Int. j. adv. multidisc. res. stud. 2026; 6(3):560-561

Received: 26-04-2026
Accepted: 06-05-2026

International Journal of Advanced Multidisciplinary Research and Studies

ISSN: 2583-049X

Letter to the Editor

As Long as not all Factors Affecting Brain Volume are Considered, Reduction of Brain-Predicted Age Difference cannot be Attributed to Physical Activity

Josef Finsterer
Department of Neurology, Neurology & Neurophysiology Center, Vienna, Austria

DOI: https://doi.org/10.62225/2583049X.2026.6.3.6318
Corresponding Author: **Josef Finsterer**

Letter to the Editor

We read with interest the article by Wan *et al*. on a randomized, controlled trial investigating the effect of endurance training (150 minutes per week for 12 months) on brain age, as measured by brain-predicted age difference (BPAD), in 130 healthy subjects aged 26 to 58 years [1]. The study showed that endurance training reduced BPAD and increased maximum oxygen uptake (VO2max) [1]. While the study is interesting, it leaves some questions unanswered.

First, measuring brain age is difficult, and if the age of the brain is indeed what is meant, it corresponds to the age of the rest of the body at the time of measurement. If, on the other hand, the brain's performance, functional, or morphological changes are meant, these depend on numerous factors. The relationship between brain health and exercise is complex and requires consideration of further influencing factors. In addition to arterial blood flow, brain health depends on venous and glymphatic drainage, the function of the blood-brain barrier, genetic predisposition, personality type, socialization, available coping strategies, previous cognitive performance, educational level, socioeconomic status, sleep, environmental factors, nutrition, comorbidities (other than hypertension or neurological disorders), concomitant medication, mood, and alertness. Since the musculature is also an endocrine organ [2], physical exercise can not only improve cardiovascular function but also stimulate the secretion of myokines such as irsin or Metrnl-like myokines.

Second, brain volume depends not only on physical activity but also on various other factors. These include age, sex, time of day (brain volume is higher in the morning than in the evening), hydration status, comorbidities (e.g., diabetes), previous brain surgery, the use of concomitant medications, sleep (which leads to a redistribution of fluids in the brain), and the method used to measure brain volume [3].

Third, we disagree with the view expressed in the introduction that only midlife is a dynamic phase of life. In general, all phases of life can be dynamic, depending on individual circumstances and events. If a child suffers from early childhood, treatment-resistant epilepsy, their early childhood is characterized by attempts to stop seizures, and their life is extremely dynamic due to the numerous medical needs.

The fourth point is that cerebral atrophy does not necessarily imply cognitive decline [1]. There are numerous reports of patients with congenital or acquired focal cerebral atrophy who did not develop any impairment of their cognitive functions during their lifetime [4]. For example, patients with arachnoid cysts and reduced brain volume usually behave normally and do not develop any impairment of their higher brain functions. Similarly, patients with porencephaly do not necessarily exhibit cognitive impairment. Unless all factors influencing brain volume are included in the analysis, a reduction in BPAD cannot necessarily be attributed to regular, long-term physical exercise.

Declarations
Ethical Approval: Not applicable.

Consent to Participation: Not applicable.

Consent for Publication: Not applicable.

Funding: None received.

Availability of Data and Material: All data are available from the corresponding author.

Completing Interests: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contribution: JF was responsible for the design and conception, discussed available data with coauthors, wrote the first draft, and gave final approval. xx: contributed to literature search, discussion, correction, and final approval.

Acknowledgements: None.

Keywords: Aerobic Exercise, Brain Volume, Brain-Predicted Age Difference, Cardiovascular Risk

References
1. Wan L, Molina-Hidalgo C, Crisafio ME, Grove G, Leckie RL, Kamarck TW, *et al*. Fitness and exercise effects on brain age: A randomized clinical trial. J Sport Health Sci, Aug 13, 2025; 15:101079. Doi: 10.1016/j.jshs.2025.101079
2. Iglesias P. Muscle in Endocrinology: From Skeletal Muscle Hormone Regulation to Myokine Secretion and its Implications in Endocrine-Metabolic Diseases. J Clin Med, Jun 25, 2025; 14(13):4490. Doi: 10.3390/jcm14134490
3. Dieleman N, Koek HL, Hendrikse J. Short-term mechanisms influencing volumetric brain dynamics. Neuroimage Clin, Sep 6, 2017; 16:507-513. Doi: 10.1016/j.nicl.2017.09.002
4. Morrison C, Dadar M, Shafiee N, Villeneuve S, Louis Collins D. For Alzheimer's Disease Neuroimaging Initiative. Regional brain atrophy and cognitive decline depend on definition of subjective cognitive decline. Neuroimage Clin. 2022; 33:102923. Doi: 10.1016/j.nicl.2021.102923.