

RESEARCH

Open Access



Combined physical and cognitive training enhances telomere length in mild cognitive impairment patients

Andrea Borghini^{1†}, Paola Canale^{1,2†}, Rosa Sicari¹, Nicoletta Berardi³, Fabrizio d'Adda di Fagagna^{4,5}, Alessandro Sale³, Maria Grazia Andreassi^{1*} and Train the Brain Consortium

Abstract

Background Environmental enrichment training may delay cognitive decline in mild cognitive impairment (MCI) by reducing telomere shortening, a cellular marker of aging. We investigated whether combined physical/cognitive training affects leukocyte telomere length (LTL) in the randomized trial “Train the Brain”.

Methods LTL was assessed in 94 MCI (75.1 ± 5.1 years) subjects and 37 non-MCI subjects (73.2 ± 4.6 years). MCI patients were assigned to receive either 7 months of training or standard care. After 7 months, both groups were reassessed for changes in LTL and the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog). Telomerase reverse transcriptase (hTERT) mRNA and telomeric repeat-containing RNA (TERRA) were also tested in 24 patients.

Results MCI patients had shorter LTL than controls ($p = 0.02$), and short LTL was associated with a higher risk of MCI ($OR_{\text{adjusted}} = 2.6$; 95%CI, 1.1–6.0; $p = 0.03$). Training improved ADAS-cog scores ($T_0 = 15.1 \pm 4.8$ to $T_7 = 13.4 \pm 5.0$, $p = 0.01$) and increased LTL ($T_0 = 0.97 \pm 0.21$ to $T_7 = 1.04 \pm 0.23$, $p = 0.04$). hTERT mRNA levels were negligible in MCI patients at T0 and T7, indicating inactive telomerase. TERRA expression increased in untrained MCI ($p = 0.02$), which may reflect impaired telomere homeostasis.

Conclusions MCI patients have shorter telomeres, and combined training lengthens them, suggesting modifiable telomere homeostasis through non-pharmacological intervention. Telomere shortening may underlie increased telomeric transcription in untrained individuals, highlighting telomeric non-coding RNAs as potential therapeutic targets in age-related disease.

Keywords Mild cognitive impairment, Environmental enrichment training, Leukocyte telomere length, Telomeric non-coding RNA

[†]Andrea Borghini and Paola Canale contributed equally to this work.

*Correspondence:

Maria Grazia Andreassi
mariagrazia.andreassi@cnr.it

¹CNR Institute of Clinical Physiology, Pisa, Italy

²Health Science Interdisciplinary Center, Sant'Anna School of Advanced Studies, Pisa, Italy

³Institute of Neuroscience of CNR, Pisa, Italy

⁴IFOM ETS - The AIRC Institute of Molecular Oncology, Milan, Italy

⁵Istituto Di Genetica Molecolare, Consiglio Nazionale Delle Ricerche (IGM-CNR), Pavia, Italy



© The Author(s) 2026. **Open Access** This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc-nd/4.0/>.

Introduction

Mild cognitive impairment (MCI) is a clinical stage indicating individuals at heightened risk of developing dementia, notably Alzheimer's disease [1]. Nonetheless, MCI does not invariably progress to dementia, and timely interventions can potentially delay its advancement [2].

The Train the Brain study examined the efficacy of a comprehensive environmental enrichment program involving physical and mental training in postponing cognitive decline among older MCI patients [3]. The findings revealed that a non-pharmacological intervention combining physical and cognitive activities over seven months led to improved cognitive function and increased parahippocampal cerebral blood flow, although it did not affect gray matter volume loss [3]. Strikingly, the beneficial impact of the Train the Brain intervention on cognitive functions was also preserved at the 14-month follow-up (i.e., 7 months past the end of the intervention) program [4]. Moreover, the beneficial effects were greater in low-educated individuals compared to highly educated individuals, and were more evident in women than in men.

Similarly, the extensive, long-term FINGER trial, which enrolled 1260 older individuals at risk of cognitive decline and dementia from the general population, randomized participants to a two-year multidomain intervention comprising dietary changes, exercise, cognitive training, and vascular risk monitoring. This trial demonstrated either improved or sustained cognitive performance among those in the intervention group [5].

Despite the clinical relevance of these studies, the molecular mechanisms underlying the reported beneficial effects remain elusive. Telomere shortening is associated with aging and various age-related diseases such as cardiovascular disease, cognitive decline, and neurodegenerative disorders [6, 7]. Accordingly, we hypothesized that combined physical and cognitive training could also result, in parallel to its beneficial impact on cognitive decline in individuals with MCI, in a modulation of mechanisms controlling telomere length.

In agreement with this hypothesis, here we aimed to assess whether a multi-domain training and cognitive program impacts leukocyte telomere length (LTL).

Materials and methods

Study population

The detailed study design, inclusion and exclusion criteria, and recruitment and training methods for the open-label clinical trial Train The Brain have been extensively described elsewhere [3]. In summary, the study targeted older individuals aged between 65 and 89 years with MCI recruited from the general population. Participants meeting the specified criteria for MCI diagnosis were randomly allocated to either the multidomain

training group (MCI-training) or the no-training group (MCI-no-training).

After 7 months of either training or usual daily activities, assessments were conducted again, including baseline measurements (T_0) using the Alzheimer's Disease Assessment Scale-cognitive (ADAS-Cog) to assess the severity of key symptoms associated with Alzheimer's disease [3, 8]. Based on a previous average ADAS-Cog [8], and using a 5% significance level with 90% power, a sample size of 42 subjects per group was needed. After accounting for a 30% dropout rate, the final sample size was increased to 60 subjects per group [3]. The study design and protocol, encompassing subject privacy and handling of sensitive data, received approval from the Regional Ethical Committee for Clinical Experimentation. The ethical approval explicitly authorized blood sample collection and subsequent biochemical analyses for biomarker assessment. All participants provided written informed consent covering biological sample collection and analyses related to aging and cognitive impairment. Peripheral venous blood was collected from all participants between 07:00 and 09:00 a.m. using standard venipuncture techniques into specific vacutainer tubes for plasma and serum separation and for DNA and RNA extraction. Samples were processed within 30 min of collection, centrifuged at $1500 \times g$ for 20 min, and plasma and serum were aliquoted and stored at -80°C . Whole blood for DNA extraction was stored at -20°C , while RNA samples were stabilized and stored at -80°C until analysis.

The trial is registered under ClinicalTrials.gov Identifier NCT01725178 (November 8, 2012), and participants provided written informed consent before participation. Among the 113 MCI subjects randomized in the Train the Brain study, LTL was evaluated in 94 individuals. Additionally, an age- and gender-matched control group (No-MCI) comprising individuals with normal cognitive function upon study entry ($n=37$) was included for comparison (Fig. 1). The study adhered to the CONSORT guidelines and the additional file 1 provides the CONSORT check list.

Multidomain training

MCI training subjects, organized into classes with a maximum of 10 participants each, underwent supervised cognitive and aerobic exercise training three times a week over a period of 7 months. The training regimen included two 120-min sessions of cognitive training, which involved both single cognitive modality activities and multimodal exercises such as watching movies, engaging in discussions, and participating in music therapy sessions. Additionally, participants engaged in a 60-min session of aerobic exercise and coordinative capacity activities [3].

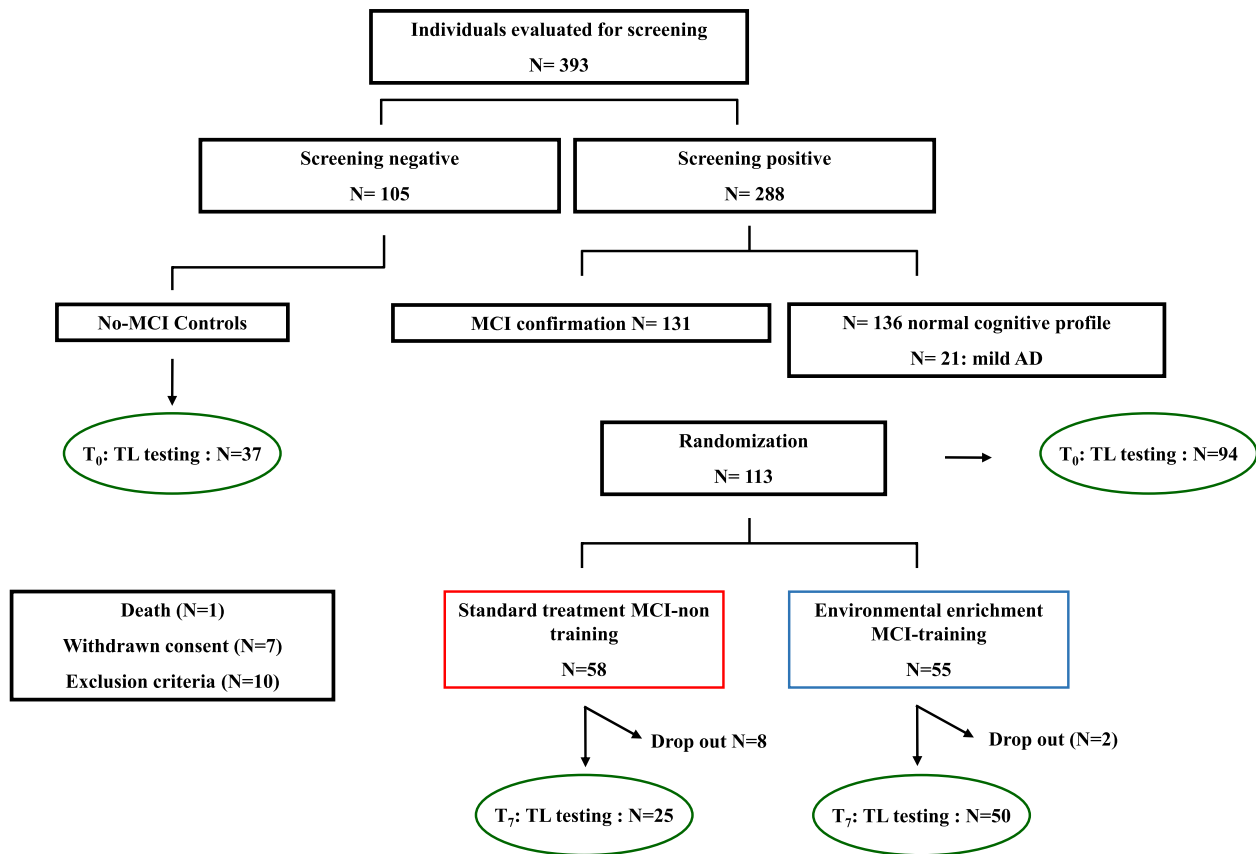


Fig. 1 The train the brain study: Flowchart depicting the Train the Brain trial and the final study population for telomere length analysis

Telomere length analysis

Quantitative measurement of LTL was conducted using genomic DNA extracted from whole blood through the quantitative real-time PCR method as previously detailed [9]. The relative TL was determined by calculating the ratio of telomere repeat copy number (T) to single copy gene (SG) copy number (T/S ratio) in experimental samples compared to a reference sample [9]. All PCR assays were conducted in triplicate in 384-well plates using a CFX RT-PCR System (Bio-Rad, Hercules, CA, USA).

RNA isolation and quantification of lncRNA TERRA and hTERT

To evaluate the effects of training on telomere biology, we measured the expression of telomerase reverse transcriptase (hTERT) and the telomeric repeat-containing RNA (TERRA), which is transcribed from the sub-telomeric to the telomeric region, and it can inhibit telomerase [10].

We measured lncRNA TERRA and hTERT in a subset of 24 patients (12 trained and 12 untrained MCI), as some participants had insufficient blood samples and RNA from certain samples did not meet the quality or quantity criteria required for analysis.

Briefly, total RNA was extracted from whole blood samples using the RiboPure™ RNA Purification Kit

(Thermo Fisher Scientific, Waltham, MA, USA) according to the manufacturer's instructions. RNA quality and quantity were evaluated using a NanoDrop™ Lite Plus Spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA).

For molecular analyses, 500 ng of total RNA was reverse-transcribed into cDNA using the SuperScript™ IV VILO™ Master Mix (Thermo Fisher Scientific, Waltham, MA, USA), following the manufacturer's protocol.

Reverse transcription–quantitative polymerase chain reaction (RT-qPCR) was performed to quantify hTERT transcripts and lncRNA TERRA using specific primers. Specifically, we measured a collective TERRA level from different chromosome ends (chromosomes 1q, 2q, 4q, 10q, 13q, and 22q) using RT-specific primers (F 5'-GAAT CCTGCGCACCGAGAT and R 5'-CTGCACTTGAACC CTGCAATAC), as previously described [11].

For hTERT detection, the primers used were forward 5'-CACCTCACCCACGCGAAAA-3' and reverse 5'-CAAAGAGTTTGGCGACGCATGTT-3. GAPDH served as the reference gene, with primers forward 5'-TGGTATCGTGGAAGGACTCATG-3' and reverse 5'-GCTTCAACCCTTCTTGATGTC-3', for normalization of all expression analyses. HeLa cancer cells were included as a positive control for hTERT expression.

Table 1 Clinical and demographic characteristics of study population

Variable	MCI (n = 94)	Non-MCI (n = 37)	p value
Age (years)	75 ± 5	73 ± 5	0.06
Men, n (%)	44 (47)	20 (55)	0.4
Smoking (%)	6 (6)	1 (3)	0.4
Hypertension (%)	46 (49)	23 (62)	0.1
Diabetes (%)	11 (12)	5 (13)	0.7
Dyslipidemia (%)	48 (51)	22 (59)	0.3
Previous CV events (%)	12 (13)	3 (8)	0.5

Each reaction was conducted in triplicate, amplifying 10 ng of cDNA using the CFX384 Touch Real-Time PCR Detection System (Bio-Rad, Hercules, CA, USA) and the SsoAdvanced™ Universal SYBR® Green SuperMix (Bio-Rad, Hercules, CA, USA).

Relative transcript levels were calculated using the $\Delta\Delta C_q$ method, normalized to GAPDH, with data analysis performed using the Bio-Rad CFX Manager software (Bio-Rad, Hercules, CA, USA).

Statistical analysis

Statistical analyses were performed using the StatView statistical package, version 5.0.1 (Abacus Concepts, Berkeley, CA, USA). Descriptive statistics are presented as mean ± SD, median (interquartile range), or

percentage, depending on the nature of the data. Characteristics of both cases and controls were compared using the χ^2 test for categorical variables and the two-sample t-test or Mann–Whitney test for quantitative variables, as appropriate. Regression analysis was employed to assess correlations between variables. Multivariate logistic regression was utilized to calculate odds ratios (ORs) and their corresponding 95% confidence intervals (CIs), adjusting for age, gender, and vascular risk factors. A significance level of $p < 0.05$ was applied to all statistical analyses.

Results

MCI and telomeres

Ninety-four individuals with MCI (44 males; mean age 75.1 ± 5.1 years) and 37 age- and gender-matched controls (21 males; mean age 73.2 ± 4.6 years) underwent baseline LTL measurements screening. Table 1 displays the demographic and clinical parameters of both MCI patients and the control group. There were no significant differences between the two groups in terms of age, gender, smoking status, and major cardiovascular risk factors.

At study entry, MCI patients exhibited shorter LTL compared to healthy controls (0.96 ± 0.23 vs. 1.07 ± 0.3 , $p = 0.02$, Fig. 2a). In MCI cases, there was a significant negative correlation between T/S ratio and age

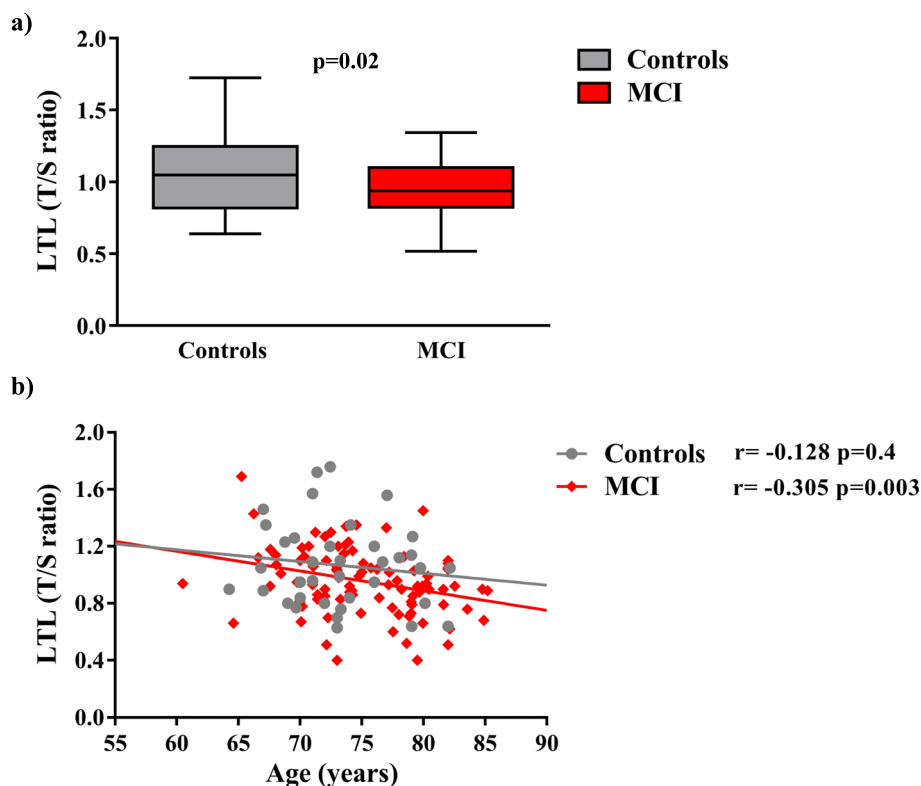
**Fig. 2** **a** Box plots illustrate differences in LTL between individuals with MCI and controls; **b** Regression lines depicting LTL and their corresponding equations as a function of age for MCI cases (red points) and controls (gray points)

Table 2 Odds ratio (ORs) and 95% CIs for MCI adjusted by median TL and risk factors

Variable	Unadjusted OR (95%CI)	p	Adjusted OR (95%CI)	p
Age (years)	1.0 (0.9–1.0)	0.05	1.1 (0.9–1.2)	0.09
Male gender	1.5 (0.7–3.2)	0.3	0.7 (0.3–1.7)	0.4
Smoking	0.9 (0.4–1.9)	0.5	2.5 (0.2–26)	0.6
Hypertension	1.8 (0.8–4.2)	0.1	0.4 (0.2–1.1)	0.1
Diabetes	1.2 (0.4–3.7)	0.7	1.6 (0.4–6.6)	0.5
Dyslipidemia	1.5 (0.7–3.3)	0.3	0.8 (0.3–2.0)	0.3
Previous CV events	0.6 (0.1–2.2)	0.5	1.6 (0.4–7.1)	0.6
Median TL ≤ 0.96	2.5 (1.1–5.4)	0.03	2.6 (1.0–6.0)	0.03

($r = -0.305$, $p = 0.0028$), whereas such a correlation was not observed in controls (Fig. 2b). No correlations were found between LTL and ADAS-Cog score in the overall study population or within the MCI group (data not shown).

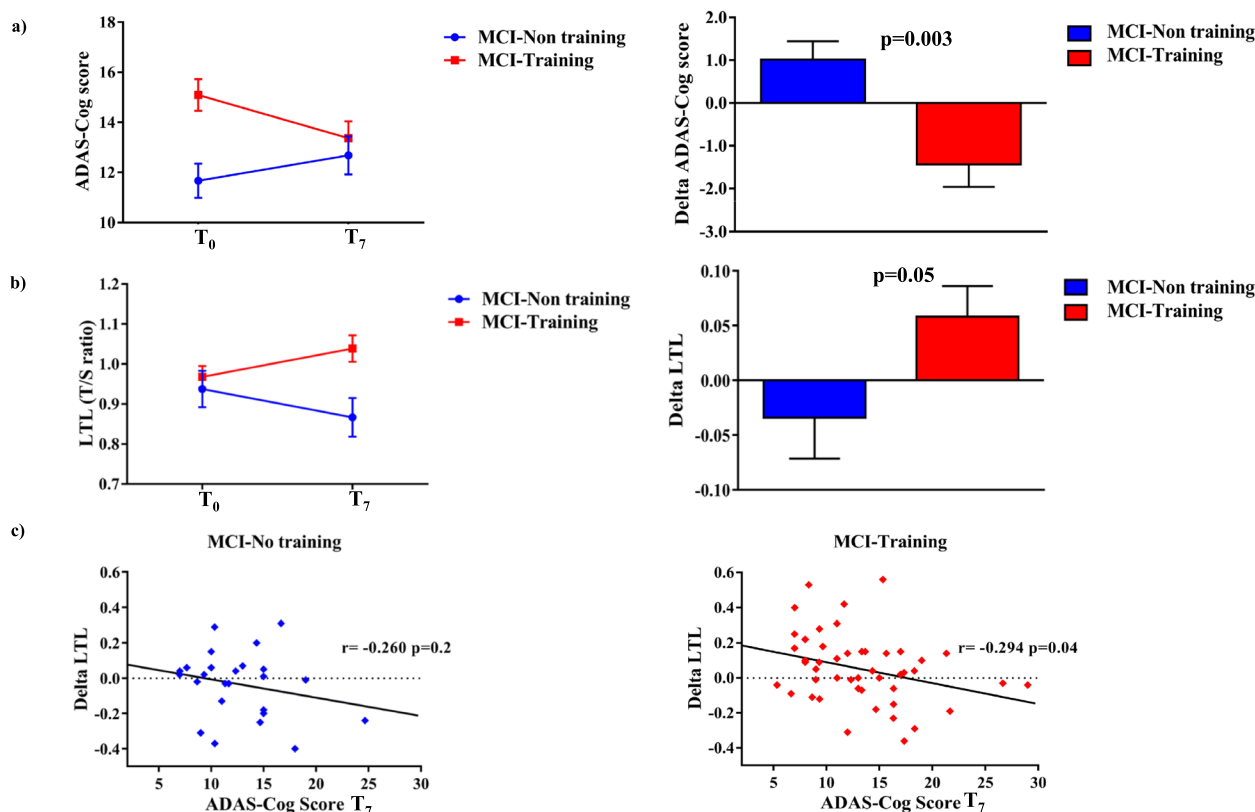
Upon dichotomizing individuals into long and short TL groups based on the median LTL value in controls, those with short LTL demonstrated a significantly elevated risk of MCI (OR_{adjusted} = 2.6; 95% CI: 1.1–6.0; $p = 0.03$) compared to individuals with long LTL after adjusting for age, gender, and vascular risk factors (see Table 2).

Baseline characteristics of MCI-training and MCI-no training

At baseline, there were no differences in demographic and clinical characteristics between groups, except for a significantly higher ADAS-Cog score in the MCI-training group compared to the MCI-no-training subjects (15.1 ± 4.8 vs. 11.7 ± 3.6 , $p = 0.001$). No significant difference in LTL was observed between the MCI-training and MCI-no-training groups ($p = 0.5$). Additionally, TL T_0 was not correlated with ADAS-Cog score T_0 in the total study population ($p = 0.9$) or in the MCI-training and MCI-no-training groups ($p = 0.5$ and $p = 0.4$, respectively).

Effects of training on cognitive status and telomere

A significant beneficial effect of combined training was observed in the decline of ADAS-Cog score in the MCI-training group at the 7-month follow-up ($T_0 = 15.1 \pm 4.8$ to $T_7 = 13.4 \pm 5.0$, $p = 0.01$, Fig. 3a). Conversely, there was a significant increase in the mean ADAS-Cog score in the MCI-no-training group ($T_0 = 11.7 \pm 3.6$ to $T_7 = 12.7 \pm 4.0$, $p = 0.02$), as depicted in Fig. 3a. The mean change from baseline in ADAS-Cog score at the 7-month follow-up was -1.44 for the MCI-training group and 1.0 for the MCI-no-training group (mean difference between groups: 2.5 ; 95% CI: 0.88 to 4.0 , $p = 0.003$).

**Fig. 3** LTL and ADAS-cog score changes: **a** Changes in ADAS-cog scores and **b** LTL in the MCI-training and MCI-no training groups after a 7-month of training; **c** relationship between LTL changes and ADAS-cog score at T_7

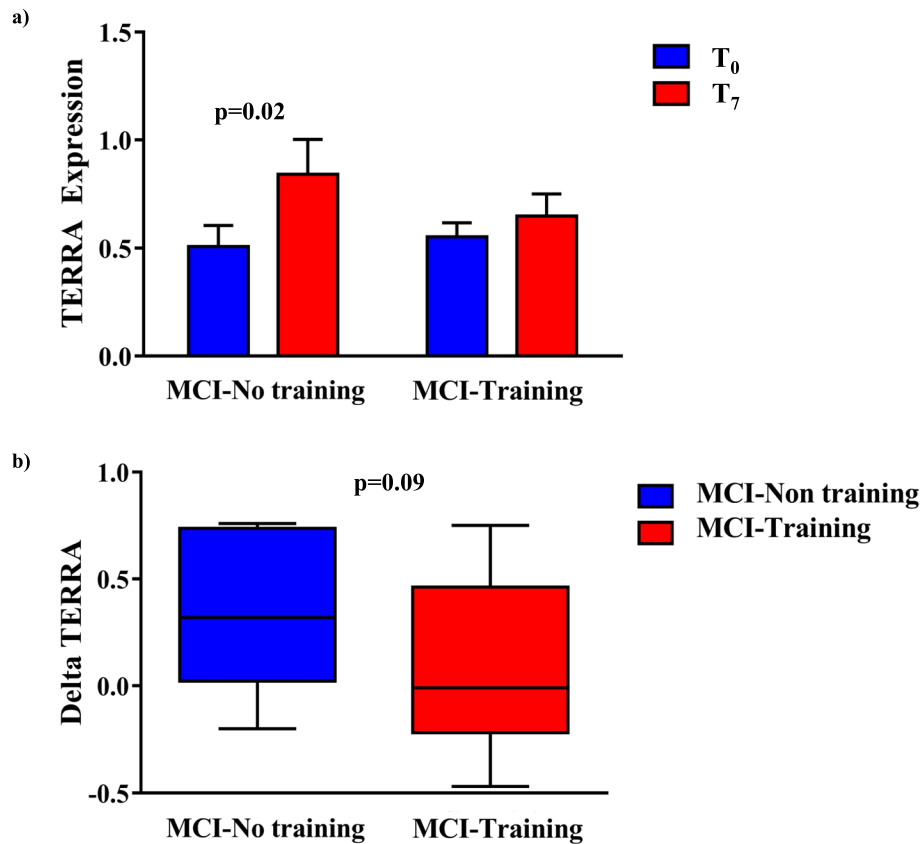


Fig. 4 **a** The expression of telomeric repeat-containing RNA (TERRA) in the MCI-training and MCI-no training groups at T₀ and T₇, and **b** comparison of the changes in TERRA levels between the two groups

Combined cognitive and physical training also resulted in a significant increase in LTL in the MCI-training group (T₀ = 0.97 ± 0.21 to T₇ = 1.04 ± 0.23, $p = 0.04$). Although not significant, an opposite trend was observed in the MCI-no-training group (Fig. 3b). LTL increased by a mean of 0.058 T/S units in the intervention group and decreased by a mean of -0.034 T/S units in the MCI-no-training group (mean difference between groups: -0.092; 95% CI: -0.187 to 0.003, $p = 0.05$). An inverse significant correlation was observed between LTL changes and ADAS-Cog score at T in the MCI-training group ($r = -0.294$, $p = 0.04$), indicating that higher ADAS-Cog scores (greater cognitive impairment) were associated with greater reductions in telomere length (Fig. 3c).

TERT and TERRA RNA expression

Comparative analyses within the participant subsample for gene expression showed no statistically significant differences between trained and untrained MCI groups in demographic or baseline clinical variables (data not shown). The expression of hTERT mRNA was negligible at both T₀ and T₇, suggesting that all patients have hTERT mRNA levels below detection in their whole blood. At baseline, TERRA expression was not significantly

different between the MCI-training and MCI-no-training groups ($p = 0.3$). Significantly higher levels of TERRA were, however, observed at T₇ in the MCI-no-training group ($p = 0.02$), whereas there was no change in the level of TERRA expression after the combined cognitive and physical training (Fig. 4a). Changes in TERRA levels also tended to be higher in the MCI-no-training groups compared to the MCI-training groups (Fig. 4b).

Discussion

The current study revealed significantly shorter LTL in individuals with MCI compared with cognitively healthy controls. Moreover, seven months of combined cognitive and physical training resulted in a significant increase in LTL in the intervention group, suggesting that telomere homeostasis is altered in MCI but maintains biological plasticity in response to a structured intervention.

Comparison with previous literature on TL and cognition

Telomeres are highly conserved, noncoding tandem repeat DNA sequences (TTAGGG)_n located at chromosome ends, where they safeguard genomic stability and prevent cellular senescence [5–7]. They are elongated by the enzyme telomerase, which typically exhibits low or

absent activity in most human somatic cells. As a result, telomeres progressively shorten with each cell division and in response to cumulative oxidative and inflammatory stress. This gradual attrition contributes to cellular aging and has been implicated in the pathogenesis of age-related disorders, including neurodegenerative diseases such as Alzheimer's disease [7].

Our observation of shorter LTL in individuals with MCI is consistent with previous studies linking telomere shortening to age-related cognitive decline, thereby supporting the concept that accelerated biological aging accompanies MCI [12–22].

However, other investigations have shown relatively weak or absent associations between telomere length and cognitive performance [23–29]. For instance, the Long-Life Family Study reported no significant association between LTL and multiple cognitive domains in both non-demented individuals and those with dementia or incipient dementia [30].

Discrepancies across studies may reflect heterogeneity in study design (cross-sectional versus longitudinal), cognitive assessments, covariate adjustment, telomere measurement methodologies, and inter-individual variability in telomere dynamics [20–22]. Moreover, these conclusions are limited to telomere length alone and do not inform on the presence of dysfunctional or long but damaged telomeres [6].

Nonetheless, our results strengthen the evidence of a link between telomere attrition and MCI and support the notion that telomere dynamics remain modifiable through non-pharmacological intervention. Our data also highlights the potential to modulate telomere length as an emerging therapeutic opportunity for mitigating aging and age-associated diseases [31, 32].

Telomere elongation and intervention studies

While telomere shortening is commonly viewed as a unidirectional process, longitudinal studies have shown that telomere length in leukocytes can fluctuate and even increase over time in response to physiological changes [33].

Thus, the telomere lengthening observed in the intervention group is biologically plausible and consistent with prior intervention studies suggesting that lifestyle modifications can influence telomere biology [34–36]. However, given the known intra-individual variability of leukocyte telomere length measurements, longitudinal changes should be interpreted with caution and in the context of technical and biological variability [37]. In the cognitive area, daily meditation practice (Kundalini yoga Kirtan Kriya) for 12 min per day over eight weeks improved cognitive function and increased telomerase activity in dementia caregivers with mild depressive symptoms [38]. Similarly, ω -3 PUFA supplementation has been

suggested to mitigate telomere shortening in older adults with MCI [39]. Non-pharmacological enrichment interventions such as art therapy, meditation, and music listening have also been associated with higher telomere length values in older individuals with MCI [40–42]. Our findings extend this literature by demonstrating telomere lengthening in response to a multidomain cognitive and physical training program.

Mechanistic considerations

The specific molecular mechanisms involved in telomere maintenance or reduced telomere attrition remain complex and poorly understood. In principle, two non-exclusive explanations may underlie the observed telomere changes. First, true telomere elongation could result from telomerase activation or altered leukocyte population dynamics, shifting the proportion of circulating cells toward those with longer telomeres. Second, reductions in oxidative stress, inflammation, and stress hormone signaling induced by the intervention may decrease telomerase-associated DNA damage and slow attrition. The Train the Brain intervention previously demonstrated modulation of cytokines and immune markers linked to neuroinflammation and aging [43], supporting the plausibility of reduced inflammatory burden as a contributing mechanism [43].

Although exercise training has been reported to increase TERT expression and telomerase activity [44], we detected negligible hTERT mRNA levels in peripheral blood at both baseline and follow-up. This finding is consistent with prior work showing unchanged telomerase activity after resistance training [36]. However, hTERT mRNA levels may not fully reflect enzymatic activity, and transient or cell-specific telomerase activation cannot be excluded. Thus, while telomerase activation remains a theoretical possibility, alternative mechanisms such as reduced inflammatory damage or repopulation of peripheral blood by progenitor cells with longer telomeres may better explain our findings [45].

Additionally, we also observed increased TERRA expression in the untrained MCI group. Accelerated telomere shortening may drive elevated transcriptional activity at telomeres in untrained individuals. Consistent with this interpretation, aging has been associated with increased TERRA levels in sedentary populations, whereas endurance training appears to mitigate this rise [46].

Overall, our data underscore the importance of an integrated analysis of telomeres, telomerase, and TERRA to advance our understanding of aging and age-related diseases, as well as the need for further research to validate and establish these biomarkers for routine clinical use [47].

Additionally, our findings suggest that the intervention may preserve telomere homeostasis at both structural and transcriptional levels. This is particularly relevant, as dysregulated telomeric transcription is increasingly

implicated in aging and age-related diseases. Targeting telomeric non-coding RNAs such as TERRA may therefore offer a promising strategy to mitigate phenotypes associated with telomere shortening [6].

Study limitations

However, several limitations should be acknowledged. The relatively low acceptance rate for telomere testing in the MCI no-training group may have introduced selection bias. In addition, telomerase enzymatic activity was not directly measured, limiting mechanistic interpretation of the observed telomere length changes. Moreover, the absolute cognitive improvement did not reach the conventional 4-point threshold on the ADAS-Cog commonly applied in dementia trials [48], suggesting stabilization rather than reversal of impairment. The higher baseline ADAS-Cog score in the intervention group also raises the possibility of regression to the mean. However, stronger intervention effects among individuals at greater baseline risk are frequently observed in clinical studies.

Importantly, findings from a subsample of participants in the FINGER trial demonstrated that a multidomain lifestyle intervention promoted LTL maintenance in individuals at risk for dementia [49], supporting the broader relevance and plausibility of our observations.

Conclusions

In conclusion, individuals with MCI exhibit shorter leukocyte telomeres compared with cognitively healthy controls, supporting the link between telomere attrition and neurodegenerative processes. Notably, seven months of combined physical and cognitive training was associated with telomere lengthening, suggesting that biological aging trajectories in MCI may retain a degree of reversibility under structured multidomain intervention. Impaired telomere homeostasis may underlie the increased transcriptional activity observed in untrained individuals, underscoring the potential relevance of telomeric non-coding RNAs as therapeutic targets in age-related diseases.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12877-026-07380-3>.

Supplementary Material 1.

Acknowledgements

Acknowledgement of collaborative consortium The Train the Brain Consortium members are: L. Maffei, E. Picano, M. G. Andreassi, A. Angelucci, F. Baldacci, L. Baroncelli, T. Begenisic, P. F. Bellinva, N. Berardi, L. Biagi, J. Bonaccorsi, E. Bonanni, U. Bonuccelli, A. Borghini, C. Braschi, M. Broccardi, R. M. Bruno, M. Caleo, C. Carlesi, L. Carnicelli, G. Cartoni, L. Cecchetti, M. C. Cenni, R. Ceravolo, L. Chico, S. Cintoli, G. Cioni, M. Coscia, M. Costa, G. D'Angelo, P. D'Ascanio, M. De Nes, S. Del Turco, E. Di Coscio, M. Di Galante, N. di Lascio, F. Faita, I. Falorni, U. Faraguna, A. Fenu, L. Fortunato, R. Franco, L. Gargani, R. Gargiulo, L. Ghiadoni, F. S. Giorgi, R. Iannarella, C. Iofrida, C. Kusmic, F. Limongi, M. Maestri, M. Maffei, S. Maggi, M. Mainardi, L. Mammana, A. Marabotti,

Mariotti V., E. Melissari, A. Mercuri, S. Micera, S. Molinaro, R. Narducci, T. Navarra, M. Noale, C. Pagni, S. Palumbo, R. Pasquariello, S. Pellegrini, P. Pietrini, T. Pizzorusso, A. Poli, L. Pratali, A. Retico, E. Ricciardi, G. Rota, A. Sale, S. Sbrana, G. Scabia, M. Scali, D. Scelfo, R. Sicari, G. Siciliano, F. Stea, S. Taddei, G. Tognoni, A. Tonacci, M. Tosetti, S. Turchi & L. Volpi.

Authors' contributions

All authors have read and approved the submission of this manuscript. AB, PC contributed to the acquisition, analysis, and interpretation of data. RS, NB, F.d'A.d.F. and AS contributed to the study concept and interpretation of data. MGA was responsible for designing the study, supervision, and drafting the manuscript. All authors contributed to critical revisions of the manuscript for important intellectual content.

Funding

The Train the Brain study was supported by a grant from the Fondazione Pisa (Bando Ricerca Scientifica in Neuroscienze 2007 of Fondazione Cassa di Risparmio di Pisa; Pisa, Italy). The authors also acknowledge co-funding European Union – Next Generation EU, in the context of The National Recovery and Resilience Plan, Investment Partenariato Esteso PE8 "Conseguenze e sfide dell'invecchiamento", Project Age-It (Aging Well in an Aging Society).

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The Train the Brain study was carried out in accordance with the Declaration of Helsinki and participants gave written informed consent. The protocol was approved by the the Regional Ethical Committee for Clinical Experimentation. (Azienda Ospedaliera Universitaria, Pisa, Italy) and registered at ClinicalTrials.gov (Identifier NCT01725178). A written informed consent form was signed by each participant.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 17 July 2025 / Accepted: 19 March 2026

Published online: 31 March 2026

References

1. Langa KM, Levine DA. The diagnosis and management of mild cognitive impairment: a clinical review. *JAMA*. 2014;312:2551–6.
2. Pandya SY, Clem MA, Silva LM, Woon FL. Does mild cognitive impairment always lead to dementia? A review. *J Neurol Sci*. 2016;369:57–66.
3. Train the Brain Consortium. Randomized trial on the effects of a combined physical/cognitive training in aged MCI subjects: theTrain the brain study. *Sci Rep*. 2017;7:39471.
4. Sale A, Noale M, Cintoli S, Train the Brain Consortium, et al. Long-term beneficial impact of the randomised trial 'Train the Brain', a motor/cognitive intervention in mild cognitive impairment people: effects at the 14-month follow-up. *Age Ageing*. 2023;52:afad067.
5. Ngandu T, Lehtisalo J, Solomon A, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. *Lancet*. 2015;385:2255–63.
6. Rossiello F, Jurk D, Passos JF, d'Adda di Fagagna F. Telomere dysfunction in ageing and age-related diseases. *Nat Cell Biol*. 2022;24:135–47.
7. Kuan XY, Fauzi NSA, Ng KY, Bakhtiar A. Exploring the causal relationship between telomere biology and Alzheimer's disease. *Mol Neurobiol*. 2023;60:4169–83.

8. Pyo G, Elble RJ, Ala T, Markwell SJ. The characteristics of patients with uncertain/mild cognitive impairment on the Alzheimer disease assessment scale-cognitive subscale. *Alzheimer Dis Assoc Disord*. 2006;20:16–22.
9. Borghini A, Giardini G, Tonacci A, Mastorci F, Mercuri A, Mrakic-Spota S, et al. Chronic and acute effects of endurance training on telomere length. *Mutagenesis*. 2015;30:711–6.
10. Azzalin CM, Reichenbach P, Khoraiouli L, Giulotto E, Lingner J. Telomeric repeat containing RNA and RNA surveillance factors at mammalian chromosome ends. *Science*. 2007;318(5851):798–801.
11. Adishesh M, Alnafakh R, Baird DM, Jones RE, Simon S, et al. Human Endometrial Carcinogenesis Is Associated with Significant Reduction in Long Non-Coding RNA, TERRA. *Int J Mol Sci*. 2020;21(22):8686.
12. Grodstein F, van Oijen M, Irizarry MC, et al. Shorter telomeres may mark early risk of dementia: preliminary analysis of 62 participants from the nurses' health study. *PLoS One*. 2008;3:e1590.
13. Harris SE, Deary IJ, MacIntyre A, et al. The association between telomere length, physical health, cognitive ageing, and mortality in non-demented older people. *Neurosci Lett*. 2006;406:260–4.
14. Martin-Ruiz C, Dickinson HO, Keys B, Rowan E, Kenny RA, Von Zglinicki T. Telomere length predicts poststroke mortality, dementia, and cognitive decline. *Ann Neurol*. 2006;6:174–80.
15. Devore EE, Prescott J, De Vivo I, Grodstein F. Relative telomere length and cognitive decline in the Nurses' health study. *Neurosci Lett*. 2011;492:15–8.
16. Yaffe K, Lindquist K, Kluse M, et al. Telomere length and cognitive function in community-dwelling elders: findings from the health ABC study. *Neurobiol Aging*. 2011;32:2055–60.
17. Honig LS, Kang MS, Schupf N, Lee JH, Mayeux R. Association of shorter leukocyte telomere repeat length with dementia and mortality. *Arch Neurol*. 2012;69:1332–9.
18. Roberts RO, Boardman LA, Cha RH, et al. Short and long telomeres increase risk of amnesic mild cognitive impairment. *Mech Ageing Dev*. 2014;141–142:64–9.
19. Cohen-Manheim I, Doniger GM, Sinnreich R, et al. Increased attrition of leukocyte telomere length in young adults is associated with poorer cognitive function in midlife. *Eur J Epidemiol*. 2016;31:147–57.
20. Hägg S, Zhan Y, Karlsson R, Gerritsen L, Ploner A, van der Lee SJ, Neuro-CHARGE Cognitive Working Group, Adolfsen AN, Reynolds CA, Samani NJ, Suchiman HED, Viljanen A, von Zglinicki T, Wright MJ, Hottenga JJ, Boomsma DI, Rantanen T, Kaprio JA, Nyholt DR, Martin NG, Nyberg L, Adolfsen R, Kuh D, Starr JM, Deary IJ, Slagboom PE, van Duijn CM, Codd V, Pedersen NL, et al. Short telomere length is associated with impaired cognitive performance in European ancestry cohorts. *Transl Psychiatry*. 2017;7(4):e1100.
21. Ma F, Lv X, Du Y, Chen H, Liu S, Zhao J, et al. Association of leukocyte telomere length with mild cognitive impairment and Alzheimer's disease: role of folate and homocysteine. *Dement Geriatr Cogn Disord*. 2019;48:56–67.
22. Leibel DK, Shaked D, Beatty Moody DL, Liu HB, Weng NP, et al. Telomere length and cognitive function: differential patterns across sociodemographic groups. *Neuropsychology*. 2020;34(2):186–98.
23. Zekry D, Herrmann FR, Irminger-Finger I, et al. Telomere length is not predictive of dementia or MCI conversion in the oldest old. *Neurobiol Aging*. 2010;31:719–20.
24. Mather KA, Jorm AF, Anstey KJ, Milburn PJ, Easteal S, Christensen H. Cognitive performance and leukocyte telomere length in two narrow age-range cohorts: a population study. *BMC Geriatr*. 2010;10:62.
25. Harris SE, Martin-Ruiz C, von Zglinicki T, Starr JM, Deary IJ. Telomere length and aging biomarkers in 70-year olds: the Lothian Birth Cohort 1936. *Neurobiol Aging*. 2012;33:1486.e3–8.
26. Lee J-Y, Kim J-H, Lee D-C. Combined impact of telomere length and mitochondrial DNA copy number on cognitive function in community-dwelling very old adults. *Dement Geriatr Cogn Disord*. 2017;44:232–43.
27. Brown LL, Zhang YS, Mitchell C, Ailshire J. Does telomere length indicate biological, physical, and cognitive health among older adults? Evidence from the health and retirement study. *J Gerontol Ser A*. 2018;73:1626–32.
28. Mahoney ER, Dumitrescu L, Seto M, Nudelman KNH, Buckley RF, Gifford KA, et al. Telomere length associations with cognition depend on Alzheimer's disease biomarkers. *Alzheimers Dement Transl Res Clin Interv*. 2019;5:883–90.
29. Zhang J, Rane G, Dai X, Shanmugam MK, Arfuso F, Samy RP, et al. Ageing and the telomere connection: an intimate relationship with inflammation. *Ageing Res Rev*. 2016;25:55–69.
30. Ashrafi A, Cosentino S, Kang MS, Lee JH, Schupf N, Andersen SL, et al. Leukocyte telomere length is unrelated to cognitive performance among non-demented and demented persons: an examination of long life family study participants. *J Int Neuropsychol Soc*. 2020;26(9):906–17.
31. Epel E. How "reversible" is telomeric aging? *Cancer Prev Res (Phila)*. 2012;5:1163–8.
32. Di Micco R, Krizhanovsky V, Baker D, d'Adda di Fagnana F. Cellular senescence in ageing: from mechanisms to therapeutic opportunities. *Nat Rev Mol Cell Biol*. 2021;22:75–95.
33. Svenson U, Nordfjall K, Baird D, et al. Blood cell telomere length is a dynamic feature. *PLoS One*. 2011;6:e2148.
34. Ornish D, Lin J, Chan JM, et al. Effect of comprehensive lifestyle changes on telomerase activity and telomere length in men with biopsy-proven low-risk prostate cancer: 5-year follow-up of a descriptive pilot study. *Lancet Oncol*. 2013;14:1112–20.
35. Deng W, Cheung ST, Tsao SW, Wang XM, Tiwari AF. Telomerase activity and its association with psychological stress, mental disorders, lifestyle factors and interventions: a systematic review. *Psychoneuroendocrinology*. 2016;64:150–63.
36. Werner CM, Hecksteden A, Morsch A, Zundler J, Wegmann M, Kratzsch J, et al. Differential effects of endurance, interval, and resistance training on telomerase activity and telomere length in a randomized, controlled study. *Eur Heart J*. 2019;40:34–46.
37. Carulli L, Anzivino C, Baldelli E, Zenobii MF, Rocchi MB, Bertolotti M. Telomere length elongation after weight loss intervention in obese adults. *Mol Genet Metab*. 2016;118(2):138–42.
38. Lavretsky H, Epel ES, Siddarth P, et al. A pilot study of yogic meditation for family dementia caregivers with depressive symptoms: effects on mental health, cognition, and telomerase activity. *Int J Geriatr Psychiatry*. 2012;28:57–65.
39. O'Callaghan N, Parletta N, Milte CM, Benassi-Evans B, Fenech M, Howe PR. Telomere shortening in elderly individuals with mild cognitive impairment may be attenuated with ω -3 fatty acid supplementation: a randomized controlled pilot study. *Nutrition*. 2014;30:489–91.
40. Mahendran R, Gandhi M, Moorakonda RB, Wong J, Kanchi MM, Fam J, et al. Art therapy is associated with sustained improvement in cognitive function in the elderly with mild neurocognitive disorder: findings from a pilot randomized controlled trial for art therapy and music reminiscence activity versus usual care. *Trials*. 2018;19(1):615.
41. Innes KE, Selfe TK, Brundage K, Montgomery C, Wen S, Kandati S, et al. Effects of Meditation and Music-Listening on Blood Biomarkers of Cellular Aging and Alzheimer's Disease in Adults with Subjective Cognitive Decline: An Exploratory Randomized Clinical Trial. *J Alzheimers Dis*. 2018;66:947–70.
42. Campisi M, Cannella L, Celik D, Gabelli C, Gollin D, Simoni M, et al. Mitigating cellular aging and enhancing cognitive functionality: visual arts-mediated Cognitive Activation Therapy in neurocognitive disorders. *Front Aging Neurosci*. 2024;8(16):1354025.
43. Desiato G, Bosco P, Cintoli S, Biagi L, Braschi C, Del Nero C, et al. An inflammatory fingerprint in mild cognitively impaired patients is reversed by physical and cognitive training. *Brain Behav Immun Health*. 2025;18(48):101062.
44. Denham J, Sellami M. Exercise training increases telomerase reverse transcriptase gene expression and telomerase activity: a systematic review and meta-analysis. *Ageing Res Rev*. 2021;70:101411.
45. Thijssen DH, Vos JB, Verseyden C, van Zonneveld AJ, Smits P, Sweep FC, et al. Haematopoietic stem cells and endothelial progenitor cells in healthy men: effect of aging and training. *Ageing Cell*. 2006;5(6):495–503.
46. Balan E, Diman A, Everard A, Nielens H, Decottignies A, Deldicque L. Endurance training alleviates MCP-1 and TERRA accumulation at old age in human skeletal muscle. *Exp Gerontol*. 2021;1(153):111510.
47. Mensà E, Latini S, Ramini D, Storci G, Bonafè M, Olivieri F. The telomere world and aging: analytical challenges and future perspectives. *Ageing Res Rev*. 2019;50:27–42.
48. Grundman M, Petersen RC, Ferris SH, Thomas RG, Aisen PS, Bennett DA, et al. Mild cognitive impairment can be distinguished from Alzheimer disease and normal aging for clinical trials. *Arch Neurol*. 2004;61(1):59–66.
49. Sindi S, Solomon A, Kåreholt I, Hovatta I, Antikainen R, Hänninen T, et al. Telomere Length change in a multidomain lifestyle intervention to prevent cognitive decline: a randomized clinical trial. *J Gerontol A Biol Sci Med Sci*. 2021;76:491–8.

Publisher's Note

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