved, abraded, and cleaned with alcohol before electrode placement. Heart rate signal was recorded at 2 kHz and was amplified (gain = 500) using an octal bio-amplifier (ML138, AD Instruments, Bella Vista, Australia) with a bandwidth frequency range of 10–500 Hz and digitized by a Power-Lab System (16/30-ML880/P, AD Instruments, Bella Vista, Australia). At baseline, at the end of each stage and at task failure pedals were blocked to perform NME (about 2 s after the stop of pedaling) and

participants scored their rating of perceived exertion (RPE) on a 6–20 Borg scale (Borg 1982). Stages were separated by 1 min. Exhaustion was defined as a cadence < 37.5 rpm for 6 s inducing task failure. Cadence was paced with the same soundtrack as for ISO and a visual feedback was provided. Participants received vigorous verbal encouragements during all the fatiguing tests to ensure maximal motivation.

Force and torque recordings

For ISO and CON, participants were seated on an isokinetic ergometer (Con-Trex MJ; Physiomed Elektromedizin AG, Schnaittach, Germany). They were tested on their right leg as the cycle-ergometer only allowed to evaluate this leg, with the hip and knee angles at 95° and 90° (full extension = 180°), respectively. The axis of the dynamometer was aligned with the knee joint rotational axis. The tested leg was firmly attached above the malleolus with a non-compliant strap. Seat belts were attached across the trunk to avoid extraneous movements during contractions. Participants position on the isokinetic dynamometer was recorded and kept consistent across ISO and CON conditions.

For BIKE, the custom-made cycle-ergometer enabled to reproduce a similar position than for the isokinetic dynamometer. Hip and knee angles were approximately 90° and 100° when the pedals were locked. Force was recorded by instrumented pedals with force sensors (Model PF1.0.0, Radlabor GmbH, Freiburg, Germany) located between the pedal and the crank.

Force (BIKE) and torque (ISO and CON) signals were sampled at 2 kHz without analogical or digital filters (16/30-ML880/P, AD Instruments, Bella Vista, Australia) and recorded on a computer using Labchart v8 (AD Instruments, Bella Vista, Australia).

Peripheral nerve electrical stimulation

Square-wave stimulus of 2 ms duration (400 V) were delivered over the femoral nerve by a constant current stimulator (DS7R, Digitimer, Welwyn Garden City, UK). The cathode electrode (Kendall Meditrace) was placed on the inguinal triangle and the anode (50×100 mm Easysnap electrode; DJO Global, Vista, CA) was placed midway between the great trochanter and the lower border of the iliac crest. Stimulation intensity was successively increased by 30 mA until reaching a plateau of the twitch response. Then 130% of this intensity was selected to ensure a supramaximal stimulation (mean stimulation intensity: 114 ± 32 mA).

Data analysis

Data analysis was performed offline with Labchart software (Reader v8, AD Instruments). Exercise performance was defined as the number of stages performed. If the last stage was incomplete, the number of contractions performed was proportionally included to the total stage number (e.g. 5.6 stages corresponding to 420 contractions completed). Since the cycle-ergometer recorded force signals, torque signals for ISO and CON were converted into force by dividing torque by the lever arm of each participant. MVIC was defined as the average force on a 0.5-s window on the maximal force plateau before the superimposed twitch. MVCC was the maximal value reached.

Voluntary activation (VA) was calculated with the following formula including the Strojnik and Komi correction (Strojnik and Komi 1998): $VA(\%) = [1 - ST \times (F_{stim}/F_{max})/Tw] \times 100$, where superimposed twitch (ST) and Tw are the amplitude of the twitch evoked by the electrical stimulation during the MVIC and at rest, respectively. F_{stim} is the force level at the point of the stimulation and F_{max} is the maximal force produced before the stimulation.

MVIC, MVCC and Tw were also normalized to individual body masses.

All data were obtained at baseline, at the end of each stage and at exhaustion.

Data from the accelerometer were analyzed with ActiLife[®] software (v6.13.3, Actigraph).

Statistical analysis

Results for all variables are presented as mean \pm standard deviation (SD) in the text, figures, and tables. Normality was assessed with Shapiro–Wilk test and ANOVAs homogeneity of variances with Levene test.

Unpaired t-tests were used to compare exercise performance of old and very old females at the 6MWT and TUG test. One-way ANOVAs with age as between-subjects factor were used to analyze age-related differences in participants' characteristics (age, body mass, height, body mass index (BMI) and steps.day⁻¹), differences in neuromuscular properties at baseline (normalized and absolute MVIC, MVCC and Tw and VA), exercise performance and percentage of MVCC loss at exhaustion. All the participants were included in these analyses (young and old: n = 13; very old: n = 11, n = 10 for CON).

Because participants performed different number of stages, only the stages performed by all the participants, i.e. common stages, were analyzed. However, some participants did not complete all the contractions of the first stage. To ensure a minimum number of common stages could be compared between groups while maintaining a reasonable

number of participants, we kept only the females that performed 3 stages in ISO (young and old: n = 13; very old: n = 10), 1 stage in CON (young and old: n = 13; very old: n = 7) and 2 stages in BIKE (young and old: n = 13; very old: n = 9). To investigate the effect of age on the longitudinal evolution of MVIC, Tw, VA and RPE across the common stages, Generalized Estimating Equations (Zeger et al. 1988) analyses using an autoregressive structure (AR-1) were performed on data expressed relative to baseline (except VA and RPE) for each condition, with age and time as factors. A second analysis was conducted for data (MVIC, Tw, VA and RPE) at exhaustion.

Significance was set at $p < 0.05$. For all ANOVAs and Generalized Estimating Equations, when significant effects were observed, Bonferroni correction was applied to post-hoc analysis. For clarity purposes, post hoc results for time effects are presented in the text, whereas age-related differences are presented in the figures. Statistical analysis was conducted using IBM SPSS (Version 23.0, IBM INC., Chicago, IL).

Results

Participants' characteristics are presented in Table 1. Physical activity was higher in old females compared to young ($p = 0.01$) and very old females ($p = 0.01$). Old females performed better at the 6MWT ($p < 0.001$) and the TUG test ($p < 0.001$) than very old females.

One very old female dropped the study due to pain during the study. Thus, 11 very old females completed ISO and BIKE, and 10 completed CON. Neuromuscular properties at baseline are presented in Supplementary information 1. Heart rate data are presented in Supplementary information 2.

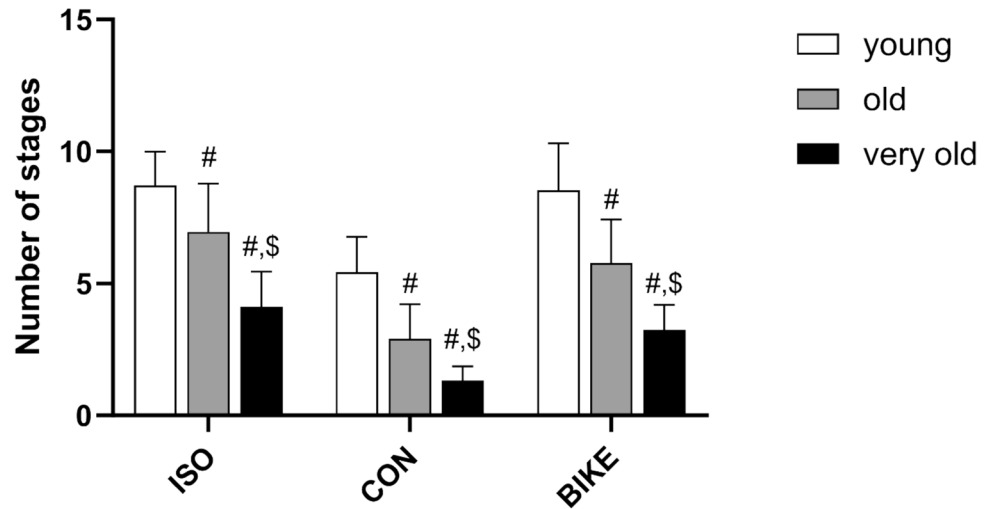
Table 1 Characteristics of the participants

	Young	Old	Very old
Age (years)	23.5 \pm 3.3	68.2 \pm 4.3 ^{***}	85.6 \pm 1.8 ^{***, †††}
Body mass (kg)	60.8 \pm 5.4	56.7 \pm 6.2	57.4 \pm 9.8
Height (cm)	166 \pm 5	162 \pm 5	158 \pm 8 [*]
BMI (kg.m ⁻²)	22.3 \pm 3.1	21.6 \pm 2.1	23 \pm 3
Steps.day ⁻¹	9,429 \pm 1,417	12,958 \pm 4264 [*]	9286 \pm 1824 [†]
6MWT (m)	–	635 \pm 88	425 \pm 75 ^{†††}
TUG test (s)	–	5.5 \pm 0.8	9.7 \pm 2.1 ^{†††}

* and *** significantly different from Young ($p < 0.05$ and $p < 0.001$, respectively)

† and ††† significantly different from Old ($p < 0.05$ and $p < 0.001$, respectively)

Fig. 2 Number of stages performed by young, old, and very old females during isometric (ISO), concentric (CON) and cycling (BIKE) quadriceps intermittent fatigue tests. # = significantly different from young females ($p < 0.05$); \$ = significantly different from old females ($p < 0.05$)



QIF tests exercise performance

Exercise performance, expressed as number of stages performed, showed a significant age effect ($p < 0.001$). In all conditions, young females performed a higher number of stages than old (ISO: $p = 0.017$; CON: $p < 0.001$; BIKE: $p < 0.001$) and very old females (all: $p < 0.001$; Fig. 2). In all conditions, old females also performed a higher number of stages than very old females (ISO: $p < 0.001$; CON: $p = 0.008$; BIKE: $p < 0.001$; Fig. 2).

Performance fatigability

For the analysis of QIF tests at common stages performed and exhaustion (MVIC, Tw, VA and RPE) we kept only the females who performed 3 stages in ISO (young and old: $n = 13$; very old: $n = 10$), 1 stage in CON (young and old: $n = 13$; very old: $n = 7$) and 2 stages in BIKE (young and old: $n = 13$; very old: $n = 9$, see *Statistical analysis* for more details).

For MVIC data, stage effect was observed with a significant decrease from baseline (all $p < 0.05$).

Common stages performed. For ISO and BIKE, the decrease in MVIC showed no age effect (ISO: $p = 0.069$, Fig. 3A; BIKE: $p = 0.160$, Fig. 3C). For CON, a stage \times age interaction was found ($p < 0.001$) with MVIC decreasing more for very old females than young females after stage 1 ($p < 0.001$) whereas no differences were found between young and old females ($p = 0.075$) and between old and very old females ($p = 0.281$) (Fig. 3B).

At exhaustion. For all conditions and age-groups, there was no age effect on the decrease of MVIC (ISO: $p = 0.489$; CON: $p = 0.364$; BIKE: $p = 0.154$).

There was no age effect on the decrease of MVCC at exhaustion either for ISO (young: $-18.9 \pm 12.4\%$; old: $-18.7 \pm 12.8\%$; very old: $-22.3 \pm 9.0\%$; $p = 0.728$) or CON (young: $-20.8 \pm 11.5\%$; old: $-14.6 \pm 12.7\%$; very old: $-15.3 \pm 28.0\%$; $p = 0.636$).

Potentiated twitch

For Tw data, stage effect was observed with a significant decrease from baseline (all $p < 0.05$).

Common stages performed. For ISO and CON, a stage \times age interaction was found (ISO: $p = 0.012$; CON: $p = 0.021$). Tw amplitude decreased more for very old than young females after stage 1 in CON ($p = 0.022$, Fig. 3E) and after stages 2 and 3 in ISO ($p = 0.013$, Fig. 3D). The decrease was also higher for very old than old females after stage 3 in ISO ($p = 0.003$). There was no age effect in BIKE on the decrease in Tw amplitude after the common stages ($p = 0.194$, Fig. 3F).

At exhaustion. For ISO and CON, there was no age effect on Tw amplitude decrease (ISO: $p = 0.125$; CON: $p = 0.132$) at exhaustion. For BIKE, young females showed a larger decrease in Tw amplitude than old and very old females (all $p < 0.001$).

Voluntary activation

For VA data, stage effect was observed with a significant decrease from baseline (all $p < 0.05$).

Common stages performed. For BIKE, there was a main effect of age ($p = 0.045$) with very old females presenting a lower VA than young females ($p = 0.032$, Fig. 3I). There was no stage \times age interaction ($p = 0.280$). There

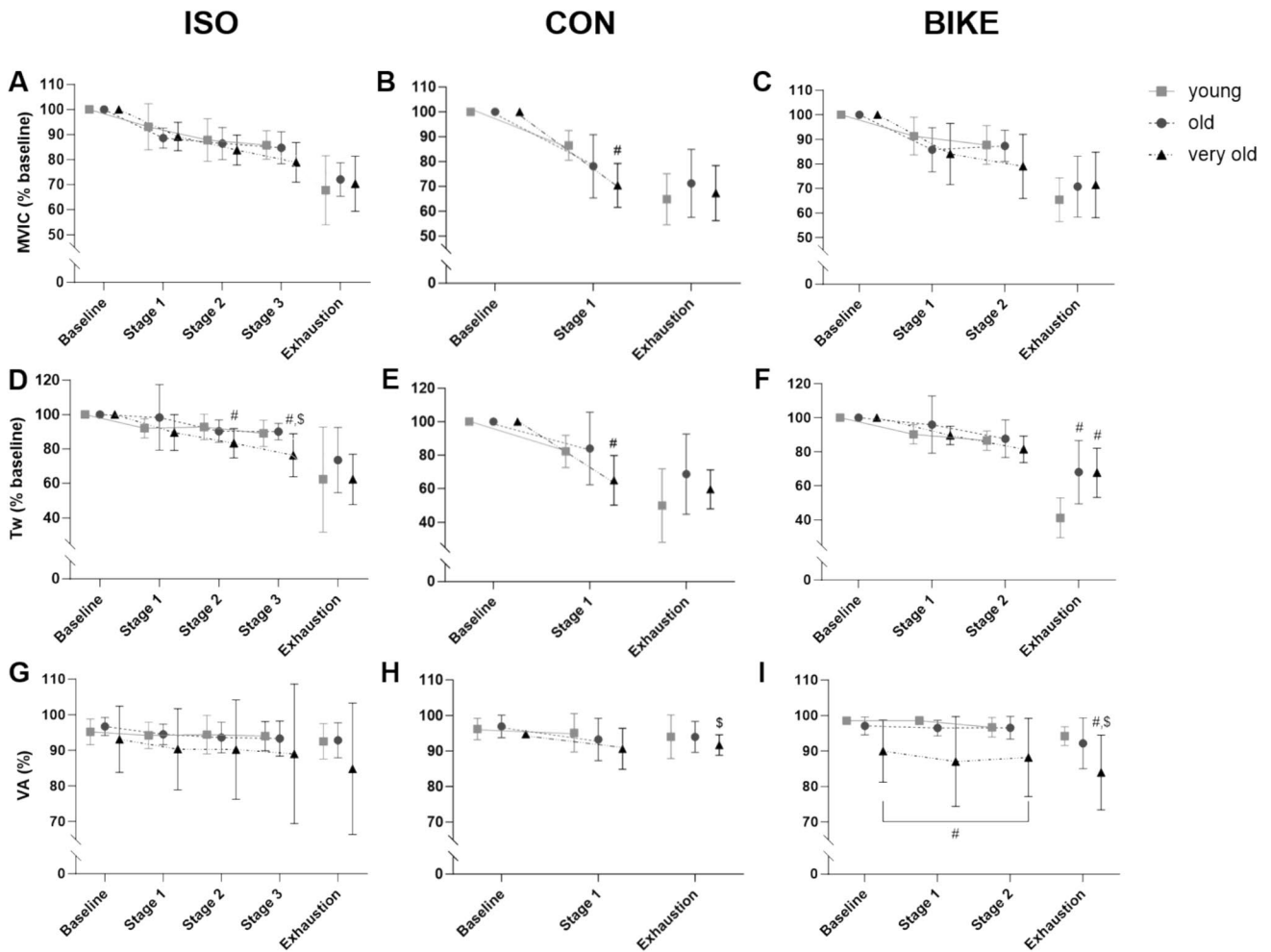


Fig. 3 Evolution of maximal voluntary isometric contraction (MVIC, upper row), twitch amplitude (Tw, middle row) and voluntary activation (VA, bottom row) for young, old, and very old females across isometric (ISO; A, D, G), concentric (CON; B, E, H) and cycling

(BIKE; C, F, I) QIF tests. The last common stage was stage 3 for ISO, stage 1 for CON and stage 2 for BIKE. # = significantly different from young females ($p < 0.05$); \$ = significantly different from old adults ($p < 0.05$)

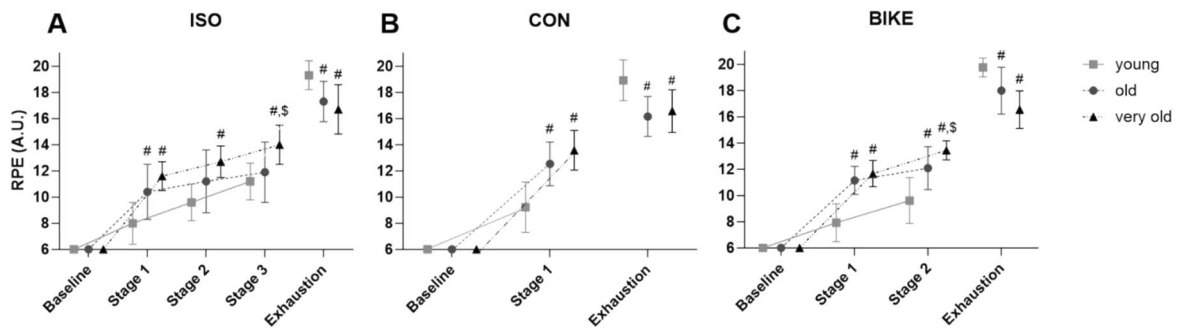


Fig. 4 Evolution of the rate of perceived exertion (RPE) for young, old, and very old women across isometric (ISO; panel A), concentric (CON; panel B) and cycling (BIKE; panel C) QIF tests. Stages 1 to 3

are the common stages performed in each condition. # = significantly different from young adults ($p < 0.05$); \$ = significantly different from old adults ($p < 0.05$)

was no effect of age in ISO ($p=0.682$, Fig. 3G) and CON ($p=0.131$, Fig. 3H).

At exhaustion. Very old females presented a lower VA compared to old females in CON ($p=0.004$) and BIKE ($p=0.013$) and to young females in BIKE ($p<0.001$).

Perceived fatigability

Common stages performed. RPE showed a stage \times age interaction in each condition (all $p<0.001$), with an increase in RPE over time (all $p<0.001$). For CON and BIKE and only the first stage for ISO, RPE was higher for very old and old women than young women (all $p<0.001$). In stages 2 and 3 in ISO, RPE was higher for very old than young women ($p<0.001$, Fig. 4A). In ISO and BIKE, RPE was also higher for very old than old women in the last common stage (ISO, stage 3: $p=0.017$; BIKE, stage 2: $p=0.025$, Fig. 4).

At exhaustion. RPE was higher than baseline (all $p<0.001$) and higher for young than for old and very old women (all $p<0.001$), with no difference between old and very old women (ISO and CON: $p=1.000$; BIKE: $p=0.237$).

Discussion

The aim of this study was to investigate the effect of age, including very old individuals, on performance fatigability during and after three fatiguing tasks involving different muscle masses and contraction modes (single-joint isometric, single-joint concentric, and cycling) in females. Contrary to our hypothesis, maximal force decreased more for very old compared to young females in CON only for the same relative workload (common stages), with no age-related difference in ISO and BIKE. At exhaustion, performance fatigability was similar across age groups for all conditions.

Functional and neuromuscular characteristics at baseline

The number of steps.day⁻¹ performed by the participants indicated that they can be considered as physically active females (Tudor-Locke et al. 2011). However, old females were more active than young and very old females, with very old being as active as young females. There was probably a selection bias for older participants, with the fittest who tended to participate in the study. Furthermore, this population potentially had more free time to engage in walking compared to younger individuals who generally

worked or studied. This may have reduced, at least in part, the age-related differences in performance fatigability. Performance at the functional tests (6MWT and TUG test) were significantly better for old than very old females, as already observed for males (Varesco et al. 2023).

Exercise performance

As expected, exercise performance decreased with age in each fatiguing task. These results can be explained by the reduction in muscle mass occurring with aging (Doherty 2003) as well as structural and functional impairments in the neuromuscular system, such as greater metabolites accumulation (Hunter et al. 2016). The reduction of cardiorespiratory fitness with aging (Harridge and Lazarus 2017) probably played a role, leading to a decrease in maximal oxygen uptake and ultimately in exercise performance. Indeed, young females reached a higher heart rate at exhaustion than older females (Supplementary information 2). Additionally, the earlier increase of RPE with aging likely explains the earlier task failure observed in older groups (Souron et al. 2020). Moreover, setting the workload as percentage of body weight led to greater workload increments in older females in terms of maximal force production capacity. For instance, each stage corresponded to an increment of $7 \pm 1\%$, $9 \pm 2\%$ and $13 \pm 5\%$ of MVIC for young, old, and very old females, respectively; or $8 \pm 1\%$, $12 \pm 2\%$ and $19 \pm 6\%$ of MVCC for young, old, and very old females, respectively. This was due to the lower strength/body weight ratio with advancing age. Each increment in intensity was thus harder for old and even more for very old females.

A recent study with the same experimental design in males (Varesco et al. 2023) showed no difference in exercise performance between old and very old males in ISO and CON. This discrepancy may suggest differential effects of sex on neuromuscular function but also on perception of effort. Moreover, males in Varesco et al. (2023) performed more stages than the females in the present study in both CON and BIKE independent of age, but not in ISO. The lower exercise performance of females when using a more ecologically valid workload (percentage of body weight) in dynamic tasks could be explained by a lower strength/body weight ratio in females compared to males. This suggests females may be working at a higher percentage of maximal strength than males during activities of daily living.

Performance fatigability at common stages

Because exhaustion is almost never reached during activities of daily living, the QIF tests allow to compare performance fatigability at submaximal workloads, especially at the common stages performed by all the participants, *i.e.* 3 stages in ISO, 1 in CON and 2 in BIKE.

In ISO, no age-related differences in performance fatigability were observed during the common stages, contrary to previous results in males (Varesco et al. 2023). Additionally, Tw amplitude loss was greater in very old than young females from stage 2, and greater than old females at stage 3. This suggests that age-related alterations in contractile function were not large enough to lead to a decrease in maximal force production using the current testing paradigm. Furthermore, the relatively short duration of the task probably prevented the appearance of deficits in voluntary activation (Jubeau et al. 2014). Longer exercises may be necessary to observe potential age-related deficits in voluntary activation. It has also been suggested that the slowing of muscle contractile properties with age would lead to lower motor units firing rates (Mota et al. 2020; Watanabe et al. 2016), decreasing the cost of contraction in isometric condition (Kent-Braun 2009). This lower cost of contraction may have counterbalanced the higher relative workload in percentage of MVIC with advancing age.

In CON, performance fatigability was greater for very old than young females after stage 1, with no differences between old and young females, or between old and very old females. Similarly, Tw amplitude loss, which is representative of contractile function and is related to metabolites accumulation, was greater for very old than young females. This accumulation increases with age in concentric mode (Sundberg et al. 2019) due to both a decrease in contraction efficiency (Layec et al. 2014) and a lower muscle oxidative capacity. This metabolites accumulation was probably emphasized by the greater workload increments with age.

In the BIKE condition, no age-related differences were observed either in performance fatigability or in Tw amplitude loss after the common stages. These results were not expected and differed from those observed in males who showed greater and earlier performance fatigability and twitch amplitude loss for old and very old males compared to young males (Varesco et al. 2023). The lack of age-related differences in the present study might be attributed to an early decrease in MVIC in young females, whereas MVIC remained similar to baseline at stage 1 in young males (Varesco et al. 2023). Additionally, the relatively high level of physical activity among older females may also help to preserve their cardiovascular capacities, involved during the cycling exercise. Finally, the limited number of common stages may have prevented the emergence of age-related differences in performance fatigability, despite an increase in perceived fatigability.

In all conditions, RPE increased, with very old and old females reporting higher RPE than young females starting from the first stage. RPE was also higher for very old females compared to old females after stage 3 in ISO and stage 2 in BIKE. This increased perceived fatigability with age is likely due to the greater workload relative to maximal

capacities in older females, and potentially participated to the earlier task failure. Specifically, the higher workload leads to greater metabolite accumulation, activating group III and IV afferent receptors in the knee extensors, and an increased neural drive from the motor cortex, which results in additional corollary discharges. Together, these factors likely contribute to the heightened perception of exertion observed in older adults (Lopes et al. 2022).

Performance fatigability at exhaustion

No age-related effects were observed on performance fatigability at exhaustion (MVIC or MVCC) in ISO, CON and BIKE. Previous studies have shown lower performance fatigability in old compared to young adults after a QIF test in isometric condition with a workload set as percentage of MVIC (Varesco et al. 2022), and lower performance fatigability in very old compared to young males when the workload was set as percentage of body weight in ISO task only (Varesco et al. 2023).

Age-related impairments in performance fatigability are usually reported following concentric exercise, depending on factors such as total work performed (Weavil et al. 2018), contraction velocity or fatiguing protocol used (Callahan et al. 2009; Senefeld et al. 2017; Sundberg et al. 2018, 2019; Weavil et al. 2018). In the present study, the age-related decrease in contraction efficiency during concentric contractions was likely compensated by a lower total work performed by older females, thereby limiting the magnitude of performance fatigability.

The results observed in the BIKE condition are in agreement with a similar study on males (Varesco et al. 2023) but differ from another study (Weavil et al. 2018) that reported increased performance fatigability in older adults. In order to match duty-cycle between conditions, participants in the present study had to cycle at 37.5 rpm, which is particularly low compared to the ~60 rpm cadence commonly used in the literature. Consequently, heart rate reached at exhaustion was ~126 and 112 bpm for old and very old females, respectively vs. ~150 bpm for old adults in previous studies (Krüger et al. 2020; Weavil et al. 2018). This lower heart rate likely prevented participants from being limited by their cardiorespiratory system as usually observed in cycling tasks.

In all conditions, old and very old females presented a lower RPE than young females at task failure. Moreover, old and very old females did not reach maximal RPE, contrary to younger females, suggesting that task failure was not due to maximal perceived fatigability in older females. Instead, task failure was likely attributed to a muscular inability to sustain exercise, possibly due to the large workload increments.

Limitations

Despite the same duty cycle used for ISO, CON and BIKE, workload was differently set for BIKE and elicited different movement coordination and muscle mass involved. Consequently, the three different conditions could not be directly compared. Moreover, the limited number of common stages analyzed due to the lower exercise performance of old and even more very old females compared to young females could have limited the full understanding of age-related differences in performance fatigability.

In the BIKE condition, we used a multi-joint dynamic fatiguing task using a cycling ergometer, aiming to better approximate real-world, ecological conditions. We believe this approach offers a more comprehensive assessment of fatigability in this population. However, the pedaling cadence was quite low (37.5 rpm) and real life also involves greater contraction velocity, which may induce greater performance fatigability in older females.

Moreover, it is possible that the familiarization with maximal voluntary contractions on the cycling ergometer was insufficient for the very old females, despite following the same protocol as for young and old females. The cycling ergometer used in our study requires more advanced muscle coordination, as it is more challenging to exert force horizontally, and the position slightly differs compared to the ergometers used in ISO and CON, leading to lower values in MVIC and ultimately in VA in the BIKE condition. However, the conditions were similar at the different time points, which allowed us to confidently assess their evolution during and after the fatiguing tasks.

Furthermore, the level of physical activity of old and very old females was relatively high, limiting the effects of physical inactivity. Thus, this sample of participants may not represent the whole population of older adults but rather the more preserved ones, and further investigations would be needed to differentiate the effects of aging from those of physical activity.

Lastly, hormonal fluctuations can influence neuromuscular function and fatigability (Ansdell et al. 2019). Regrettably, menstrual cycles were not controlled in the younger females, neither were collected data on time since menopause in the older participants. However, we are confident that the effects of age are much larger than those of menstrual cycle, so the comparison between groups would not necessarily differ with this additional information.

Conclusion

This study showed that exercise performance at the three different fatiguing tasks (isometric, single-limb dynamic and cycling) decreased with advancing age in females when

workload was set as percentage of body weight, which explain in part the reduction in the capacity to perform activities of daily living of older adults. Greater performance fatigability occurred in very old compared to young females at common stages during the concentric task but not during the isometric and cycling tasks, whereas no age-related differences were observed at exhaustion for the three tasks. These results suggest that age-related differences in performance fatigability depend on contraction mode but also on the timing of evaluation (common stages vs exhaustion), which should be further considered in future studies.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s00421-024-05637-6>.

Acknowledgements The authors thank the dedicated group of participants for their time and effort.

Author contributions G.V., T.L., G.Y.M., L.F., and V.R. conceived and designed research. M.B. and V.R. recruited the participants. M.B. conducted the experiments and collected the data. M.B. and G.V. analyzed the data. M.B., G.V., T.L., G.Y.M., L.F., and V.R. drafted the manuscript. All authors provided critical appraisal to the manuscript and approved the final version. All authors have read and approved the final version of the manuscript.

Funding No funds, grants, or other support was received.

Declarations

Conflict of interest No conflict of interest declared. The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

Ethics approval All the procedures were approved by the Comité de Protection des Personnes and were performed in accordance with the declaration of Helsinki (ClinicalTrials.gov, Identifier: NCT04516538). The University Hospital of Saint-Etienne was the promoter of the present study.

Informed consent Participants were informed of the procedures and gave their written informed consent before the beginning of the study.

References

- Ansdell P, Brownstein CG, Škarabot J, Hicks KM, Simoes DCM, Thomas K, Howatson G, Hunter SK, Goodall S (2019) Menstrual cycle-associated modulations in neuromuscular function and fatigability of the knee extensors in eumenorrhic women. *J Appl Physiol* 126(6):1701–1712. <https://doi.org/10.1152/jappphysiol.01041.2018>
- Bachasson D, Millet GY, Decorte N, Wuyam B, Levy P, Verges S (2013) Quadriceps function assessment using an incremental test and magnetic neurostimulation: a reliability study. *J Electromyogr Kinesiol* 23(3):649–658. <https://doi.org/10.1016/j.jelekin.2012.11.011>
- Bigland-Ritchie B, Woods JJ (1984) Changes in muscle contractile properties and neural control during human muscular fatigue.

- Muscle Nerve 7(9):691–699. <https://doi.org/10.1002/mus.880070902>
- Borg GAV (1982) Psychophysical bases of perceived exertion. *Med Sci Sports Exerc* 14(5):377–381
- Brownstein CG, Twomey R, Temesi J, Medysky ME, Culos-Reed SN, Millet GY (2022) Mechanisms of neuromuscular fatigability in people with cancer-related fatigue. *Med Sci Sports Exerc* 54(8):1355–1363. <https://doi.org/10.1249/MSS.0000000000002919>
- Callahan DM, Foulis SA, Kent-Braun JA (2009) Age-related fatigue resistance in the knee extensor muscles is specific to contraction mode: knee extensor fatigue. *Muscle Nerve* 39(5):692–702. <https://doi.org/10.1002/mus.21278>
- Campbell MJ, McComas AJ, Petito F (1973) Physiological changes in ageing muscles. *J Neurol Neurosurg Psychiatry* 36(2):174–182. <https://doi.org/10.1136/jnnp.36.2.174>
- Coates KD, Aboodarda SJ, Krüger RL, Martin T, Metz LM, Jarvis SE, Millet GY (2020) Multiple sclerosis-related fatigue: The role of impaired corticospinal responses and heightened exercise fatigability. *J Neurophysiol* 124(4):1131–1143. <https://doi.org/10.1152/jn.00165.2020>
- Doherty TJ (2003) Invited review: aging and sarcopenia. *J Appl Physiol* 95(4):1717–1727. <https://doi.org/10.1152/jappphysiol.00347.2003>
- Doyle-Baker D, Temesi J, Medysky ME, Holash RJ, Millet GY (2018) An innovative ergometer to measure neuromuscular fatigue immediately after cycling. *Med Sci Sports Exerc* 50(2):375–387. <https://doi.org/10.1249/MSS.0000000000001427>
- Folstein MF, Folstein SE, McHugh PR (1975) “Mini-mental state”: a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 12(3):189–198. [https://doi.org/10.1016/0022-3956\(75\)90026-6](https://doi.org/10.1016/0022-3956(75)90026-6)
- Harridge SDR, Lazarus NR (2017) Physical activity, aging, and physiological function. *Physiology* 32(2):152–161. <https://doi.org/10.1152/physiol.00029.2016>
- Hunter SK (2009) Sex differences and mechanisms of task-specific muscle fatigue. *Exerc Sport Sci Rev* 37(3):113–122. <https://doi.org/10.1097/JES.0b013e3181aa63e2>
- Hunter SK (2016) The relevance of sex differences in performance fatigability. *Med Sci Sports Exerc* 48(11):2247–2256. <https://doi.org/10.1249/MSS.0000000000000928>
- Hunter SK, Critchlow A, Enoka RM (2004) Influence of aging on sex differences in muscle fatigability. *J Appl Physiol* 97(5):1723–1732. <https://doi.org/10.1152/jappphysiol.00460.2004>
- Hunter SK, Pereira HM, Keenan KG (2016) The aging neuromuscular system and motor performance. *J Appl Physiol* 121(4):982–995. <https://doi.org/10.1152/jappphysiol.00475.2016>
- Hureau TJ, Hucteau E, Massamba A, Mallard J, Ducrocq GP (2021) Identifying sex differences in neuromuscular fatigue: the challenge of normalizing exercise intensity and interpreting the results between populations. *J Physiol* 599(11):2769–2991. <https://doi.org/10.1113/JP281755>
- Janssen I, Heymsfield SB, Wang Z, Ross R (2000) Skeletal muscle mass and distribution in 468 men and women aged 18–88 yr. *J Appl Physiol* 89(1):81–88. <https://doi.org/10.1152/jappl.2000.89.1.81>
- Jubeau M, Rupp T, Perrey S, Temesi J, Wuyam B, Levy P, Verges S, Millet GY (2014) Changes in voluntary activation assessed by transcranial magnetic stimulation during prolonged cycling exercise. *PLoS One* 9(2):e89157. <https://doi.org/10.1371/journal.pone.0089157>
- Justice JN, Mani D, Pierpoint LA, Enoka RM (2014) Fatigability of the dorsiflexors and associations among multiple domains of motor function in young and old adults. *Exp Gerontol* 55:92–101. <https://doi.org/10.1016/j.exger.2014.03.018>
- Kent-Braun JA (2009) Skeletal muscle fatigue in old age: whose advantage? *Exerc Sport Sci Rev* 37(1):3–9. <https://doi.org/10.1097/JES.0b013e318190ea2e>
- Kent-Braun JA, Ng AV, Doyle JW, Towse TF (2002) Human skeletal muscle responses vary with age and gender during fatigue due to incremental isometric exercise. *J Appl Physiol* 93(5):1813–1823. <https://doi.org/10.1152/jappphysiol.00091.2002>
- Krüger RL, Aboodarda SJ, Samozino P, Rice CL, Millet GY (2018) Isometric versus dynamic measurements of fatigue: does age matter? a meta-analysis. *Med Sci Sports Exerc* 50(10):2132–2144. <https://doi.org/10.1249/MSS.0000000000001666>
- Krüger RL, Aboodarda SJ, Jaimes LM, Vaz MA, Samozino P, Millet GY (2020) Age-related neuromuscular fatigue and recovery after cycling: measurements in isometric and dynamic modes. *Exp Gerontol* 133:110877. <https://doi.org/10.1016/j.exger.2020.110877>
- Layec G, Trinity JD, Hart CR, Kim SE, Groot HJ, Le Fur Y, Sorensen JR, Jeong EK, Richardson RS (2014) In vivo evidence of an age-related increase in ATP cost of contraction in the plantar flexor muscles. *Clin Sci* 126(8):581–592. <https://doi.org/10.1042/CS20130442>
- Lopes TR, Pereira HM, Silva BM (2022) Perceived exertion: revisiting the history and updating the neurophysiology and the practical applications. *Int J Environ Res Public Health* 19(21):14439. <https://doi.org/10.3390/ijerph192114439>
- Mota JA, Kwon DP, Kennedy M, Sobolewski EJ, Kim Y, Gonzales JU, Stock MS (2020) Compensatory adjustments in motor unit behavior during fatigue differ for younger versus older men. *Aging Clin Exp Res* 32(11):2259–2269. <https://doi.org/10.1007/s40520-019-01438-6>
- Paris MT, McNeil CJ, Power GA, Rice CL, Dalton BH (2022) Age-related performance fatigability: a comprehensive review of dynamic tasks. *J Appl Physiol* 133(4):850–866. <https://doi.org/10.1152/jappphysiol.00319.2022>
- Royer N, Brownstein CG, Kennouche D, Espeit L, Teston A, Boutet C, Féasson L, Camdessanché J-P, Millet GY (2023) A Comprehensive evaluation of multiple sclerosis-related fatigue with a special focus on fatigability. *Med Sci Sports Exerc* 55(11):2002–2013. <https://doi.org/10.1249/MSS.0000000000000323>
- Rozand V, Senefeld JW, Hassanlouei H, Hunter SK (2017) Voluntary activation and variability during maximal dynamic contractions with aging. *Eur J Appl Physiol* 117(12):2493–2507. <https://doi.org/10.1007/s00421-017-3737-3>
- Senefeld J, Yoon T, Hunter SK (2017) Age differences in dynamic fatigability and variability of arm and leg muscles: Associations with physical function. *Exp Gerontol* 87:74–83. <https://doi.org/10.1016/j.exger.2016.10.008>
- Souron R, Voirin A, Kennouche D, Espeit L, Millet GY, Rupp T, Lapole T (2020) Task failure during sustained low-intensity contraction is not associated with a critical amount of central fatigue. *Scand J Med Sci Sports* 30(12):2329–2341. <https://doi.org/10.1111/sms.13815>
- Strojnik V, Komi PV (1998) Neuromuscular fatigue after maximal stretch-shortening cycle exercise. *J Appl Physiol* 84(1):344–350. <https://doi.org/10.1152/jappl.1998.84.1.344>
- Sundberg CW, Kuplic A, Hassanlouei H, Hunter SK (2018) Mechanisms for the age-related increase in fatigability of the knee extensors in old and very old adults. *J Appl Physiol* 125(1):146–158. <https://doi.org/10.1152/jappphysiol.01141.2017>
- Sundberg CW, Prost RW, Fitts RH, Hunter SK (2019) Bioenergetic basis for the increased fatigability with ageing. *J Physiol* 597(19):4943–4957. <https://doi.org/10.1113/JP277803>
- Tudor-Locke C, Craig CL, Aoyagi Y, Bell RC, Croteau KA, De Bourdeaudhuij I, Ewald B, Gardner AW, Hatano Y, Lutes LD, Matsudo SM, Ramirez-Marrero FA, Rogers LQ, Rowe DA, Schmidt MD, Tully MA, Blair SN (2011) How many steps/day are enough? For

- older adults and special populations. *Int J Behav Nutr Phys Act* 8(1):80. <https://doi.org/10.1186/1479-5868-8-80>
- Varesco G, Royer N, Singh B, Parent A, Féasson L, Lapole T, Millet GY, Rozand V (2021) Reliability and agreement of a dynamic quadriceps incremental test for the assessment of neuromuscular function. *J Electromyogr Kinesiol* 56:102503. <https://doi.org/10.1016/j.jelekin.2020.102503>
- Varesco G, Luneau E, Féasson L, Lapole T, Rozand V (2022) Age-related differences in performance and fatigability during an isometric quadriceps intermittent fatigue test. Preprint. <https://doi.org/10.1101/2021.09.19.460938>
- Varesco G, Luneau E, Millet GY, Féasson L, Lapole T, Rozand V (2023) Age-related differences between old and very old men in performance and fatigability are evident after cycling but not isometric or concentric single-limb tasks. *Med Sci Sports Exerc* 55(9):1641–1650. <https://doi.org/10.1249/MSS.00000000000003181>
- Watanabe K, Holobar A, Kouzaki M, Ogawa M, Akima H, Moritani T (2016) Age-related changes in motor unit firing pattern of vastus lateralis muscle during low-moderate contraction. *Age* (Dordrecht, Netherlands). <https://doi.org/10.1007/s11357-016-9915-0>
- Weavil JG, Hureau T, Thurston T, Sidhu S, Garten R, Nelson A, McNeil C, Richardson R, Amann M (2018) The impact of age on the development of fatigue during large and small muscle mass exercise. *Am J Physiol Regul Integr Comp Physiol* 315(4):32. <https://doi.org/10.1152/ajpregu.00156.2018>
- Zeger SL, Liang K-Y, Albert PS (1988) Models for longitudinal data: a generalized estimating equation approach. *Biometrics* 44(4):1049. <https://doi.org/10.2307/2531734>

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.