BRAINIACS
BRAIN IMAGING AND COMPUTING SCIENCES

2025 Volume 6
Issue 1 Edoc YD2D1576B

Neurovascular Mechanisms in Peripheral Arterial Disease: Impact of Physical Exercise and Cognitive Training *

Clotilde Boffy, Camille Leroy, Stefano Lanzi, Lucia Mazzolai, Alessandra Lintas †

Abstract

Peripheral Arterial Disease (PAD) is characterized by atherosclerosis-induced vascular insufficiency, causing reduced blood flow, intermittent claudication, and, in severe cases, rest ischemia or gangrene. Beyond peripheral effects, PAD impairs neurovascular coupling and cognitive functions, such as working memory and executive processes, due to altered cerebral perfusion and chronic inflammation. This study implements a 12-week dual-intervention protocol combining supervised exercise training (SET) and working memory training (WMT) to address these deficits. SET involves individualized multimodal exercise, while WMT uses the Dual n-Back Task to enhance prefrontal connectivity. Multimodal neuroimaging (EEG, fast optical neuroimaging) assesses neurovascular biomarkers and cognitive outcomes. This approach addresses a gap in longitudinal studies, offering insights into neuroprotection and cognitive rehabilitation for patients with PAD with vascular risk profiles.

Keyphrases

Neurovascular coupling, Peripheral Arterial Disease, cognitive rehabilitation, supervised exercise training, multimodal neuroimaging.

Introduction

Peripheral Arterial Disease (PAD) results from atherosclerosis, where lipid deposits and inflammatory cells form plaques that narrow or obstruct lower limb arteries, reducing blood, oxygen, and nutrient delivery to skeletal muscles (Gardner et al. 2021). The primary symptom, intermittent claudication, manifests as muscle pain during exercise, such as walking, which subsides at rest. Advanced stages may lead to rest ischemia, ulcers, or gangrene, significantly impacting mobility and quality of life (Mazzolai et al. 2024).

Beyond peripheral effects, PAD compromises neurovascular coupling and cognitive function due to altered cerebral perfusion, arterial stiffness, and chronic inflammation (Owens et al. 2022). These changes impair neural signaling, working memory, and executive functions, increasing cognitive decline risk in older adults (Bliss et al. 2021). Patients with PAD exhibit reduced oxyhemoglobin (HbO) consumption and attenuated EEG evoked potentials during cognitive tasks, indicating neurovascular decoupling (Owens et al. 2022).

Structured physical exercise enhances cognitive function by upregulating anti-inflammatory cytokines, brain-derived neurotrophic factor (BDNF), and cerebral angiogenesis, while improving endothelial function (Leardini-Tristao et al. 2019). Cognitive training, targeting working memory, strengthens functional connectivity and information processing (Zhao et al. 2022).

Previous studies underscore a growing consensus that exercise training not only benefits physical function but may also support or enhance cognitive health in elder patients with vascular and cerebrovascular diseases, with mechanisms still under investigation (Bliss et al. 2021; Brunt et al. 2019; Leardini-Tristao et al. 2019). However, very limited interventions have systematically analyzed the association between exercise training and cognitive function in PAD (Cavalcante et al. 2018). This study addresses this gap through a dual-intervention protocol, using multimodal neuroimaging to assess neurovascular and cognitive outcomes.

Study Protocol

Our study implements a 12-week dual-intervention protocol combining supervised exercise training (SET) and working memory training (WMT), with outcomes assessed via multimodal neuroimaging (EEG, fast optical neuroimaging). Self-perceived walking (dis)abilities are assessed with the Walking Impairment Questionnaire (WIQ) (Coyne et al. 2003). Dietary evaluation is assessed with Cardiovascular Dietary Questionnaire 2 (CDQ-2) (Paillard et al. 2021). The cognitive function is assessed by the Mini-Mental State Examination (MMSE) (Folstein et al. 1975), Montreal Cognitive Assessment (MoCA) (Nasreddine et al. 2005), Dual n-Back memory task (Jaeggi et al. 2008), Corsi Block-Tapping Test (Kessels et al. 2008) and by the Wechsler Adult Intelligence Scale (Wechsler 2008).

In addition to the core neurocognitive and vascular assessments, comprehensive epidemiological and clinical data will be collected for all participants. These include pharmacological treatment regimens, comorbidities, and the presence of polyvascular disease versus isolated PAD. These variables will be systematically integrated into the final data analysis to support stratified interpretations and enhance the relevance of the findings across diverse PAD patient profiles.

*Report presented 2025-06-05, Neural Coding 2025, 16th International Neural Coding Workshop, Ascona Switzerland.
†Correspondence to alessandra.lintas@unil.ch.

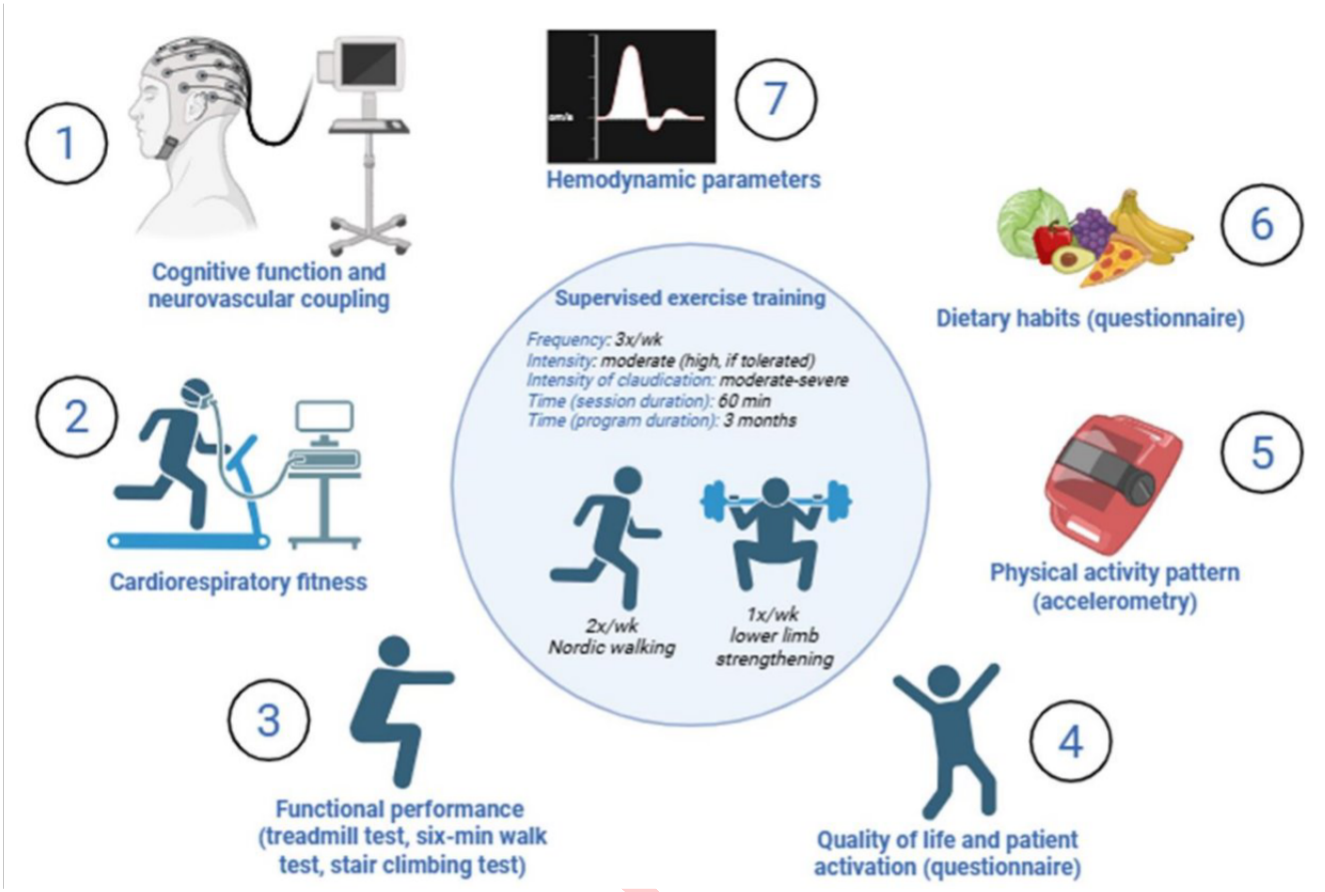

Figure 1: Schematic representation of the supervised physical training approach and studied outcomes, by courtesy of S. Lanzi.

Supervised Exercise Training (SET)

A 12-week multimodal training program, combining Nordic Walking and lower limb strengthening, involves patients participating in supervised exercise sessions three times per week, as shown in Fig. 1 (Lanzi, Boichat, et al. 2021). In accordance with current guidelines (Lanzi, Pousaz, et al. 2023; Mazzolai et al. 2024), each session lasts between 30 and 60 minutes and is mainly conducted at moderate exercise intensity (assessed using Borg's scale and heart rate). Sessions are performed at moderate to severe claudication pain levels and are supervised by clinical exercise physiologists to ensure adherence and safety.

Working Memory Training (WMT)

In a pre- and post-intervention session, at the laboratory, all participants play adaptive Dual n-Back Task (DNB). This task requires participants to simultaneously track sequences of auditory and visual stimuli, recalling items presented n steps earlier, increasing in difficulty as n grows. This adaptive task –enabling the increase in difficulty at each successful block of trials– targets both verbal and visuospatial WM, engaging the prefrontal cortex and enhancing functional connectivity in frontoparietal networks, supporting cognitive resilience. The WM training starts the day after the pre-training session. At home, the participants play DNB by mean of an Internet remote connection to a server with protected access with real-time feedback. The WMT is conducted four times weekly for 30 minutes, based on 20-blocks daily adaptive dual n-back sessions, which align with protocols previously validated for adult ADHD populations (Dotare et al. 2020; Jaquerod, Mesrobian, et al. 2020; Lintas et al. 2021).

Neuroimaging and Cognitive Assessment

Participants undergo pre- and post-intervention assessments using the Attention Network Test (ANT) to evaluate attention, memory, and executive functions. A 64-channel high-density EEG coupled with fast optical neuroimaging (referred to as FONI, i.e. frequency-domain functional near-infrared spectroscopy, Fig. 2) at 125 Hz sampling (Gratton and Fabiani 2010; Jaquerod, Knight, et al. 2024) captures stimulus-related evoked potentials and cortical hemodynamic responses (oxygenated [HbO] and deoxygenated hemoglobin [HRx]) (Owens et al. 2022).

Higher-order spectral analysis, specifically cross-bicoherence (Abe et al. 2024), will identify novel biomarkers of neurovascular coupling in the left dorsolateral prefrontal cortex (DLPFC), a key region for cognitive functions, surpassing traditional metrics like coherence or Granger causality. Machine learning models will analyze datasets integrating performance at exercise, behavioral, and brain signals data (Masulli et al. 2020).

Discussion

Therapeutic Potential and Synergies

The neurovascular decoupling observed in patients with PAD, marked by reduced [HbO] consumption and attenuated EEG potentials, underscores the urgent need for interventions that bridge peripheral and cerebral health (Owens et al. 2022). Our dual-intervention protocol,

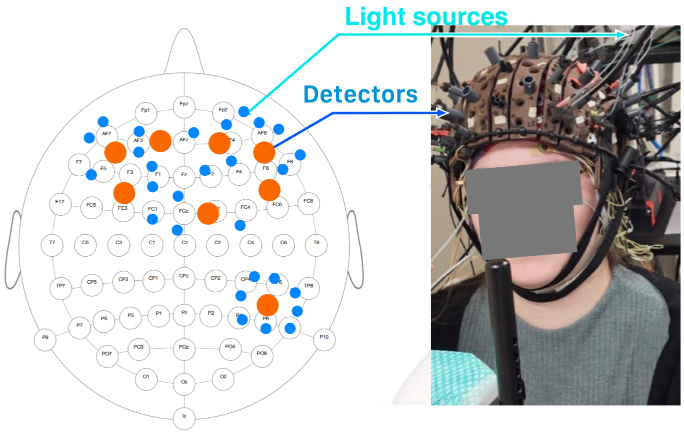

Figure 2: Multimodal neuroimaging combining EEG and FONI recording of brain signals. Schematic representation of the co-localisation of light detectors (dark blue circles) and light sources (light blue squares) and the 64-channel electrophysiological setup over prefrontal and premotor areas of the cerebral cortex. The picture illustrates our custom-made mounting system showing the photo-multiplier tube detectors and fibers optic bundles placed over the participant's head for the event-related optical signal data acquisition. Standard 64-channels EEG data acquisition is also performed during FONI recordings.

combining SET and WMT, offers a promising approach. SET fosters vascular remodeling, enhances endothelial function, and boosts anti-inflammatory cytokines and BDNF, potentially restoring cerebral perfusion (Lanzi, Pousaz, et al. 2023; Leardini-Tristao et al. 2019). Meanwhile, WMT strengthens prefrontal connectivity, bolstering working memory and executive functions (Zhao et al. 2022). But what makes this combination particularly compelling? The synergy lies in their complementary mechanisms: SET addresses the vascular roots of cognitive impairment, while WMT directly targets neural efficiency. Together, they may create a feedback loop where improved blood flow supports neural plasticity, and enhanced cognition sustains motivation for physical activity. This raises an intriguing question: could such integrative strategies redefine rehabilitation for vascular diseases in aging populations?

Beyond individual benefits, the protocol's implications extend to public health. With PAD prevalence rising alongside global aging trends, interventions that preserve cognitive function could reduce healthcare burdens and enhance quality of life (Mazzolai et al. 2024). Yet, the study's multimodal neuroimaging approach—combining EEG and FONI—adds another layer of significance. By pinpointing neurovascular biomarkers, it paves the way for personalized rehabilitation, where interventions are tailored to individual vascular and cognitive profiles (Bliss et al. 2021). Imagine a future where clinicians use real-time brain data to adjust exercise or cognitive training regimens, optimizing outcomes for each patient.

Challenges and Limitations

Despite its promise, the study faces challenges that invite reflection. The 12-week duration, while practical, may not capture the full scope of cognitive and vascular benefits, as sustained improvements often emerge over months or years (McDermott 2022). This prompts a broader question: how do we balance research feasibility with the need for long-term insights? Participant heterogeneity—spanning PAD severity, comorbidities, and cognitive baselines—further complicates outcomes, necessitating larger samples to achieve statistical robustness. Moreover, the focus on the DLPFC, while justified by its role in cognition, may overlook other regions, such as the parietal cortex, that contribute to cognitive processing. Could a whole-brain approach reveal additional insights into PAD's cognitive impact?

Real-world implementation poses another hurdle. The supervised nature of SET and WMT ensures adherence but may not translate to settings where access to physiologists or technology is limited (Mazzolai et al. 2024). This raises a critical issue: how can we democratize such interventions? Cultural and socioeconomic factors also warrant consideration—will patients in diverse contexts embrace cognitive training platforms or structured exercise? These challenges highlight the need for adaptable, scalable solutions that respect patient realities.

Future Directions

Looking ahead, this study opens exciting avenues for exploration. Extending interventions to 6–12 months could reveal whether cognitive and vascular benefits endure, informing clinical guidelines (McDermott 2022). Larger, multicenter trials would enhance generalizability, capturing diverse PAD populations. Wearable technologies, such as smartwatches monitoring exercise intensity or cognitive performance, could bridge the gap between supervised and home-based interventions, empowering patients and improving adherence (Mazzolai et al. 2024). But what if we pushed further? Investigating molecular pathways, like myokines or BDNF signaling, could unravel the biological underpinnings of cognitive gains, guiding targeted therapies (Leardini-Tristao et al. 2019).

Combining SET and WMT with pharmacological or nutritional strategies—such as statins or anti-inflammatory diets—holds additional promise. Could these multimodal approaches amplify neuroprotection? Expanding neuroimaging to include functional connectivity analyses or other brain regions might offer a holistic view of PAD's cognitive toll. Ultimately, this study invites us to reimagine rehabilitation not as a siloed endeavor but as an integrated effort to restore body and mind, addressing the complex interplay of vascular and cognitive health in PAD.

Conclusion

This study pioneers a dual-intervention protocol combining SET and WMT to tackle neurovascular and cognitive deficits in patients with PAD. Through multimodal neuroimaging (EEG, FONI), it offers a robust framework to explore neuroprotection and cognitive rehabilitation, filling a critical gap in longitudinal PAD research. The findings hold promise for enhancing cognitive resilience and quality of life in older adults with vascular risk profiles. As we look to the future, scaling these interventions, extending their duration, and personalizing them through technology and biomarkers will be key to maximizing their impact in an aging world.

Citation

Brainiacs 2025 Volume 6 Issue 1 Edoc YD2D1576B
Title: "Neurovascular Mechanisms in Peripheral Arterial Disease: Impact of Physical Exercise and Cognitive Training "
Authors: Clotilde Boffy, Camille Leroy, Stefano Lanzi, Lucia Mazzolai, Alessandra Lintas
Dates: created 2025-05-01, presented 2025-06-05, published 2025-07-18,

Contact: alessandra.lintas@unil.ch
URL: BrainiacsJournal.org/arc/pub/Boffy2025NMPADIPE
PDP: /Nexus/Brainiacs/Boffy2025NMPADIPE
DOI: /10.48085/YD2D1576B

Affiliations

Clotilde Boffy, clotilde.boffy@unil.ch; Camille Leroy, camille.leroy@unil.ch; Alessandra Lintas, alessandra.lintas@unil.ch; Neuroheuristic Research Laboratory, University of Lausanne, Lausanne, Switzerland.

Stefano Lanzi, stefano.lanzi@unil.ch; Lucia Mazzolai, lucia.mazzolai@unil.ch; CHUV Angiology Department, University of Lausanne, Lausanne, Switzerland.

Contributions

All authors contributed to the study. CB and CL contributed equally to writing the manuscript. SL and LM were responsible for the study design. AL was responsible for the study design and revision of the manuscript.

References

[1] T. Abe, Y. Asai, A. Lintas, and A. E. P. Villa. "Detection of quadratic phase coupling by cross-bicoherence and spectral Granger causality in bifrequencies interactions." *Sci Rep* 14.1 (Apr. 2024), p. 8521. DOI: 10.1038/s41598-024-59004-8 (cited p. 2).

[2] E. S. Bliss, R. H. Wong, P. R. Howe, and D. E. Mills. "Benefits of exercise training on cerebrovascular and cognitive function in ageing." *J Cereb Blood Flow Metab* 41.3 (Mar. 2021), pp. 447–470. DOI: 10.1177/0271678X20957807 (cited pp. 1, 3).

[3] A. Brunt, D. Albines, and D. Hopkins-Rosseel. "The Effectiveness of Exercise on Cognitive Performance in Individuals with Known Vascular Disease: A Systematic Review." *J Clin Med* 8.3 (Mar. 2019). DOI: 10.3390/jcm8030294 (cited p. 1).

[4] B. R. Cavalcante, A. H. Germano-Soares, A. M. Gerage, A. Leicht, et al. "Association between physical activity and walking capacity with cognitive function in peripheral artery disease patients." *Eur J Vasc Endovasc Surg* 55.5 (May 2018), pp. 672–678. DOI: 10.1016/j.ejvs.2018.02.010 (cited p. 1).

[5] K. S. Coyne, M. K. Margolis, K. A. Gilchrist, S. Grandy, and B. Papermaster. "Evaluating effects of method of administration on Walking Impairment Questionnaire." *Journal of Vascular Surgery* 38.2 (2003), pp. 296–304. DOI: 10.1016/S0741-5214(03)00387-3 (cited p. 1).

[6] M. Dotare, M. Bader, S. K. Mesrobian, Y. Asai, A. E. P. Villa, and A. Lintas. "Attention Networks in ADHD Adults after Working Memory Training with a Dual n-Back Task." *Brain Sciences* 10.10 (2020), p. 715. DOI: 10.3390/brainsci10100715 (cited p. 2).

[7] M. F. Folstein, S. E. Folstein, and P. R. McHugh. ""Mini-mental state". A practical method for grading the cognitive state of patients for the clinician." *Journal of Psychiatric Research* 12.3 (1975), pp. 189–198. DOI: 10.1016/0022-3956(75)90026-6 (cited p. 1).

[8] A. W. Gardner, P. S. Montgomery, M. Wang, B. Shen, et al. "Cognitive decrement in older adults with symptomatic peripheral artery disease." *Geroscience* 43.5 (Oct. 2021), pp. 2455–2465. DOI: 10.1007/s11357-021-00437-8 (cited p. 1).

[9] G. Gratton and M. Fabiani. "Fast optical imaging of human brain function." *Frontiers in Human Neuroscience* 4 (2010), p. 52. DOI: 10.3389/fnhum.2010.00052 (cited p. 2).

[10] S. M. Jaeggi, M. Buschkuehl, J. Jonides, and W. J. Perrig. "Improving fluid intelligence with training on working memory." *Proceedings of the National Academy of Sciences* 105.19 (2008), pp. 6829–6833. DOI: 10.1073/pnas.0801268105 (cited p. 1).

[11] M. E. Jaquerod, R. S. Knight, A. Lintas, and A. E. P. Villa. "A Dual Role for the Dorsolateral Prefrontal Cortex (DLPFC) in Auditory Deviance Detection." *Brain Sci* 14.10 (2024), p. 994. DOI: 10.3390/brainsci14100994 (cited p. 2).

[12] M. E. Jaquerod, S. K. Mesrobian, A. E. P. Villa, M. Bader, and A. Lintas. "Early Attentional Modulation by Working Memory Training in Young Adult ADHD Patients during a Risky Decision-Making Task." *Brain Sci* 10.1 (Jan. 2020), p. 38. DOI: 10.3390/brainsci10010038 (cited p. 2).

[13] R. P. C. Kessels, M. J. E. van Zandvoort, A. Postma, L. J. Kappelle, and E. H. F. de Haan. "The backward span of the Corsi Block-Tapping Task and its association with the WAIS-III Digit Span." *Assessment* 15.4 (2008), pp. 426–434. DOI: 10.1177/1073191108315611 (cited p. 1).

[14] S. Lanzi, J. Boichat, L. Calanca, P. Auberin, D. Malatesta, and L. Mazzolai. "Gait changes after supervised exercise training in patients with symptomatic lower extremity peripheral artery disease." *Vascular Medicine* 26.3 (2021), pp. 259–266. DOI: 10.1177/1358863X19848351 (cited p. 2).

[15] S. Lanzi, A. Pousaz, L. Calanca, and L. Mazzolai. "Time-course evolution of functional performance during a 3-month supervised exercise training program in patients with symptomatic peripheral artery disease." *Vascular Medicine* 28.5 (2023), pp. 404–411. DOI: 10.1177/1358863X31191908 (cited pp. 2, 3).

[16] M. Leardini-Tristao, A.-L. Charles, A. Lejay, M. Pizzimenti, et al. "Beneficial Effect of Exercise on Cognitive Function during Peripheral Arterial Disease: Potential Involvement of Myokines and Microglial Anti-Inflammatory Phenotype Enhancement." *J Clin Med* 8.5 (May 2019). DOI: 10.3390/jcm8050653 (cited pp. 1, 3).

[17] A. Lintas, S. K. Mesrobian, M. Bader, and A. E. P. Villa. "ERPs in Controls and ADHD Patients During Dual n-Back Task." In: *Advances in Cognitive Neurodynamics (VII): Proceedings of the Seventh International Conference on Cognitive Neurodynamics – 2019*. Ed. by A. Lintas, P. Enrico, X. Pan, R. Wang, and A. Villa. Springer Nature Singapore Pte Ltd., 2021, pp. 189–203. DOI: 10.1007/978-981-16-0317-4_20. URL: https://doi.org/10.1007/978-981-16-0317-4_20 (cited p. 2).

[18] P. Masulli, F. Masulli, S. Rovetta, A. Lintas, and A. E. P. Villa. "Fuzzy Clustering for Exploratory Analysis of EEG Event-Related Potentials." *IEEE Trans Fuzzy Syst* 28.1 (2020), pp. 28–38. DOI: 10.1109/TFUZZ.2019.2910499 (cited p. 2).

[19] L. Mazzolai, J. Belch, M. Venermo, V. Aboyans, et al. "Exercise therapy for chronic symptomatic peripheral artery disease." *Eur Heart J* 45.15 (Apr. 2024), pp. 1303–1321. DOI: 10.1093/eurheartj/ehad734 (cited pp. 1–3).

[20] M. M. McDermott. "Exercise therapy for peripheral artery disease in 2022: Progress and a prediction." *Vasc Med* 27.2 (Apr. 2022), pp. 113–115. DOI: 10.1177/1358863X221082702 (cited p. 3).

[21] Z. S. Nasreddine, N. A. Phillips, V. Bédirian, S. Charbonneau, I. Whitehead, I. Collin, J. L. Cummings, and H. Chertkow. "The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment." *Journal of the American Geriatrics Society* 53.4 (2005), pp. 695–699. DOI: 10.1111/j.1532-5415.2005.53221.x (cited p. 1).

[22] C. D. Owens, P. Mukli, T. Csipo, A. Lipecz, et al. "Microvascular dysfunction and neurovascular uncoupling are exacerbated in peripheral artery disease, increasing the risk of cognitive decline in older adults." *Am J Physiol Heart Circ Physiol* 322.6 (June 2022), H924–H935. DOI: 10.1152/ajpheart.00616.2021 (cited pp. 1, 2).

[23] F. Paillard, O. Flageul, G. Mahe, A. Lancry, et al. "Validation and reproducibility of a short food frequency questionnaire for cardiovascular prevention." *Archives of Cardiovascular Diseases* 114.7-8 (2021), pp. 570–576. DOI: 10.1016/j.acvd.2020.12.008 (cited p. 1).

[24] D. Wechsler. *WAIS-IV: Wechsler Adult Intelligence Scale—Fourth Edition*. San Antonio, TX: Psychological Corporation, 2008 (cited p. 1).

[25] Y. Zhao, Y. Li, L. Wang, Z. Song, et al. "Physical Activity and Cognition in Sedentary Older Adults: A Systematic Review and Meta-Analysis." *J Alzheimers Dis* 87.3 (2022), pp. 957–968. DOI: 10.3233/JAD-220073 (cited pp. 1, 3).

