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The Adaptive Potential of a Multi-Domain System:
Functional, Cognitive and Physiological Insights from an Intervention Study on Pre-Frail Older Adults

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INTRODUCTION

Population ageing is changing the fabric of modern societies and thus reframes the primary objective of health care for older adults: not merely to extend life, but to preserve functional ability and independence throughout the process. The World Health Organization's *healthy-ageing* construct is shifting the focus from mono-domain diseases-centred assessments toward a more systemic and dynamic approach, with relevance to the set of physical and mental capacities that people draw on to meet everyday challenges. Framing ageing as a problem of maintaining functional reserve, rather than only treating specific pathologies, calls for interventions and measurement strategies that consider the multi-domain facets of the system, how the whole organism responds to realistic stressors and manages to adapt and distribute resources over time.

Healthy ageing framework. *Frailty* and *Intrinsic Capacity* capture complementary expressions of diminished physiological and functional reserve: a state in which otherwise modest stressors can produce disproportionate loss of function, higher dependency and worse long-term outcomes. The Frailty phenotype and deficit-accumulation models converge on the view that Frailty is a multisystemic and probabilistic concept, not a single disease, but based on symptoms relying on different domains (Cesari et al., 2014; C. I. Cohen et al., 2023; Fried et al., 2001; Morley et al., 2013). Intrinsic Capacity (IC) is a complementary, capacity-centred frame: while Frailty denotes vulnerability, IC quantifies the reserves of functions still available to an individual (Belloni & Cesari, 2019; Cesari et al., 2018). Conceptual and longitudinal work suggests that declines in IC presage transitions into Frailty and disability (Belloni & Cesari, 2019; Sánchez-Sánchez et al., 2022; Yu et al., 2025), so detecting and strengthening IC in the *pre-Frail* window is a promising preventive strategy. The PRAISE project adopts this view, treating IC and Frailty as distinct but intertwined features of ageing that are best understood and modified within an integrated systems framework.

Probing the system. If reserve is revealed under challenge, static, one-off tests may be incomplete. Two complementary classes of dynamic probes are especially informative. First, *dual-task paradigms*, by stressing the system through concurrent cognitive and motor demands, index how well the brain-body integration reallocates limited resources in common situations (e.g. walking while talking, navigating through obstacles while reasoning). Dual-task costs quantify the performance decrement when two demands compete in relation to basic motor activity, in order to quantify the cost that the extra cognitive load is charging on the system. Second, Heart Rate Variability (HRV) at rest and under orthostatic challenge, indexes *autonomic flexibility*. Parasympathetic and Sympathetic outflows are strictly connected to cognitive performance, physical state and emotion regulation (Cattaneo et al., 2021; Thayer, Hansen, et al., 2009), and play an essential role in the system's adaptability capacity. The Neurovisceral Integration Model links prefrontal executive circuits with vagally-mediated cardiac control: stronger top-down control and higher parasympathetic driven HRV tend to associate with better executive functioning and psychological wellbeing (Thayer, Hansen, et al., 2009; Thayer & Lane, 2000a).

Combining a thorough assessment on Frailty, Intrinsic Capacity, dual-tasking and autonomic responses therefore provides a window onto cognitive, psychological, functional, nutritional, sensorial, motor and physiological reserves, at the base of a *healthy ageing* prospective. From a systems perspective, Frailty emerges when the cognitive, psychological and/or motor subsystems weakens. Thus, an intervention that challenges cognitive-motor integration and controls for physiological adaptability may restore or increase functional reserve and reduce Frailty, while controlling for associated changes in autonomic flexibility. The PRAISE design tests this conceptual cascade by measuring dual-task performance, HRV reactivity (including orthostatic challenge), Intrinsic Capacity, Frailty status and daily levels of motor activity.

EXERGAMING. Moreover, a recent and promising method to probe and the engage the system's multi-domains is *Exergaming*, interactive, engaging tasks executed on platforms that combine physical movement and cognitive demands, naturally embedding dual-task challenges. Systematic reviews and trials report cognitive and, to a lesser extent, motor benefits from exergame programs (Maggio et al., 2025); some studies even show HRV improvements after exergame training, suggesting effects on autonomic regulation (Eggenberger et al., 2020). However, most prior studies examine a limited set of outcomes in isolation (whether it is cognition or gait or HRV), leaving open the critical question whether a *personalized, multi-domain exergame program* can shift global IC composites and alter Frailty trajectories by acting simultaneously on cognitive, motor, psychological and autonomic subsystems. The PRAISE project was designed specifically to address this gap.

METHODS. PRAISE is a monocentric, randomized, two-arm pilot trial that enrols older adults in the pre-Frailty range (FI 0.10–0.40), funded by the Romeo and Enrica Invernizzi Foundation. Participants are randomized to a year-long, personalized exergame dual-task intervention delivered via the Dividat Senso platform (see Chapter 2) or to a control arm receiving good-practice advice. Assessments occur at baseline (T0) and after ≈12 months (T1) and include: Frailty Index, composite IC scores; an expanded neuropsychological battery including dual-task paradigms; physical performance measures; pulmonary function; psychological and social scales; continuous activity monitoring through actigraphic registration; HRV recorded supine and during active standing.

Detailed inclusion/exclusion, ethical approvals and sample flows are reported in Chapter 2.

The analytic plan is intentionally exploratory and multimodal. First, cross-sectional network and clustering analyses at T0 (and again at T1) map how IC domains, Frailty and physiological markers organize into communities. Second, longitudinal mixed-effects models test group x time interactions for primary outcomes (Frailty, IC composites) and secondary outcomes. This combination of exploratory networks mapping and confirmatory longitudinal inference is chosen to reflect the study's systems hypothesis while maintaining statistical rigor despite the relatively modest sample size.

Expected results and hypotheses. Grounded in theory and prior evidence, PRAISE hypothesized that: (1) the exergame dual-task intervention would reduce Frailty and increase the IC composites, with a particular focus on cognitive and locomotor domains; (2) dual-task performance would improve and mediate functional gains; (3) autonomic adaptability would increase after training.

Rationale and significance. PRAISE addresses different literature gaps: previous work has largely examined IC, Frailty, HRV or exergames in isolation, leaving unanswered whether a personalized, multi-domain dual-task intervention can shift the integrated system that underlies healthy ageing. By combining dynamic assessments (dual-task costs, orthostatic HRV), ecological monitoring (actigraphy), multi-domain evaluations, and a tailored exergame training program, the study aims to demonstrate not only whether change is possible in pre-frail older adults but also *how* change propagates across cognitive, affective, autonomic and motor subsystems. If successful, this systems-oriented approach would support interventions that restore adaptive responses thereby preserving independence and improving quality of life in later life.

The thesis will be organised into four principal chapters that move from theory to evidence and interpretation.

Chapter 1 will analyse the current research background, including the WHO Intrinsic Capacity framework, Frailty models, the brain-heart axis interplay and the relevance of dual-task assessments and interventions.

Chapter 2 will provide the scopes and methods of the project by detailing the study design, eligibility criteria, intervention and control conditions, data collection procedures and assessment protocols. Statistical analysis implemented are described along with data quality and sample characterization.

Chapter 3 presents the empirical findings from baseline descriptive and network analyses, clustering structures, and longitudinal mixed-effects and within-group contrasts of T1 vs T0.

Chapter 4 will focus on the discussion of the results in light of the theoretical background, highlighting implications for adaptive reserve across cognitive, physiological and functional domains, while considering methodological limitations.

Additional material (detailed protocols, full tables, and supplementary figures) is provided in appendices, and references are listed at the end of the thesis.

A repository of the study containing visual interactive networks is available at the following link: https://lucia-pp.github.io/PRAISE/.

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CHAPTER 1

BACKGROUND

1.1 HEALTHY AGING

The demographic transformation that global population is facing is unprecedented: according to the World Health Organization (WHO), by 2050, the number of people aged 60 years and older is projected to more than double, reaching 2.1 billion worldwide (WHO, 2021). The world's population is rapidly and continuously ageing (Fig. 1) and thus is life's expectancy (Fig 2,3,4). This progressive shift of the population towards older age is largely attributed to improvements in healthcare, nutrition, sanitation, and education, which have extended life expectancy across both developed and developing nations (United Nations, 2020). In this scenario ageing becomes one of the most profound and widespread public health challenges of the 21st century. An increase in longevity and life expectancy does not necessarily correspond to an improvement in lifestyle expectancy. Many older adults spend their final years living with significant functional impairments, multiple chronic conditions, and heightened vulnerability (Beard et al., 2016).

The WHO faced this demographic challenge by introducing the concept of *healthy ageing*, which emphasizes the need of preservation of individual's functional abilities and of promoting autonomy and quality of life as people grow older. Accordingly, WHO redefined ageing policy through its World Report on Ageing and Health (WHO, 2015) and the Decade of Healthy Ageing 2021–2030 initiative (WHO, 2020). These guidelines, by moving beyond the disease-focused approaches, aim at improving the lives of older people, their families, and communities by focusing on fostering healthy ageing through integrated care and age-friendly environments to promote resilience, participation and independence in older age.

The emphasis on the concept of *functional ability* marks a paradigmatic shift in geriatric care and public health strategy (Cesari et al., 2018). Within this context, addressing the continuum of ageing becomes central to design effective healthy ageing policies and programs, promoting interventions to maintain mobility, cognitive function, and social engagement, mandatory conditions grounding the quality of life in humans.

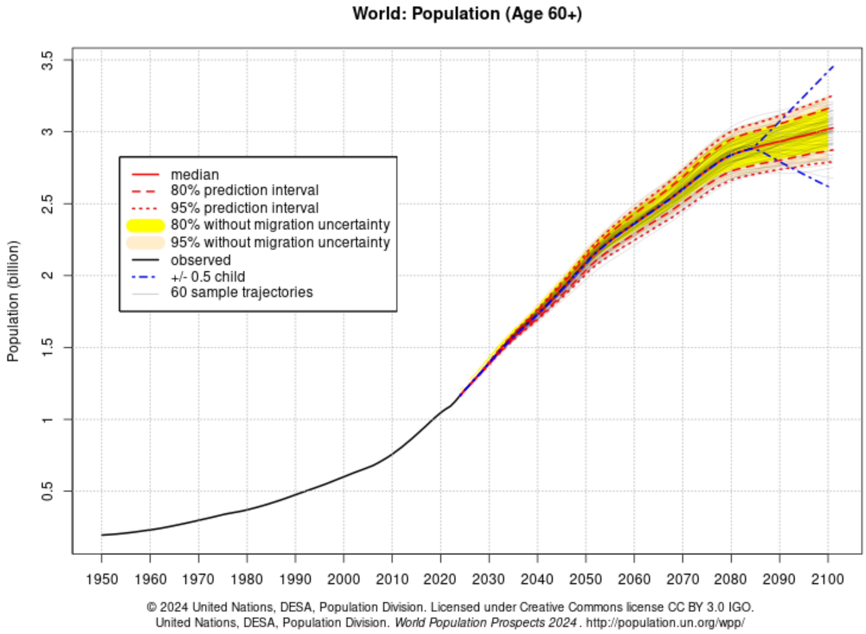


FIGURE 1. *Probabilistic projection of world population (billions) aged 60+ from year 1950 to 2100.*

This chapter provides an overview of the *healthy ageing* perspective based on its pillars: the concepts of *Frailty* and *Intrinsic Capacity* (IC). Understanding these foundational principles is essential to address age-related physiological decline and to develop effective interventions to support older adults across the full ageing process.

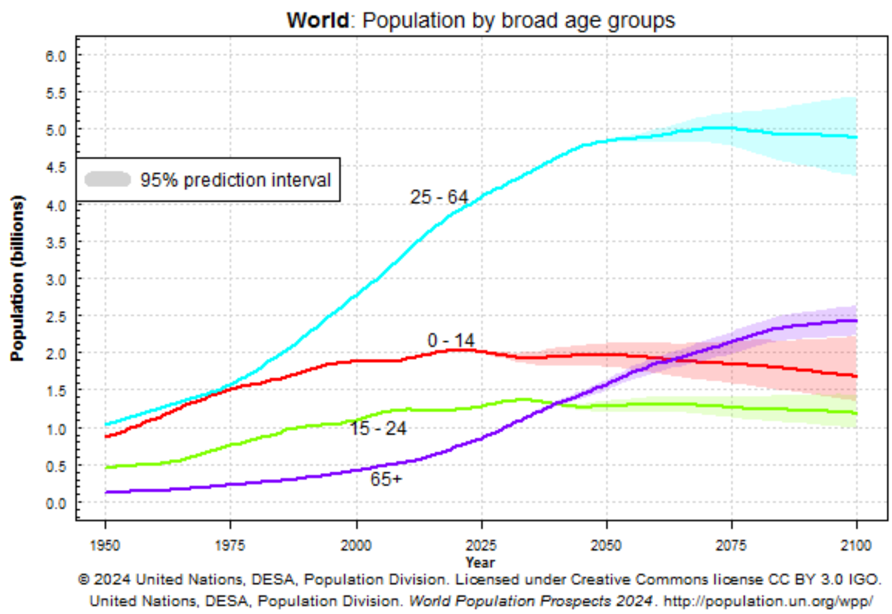


FIGURE 2 *World population prospect (2024) by broad age groups.*

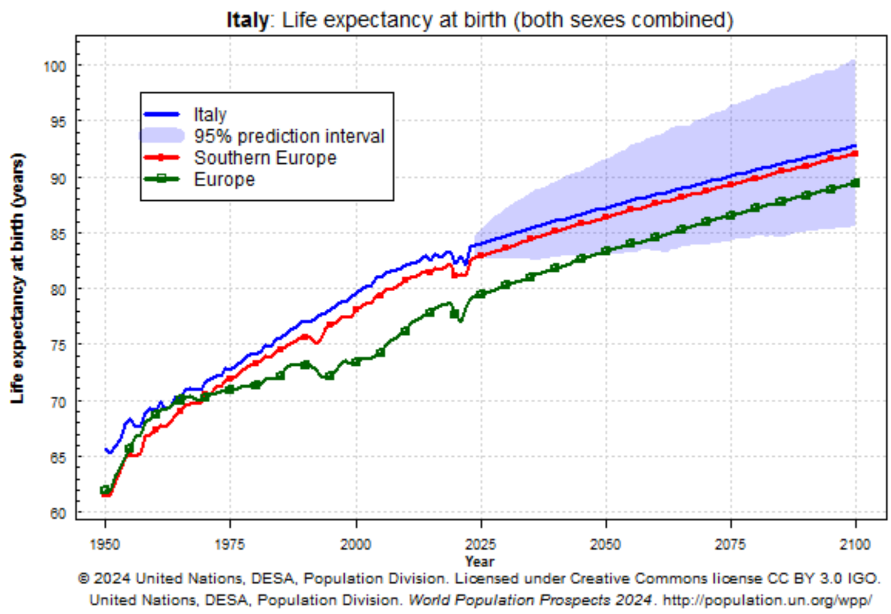


FIGURE 3 *Life expectancy at birth in Italy compared to Europe and Southern Europe countries.*

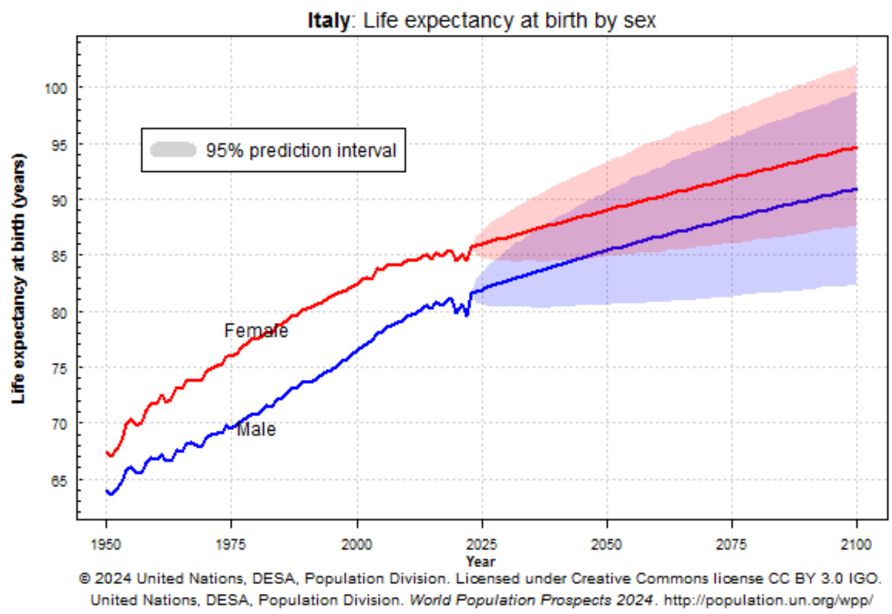


FIGURE 4 *Life expectancy at birth in Italy by sex.*

1.1.1 FRAILTY

Frailty is a clinical condition characterized by *the reduction of homeostatic reserves, resulting in a vulnerable state and an increased risk of adverse health outcomes following the exposition to a stressor* (Morley et al., 2013). Frailty symptoms can be either physical or psychological, or a combination of the two

(Morley et al., 2013). Frailty is an urgent public health issue given its significant association with augmented risk of falls, cognitive impairment, disability, hospitalization, long-term residential care, post-operative complications and mortality *(*Clegg et al., 2013; Martin & O'Halloran, 2020; Morley et al., 2013; Roe et al., 2017; Sirven & Rapp, 2017). Notably, Frailty is not a synonym of Multimorbidity that instead defines the clinical condition of combination of two or more diseases, based on a mono-dimensional characterization of the patient evaluating solely the disease. Multimorbidity must be distinguished from Frailty, that captures complex and multifactor profiles (Proietti & Cesari, 2020) and is indeed based on an assessment encompassing a broader set of variables.

There are currently two main models applied to identify and describe Frailty.

THE FRAILTY PHENOTYPE. The first approach grounds on the individuation of five physical symptoms (weight loss, fatigue, weakness, slowness, reduced physical activity) as signatures of underlying multilevel dysregulation (Fried et al., 2001). Known as the Fried phenotype, this model was validated on 5317 individuals aged 65 years and older, as a predictor of adverse outcomes in the Cardiovascular Health Study. According to the Fried phenotype model, Frailty is defined by the presence of three or more out of five specific symptoms falling outside the normal range. These symptoms may lead to, or be associated with, a decline in functional abilities, whether physical and/or cognitive.

THE FRAILTY INDEX (FI). The second model relies on the progressive aggregation of clinical deficits, behavioural factors, and functional impairments, which are used to compute the Frailty Index (FI). FI is calculated from the collection of symptoms (Mitnitski et al., 2001), by dividing the number of deficits assessed for the total number of variables investigated. The Frailty checklist implemented in clinical use is usually multidimensional, and must include a wide range of domains and more than 30 items (Searle et al., 2008).

The two approaches are conceptually very different (Cesari et al., 2014): while the first is based on few physical parameters, the Frailty Index is based on an holistic evaluation encompassing a broad range of physiological, psychological and behavioural information to depict the heterogeneity of possible deficiencies (Proietti & Cesari, 2020). Despite the continue debate over Frailty definitions and assessment tools, consensus has emerged on the basic concept that Frailty must be considered a dynamic condition and therefore potentially modifiable, especially in its early stages (the so-called pre-Frailty state).

According to the Survey of Health, Aging and Retirement in Europe (SHARE) (Santos-Eggimann et al., 2009) Frailty's prevalence significantly varies across European countries, the mean prevalence being of 17%, ranging from 5.8% in Switzerland, to the "high prevalence rate" countries, like Spain (27.3%), or Italy (23%). On the other hand, pre-Frailty, a transitional state between robustness and Frailty, seems evenly distributed across countries with a mean prevalence rate of

42.23% with Italy setting at 45.6%. Although the prevalence of pre-Frailty is relatively uniform across different countries, Frailty levels show substantial variation according to socioeconomic status, gender, educational attainment, and geographic region (Rohrmann, 2020). Specifically, regarding gender differences, incidence is higher in women for both Frailty (21% of women vs 11.9 % of men) and pre-Frailty (42.7% of women vs. 41.9% of men) (Rohrmann, 2020).

A crucial attribute of Frailty is that it is in all a dynamic condition evolving in two possible directions: worsening over time (often) or improving when treated or, better, prevented. A longitudinal study, the Progetto Veneto Anziani (Trevisan et al., 2017), showed that during a follow-up of 4.4 years on 2925 subjects (mean age 74.4 ± 7.3), in 36.4 % of older subjects the Frailty status changed (in either direction), while 38.1% of individuals maintained the same level of Frailty and the rest of the cohort died during follow-up. Data collected from this and other studies has prompted growing interest in preventive and rehabilitative interventions targeting especially the pre-Frailty status, to impact on its evolution in the overt Frail state.

1.1.1.1 PRE-FRAILTY

Pre-Frailty, the intermediate stage between Robustness and Frailty, is itself associated (as Frailty) with an increased risk for negative health outcomes, thus is considered a clinically significant state. The World Health Organization highlighted the importance of early, targeted interventions to maintain the functional capacity in older adults to delay or prevent progression to Frailty, as part of its *Decade of Healthy Ageing 2021–2030* strategy (2020, 2024). Longitudinal studies reinforce the importance of this early stage. Findings from the Progetto Veneto Anziani suggest that individuals in a pre-Frail state are more likely to revert to Robustness than those overtly Frail are to recover to a pre-Frail state (Trevisan et al., 2017), reinforcing the concept that Frailty is, to some extent, reversible, especially in its initial stage.

Due to these premises, classification, subdivision and operationalisation of Frailty vs pre-Frailty and Robustness states is at present one of the most debated and investigated issues in the field.

CALCULATION OF PRE-FRAIL STATE. According to Fried's physical phenotype model, pre-Frailty is diagnosed when an individual shows 1-2 out of five Frailty symptoms: unintentional weight loss, exhaustion, weakness, slow walking speed, and low physical activity (Fried et al., 2001).

Conversely, the Frailty Index (FI), calculated as the ratio of the detected deficits to the total number of variables considered, produces a continuous score ranging from 0 (no deficits) to 1 (all deficits), thus pre-Frailty categorization based on FI varies between studies. Early work by Kulminski and colleagues (2008) defined the pre-Frailty status for FI = 0.20-0.35, with robustness below 0.20 and overt Frailty status for FI> 0.35, updated by Kim and Rockwood (2024) as follows:

- Robust: FI < 0.10
- Pre-frail: FI 0.10–0.20
- Frail: FI 0.20–0.55
- Severely Frail: FI ≥ 0.55

The Italian version of the Frailty checklist (Abete et al., 2017) includes 40 items, providing a categorization based on FI values:

- Light Frailty: FI 0.0025 - 0.40
- Moderate Frailty: FI 0.4025 - 0.675
- Severe Frailty: FI 0.6775 - 1.00

While the Italian model does not explicitly designate a "pre-Frail" state, the "light Frailty" category conceptually overlaps with international definitions of pre-Frailty.

As already mentioned, pre-Frailty potential reversibility opens the field to early-stage interventions, designed to delay or prevent the worsening of the condition into Frailty. These interventions are actually those most adherent to the concept of *healthy ageing*, aiming at improving quality of life and autonomy in older adults. Interventions during the pre-Frail stage yield significantly high reversal rates compared to severe Frail stage, more challenging in the attempt to revert to lighter condition (Romero-Ortuno et al., 2021; Serra-Prat et al., 2025). However, many studies do not clearly specify or stratify participants by baseline Frailty grade, making it difficult to precisely determine how effectiveness varies according to initial Frailty severity (Racey et al., 2021).

1.1.1.2 Cognitive Frailty

Cognitive Frailty (CF) was first defined by the International Academy on Nutrition and Ageing (I.A.N.A) and the International Association of Gerontology and Geriatrics (I.A.G.G) as a condition characterized by the simultaneous presence of physical Frailty and mild cognitive impairment (MCI) (Kelaiditi et al., 2013). Cognitively impaired elders are more likely to be frail and vice versa, and cognitive Frailty often signify a “predementia state” (Halil et al., 2015). Thus, Cognitive Frailty is defined at the intersection of dementia and physical Frailty, with potential reversibility when identified and faced early. Ruan and colleagues (2015) suggested two subtypes of CF: the “reversible” cognitive Frailty (characterized by physical pre-Frailty and subjective cognitive decline, SCD) and a “potentially reversible” cognitive Frailty (characterized by physical Frailty and MCI). Figure 5 shows the relationships between the aforementioned Frailty stages and possible health outcomes as described by the authors. This extended definition broadens the original consensus by including a spectrum from subjective cognitive decline (SCD) to mild cognitive impairment (MCI), in combination with physical pre-Frailty or Frailty (Ma & Chan, 2020a; Ruan et al., 2015).

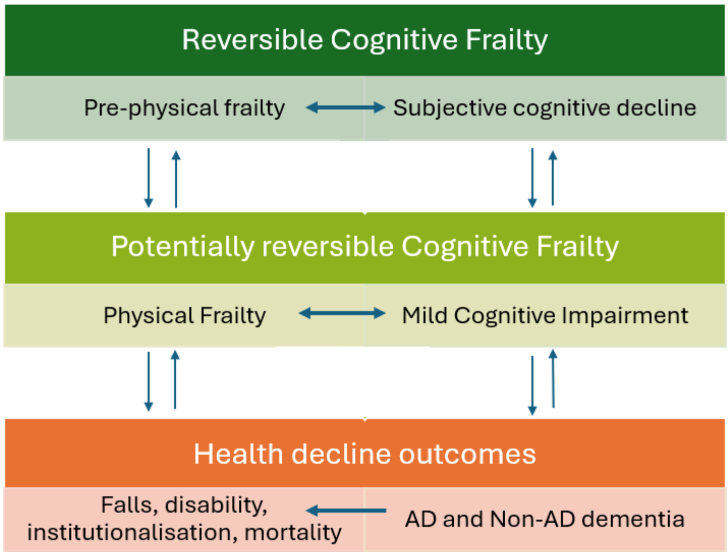


FIGURE 5 *Conceptual model of cognitive Frailty (Ruan et al., 2015). Cognitive Frailty is defined as the overlap of physical Frailty and cognitive impairment without dementia. The framework spans a spectrum from "reversible Cognitive Frailty" (pre-Frailty and subjective cognitive decline) to "potentially reversible cognitive Frailty" (Frailty and mild cognitive impairment).*

Frailty and Cognitive Frailty result from multifactorial biological processes spanning vascular, metabolic, immune and neurodegenerative pathways, both sharing common mechanisms, including chronic inflammation, endocrine dysregulation, impaired metabolism, and brain pathology (Ma & Chan, 2020b). The prime suspects of pathophysiological pathways associating physical Frailty and Cognitive Frailty are listed below.

- *Inflammation and Immunosenescence*. Ageing is characterized by a state of "inflammaging", a chronic low-grade inflammation that correlates with muscle deterioration and cognitive impairment. Chronic inflammation can erode physical reserve and synaptic integrity simultaneously (Soysal et al., 2016).
- *Endocrine and Metabolic Dysfunction*. Hormonal changes in ageing, such as dysregulated cortisol (hypothalamic pituitary axis -HPA-) and reduced testosterone, have been implicated in both Frailty and CF. Impaired hypothalamic-pituitary function, insulin resistance, and metabolic imbalance can affect muscle and brain alike (Ma & Chan, 2020b).
- *Cardiovascular risk*. Vascular risk factors are common to both Frailty and dementia. The relationship between Frailty and cardiovascular diseases seems to be bidirectional (Ijaz et al., 2022) (see 1.1.1.4).

Although Frailty has often been associated with general cognitive decline, growing evidence suggests that the cognitive impairment observed in frail individuals is not global, but rather selectively involves specific domains -most notably executive functions, attention, verbal fluency, and processing speed (Apóstolo et al., 2018a; Halil et al., 2015; Langlois et al., 2012a; Robertson et al., 2013; Robinson et al., 2022). This domain-specific profile is consistent with findings from both cross-sectional and longitudinal studies, which show that frail older adults tend to underperform particularly in tasks requiring fast executive processing and verbal fluency, even after controlling for other factors such as depressive symptoms or comorbidities (Buchman et al., 2007; Langlois et al., 2012b; Robertson et al., 2013).

This selective cognitive vulnerability may be partly explained by the close interdependence between executive functions and physical performance in ageing. Executive processes such as planning, inhibition, cognitive flexibility, and task switching are known to play a pivotal role in motor execution, including gait, balance, and mobility (Al-Yahya et al., 2011; Chhetri et al., 2017; Robinson et al., 2022; Yogev-Seligmann et al., 2008). Moreover, longitudinal data indicate that stronger executive functioning is associated with better handgrip strength, endurance, and physical activity engagement (Cheval et al., 2020; Watson et al., 2010; Zammit et al., 2021).

Thus, the overlap between cognitive and motor control systems could explain why impairments in specific cognitive functions are particularly pronounced in frail individuals.

In summary, Cognitive Frailty is a distinct clinical entity characterized by the simultaneous presence of physical Frailty and Mild Cognitive Impairment (MCI), in absence of overt dementia. While Frailty, in its broader definition, includes cognitive aspects among other domains, the concept of Cognitive Frailty highlights the synergistic effect of dual impairments. This phenotype identifies a subgroup at particularly high risk for adverse health outcomes and may represent a critical window for targeted, multi-domain interventions.

1.1.1.3 Delaying or reversing Frailty

A defining feature of Frailty is its potential reversibility that has led researchers to develop and test different intervention paradigms by targeting its physical, social, psychological and cognitive components. Current strategies can be multimodal, focusing mostly on physical fitness, nutrition and cognition.

Physical training

Physical training is the type of intervention most frequently reported in literature (Apóstolo et al., 2018a). A meta-analysis study provided evidence on the efficacy of exercise interventions in improving global cognition, physical Frailty, gait ability, and walking speed in older adults with Cognitive Frailty, although without effect on overall physical fitness or quality of life. Interestingly mind-body exercises (e.g., Baduanjin, Tai Chi) emerged to be more effective in enhancing cognitive function than resistance training (Yuan et al., 2025). Coherently a sedentary lifestyle has been reported to be associated with physical and cognitive Frailty (Sugimoto et al., 2022).

The comprehensive analysis of 21 intervention studies, with a total of 5275 subjects (Apóstolo et al., 2018a) highlights that the protocol and type of physical training seems to be relevant in achievement of results. Physical training seems to be effective in postponing physical decline and Frailty only when performed in group sessions: in this condition different types of training impact positively on prevention of Frailty or pre-Frailty progression, including aerobic and resistance training, Tai-Chi and multicomponent trainings focusing on gait, balance and strength (Luo et al., 2024). On the other hand, physical exercises delivered by a professional to a single person or performed individually fail to be effective.

In summary, physical training is a key, evidence-based component of interventions targeting Frailty, particularly when delivered in group settings, showing benefits for both physical and cognitive aspects of Frailty. Mind-body exercises like Tai Chi are especially effective for cognitive improvement, whereas individually delivered or non-physical interventions tend to be ineffective.

NUTRITIONAL SUPPORT

Adequate protein and micronutrients intake is essential for muscle and brain health. Trials using nutritional supplementation or diet enhancement show improvements in Frailty indices (Apóstolo et al., 2018a). Diets supplied with antioxidants, B-vitamins and omega-3, such as a Mediterranean diet, are associated to lower rates of physical and cognitive Frailty. Nutritional interventions seem therefore suitable to support cognition and muscle mass concurrently by providing tailored programs of energy intake (Ng et al., 2015).

COGNITIVE AND DUAL TASK TRAINING

Despite the acknowledged role of cognitive functions in supporting coping mechanisms and functional reserves in older age, few studies directly investigated the impact of cognitive training on Frailty, yet obtaining significant positive results (Apóstolo et al., 2018a; Bennett et al., 2014). Interestingly the combination of physical and cognitive training reported significative effects in improving both physical parameters and cognition (especially executive functioning), but few studies directly investigated the impact of combined training on Frailty as a primary outcome (Ng et al., 2015; Zhou et al., 2025).

MULTIMODAL PROGRAMS

Multicomponent strategies encompassing physical exercises, nutritional support, cognitive training, and psychosocial stimulation have been adopted in recent research but results are highly heterogenous based on type of intervention, preventing any general conclusion (Apóstolo et al., 2018b).

In summary, research on Frailty prevention primarily implemented a mono-dimensional approach, often consisting in physical resistance and endurance (Romera-Liebana et al., 2018). However, given the *bio-psycho-social* nature of

Frailty (C. I. Cohen et al., 2023), there is now growing interest in research focused on approaches tailored to reverse all the Frailty's different components.

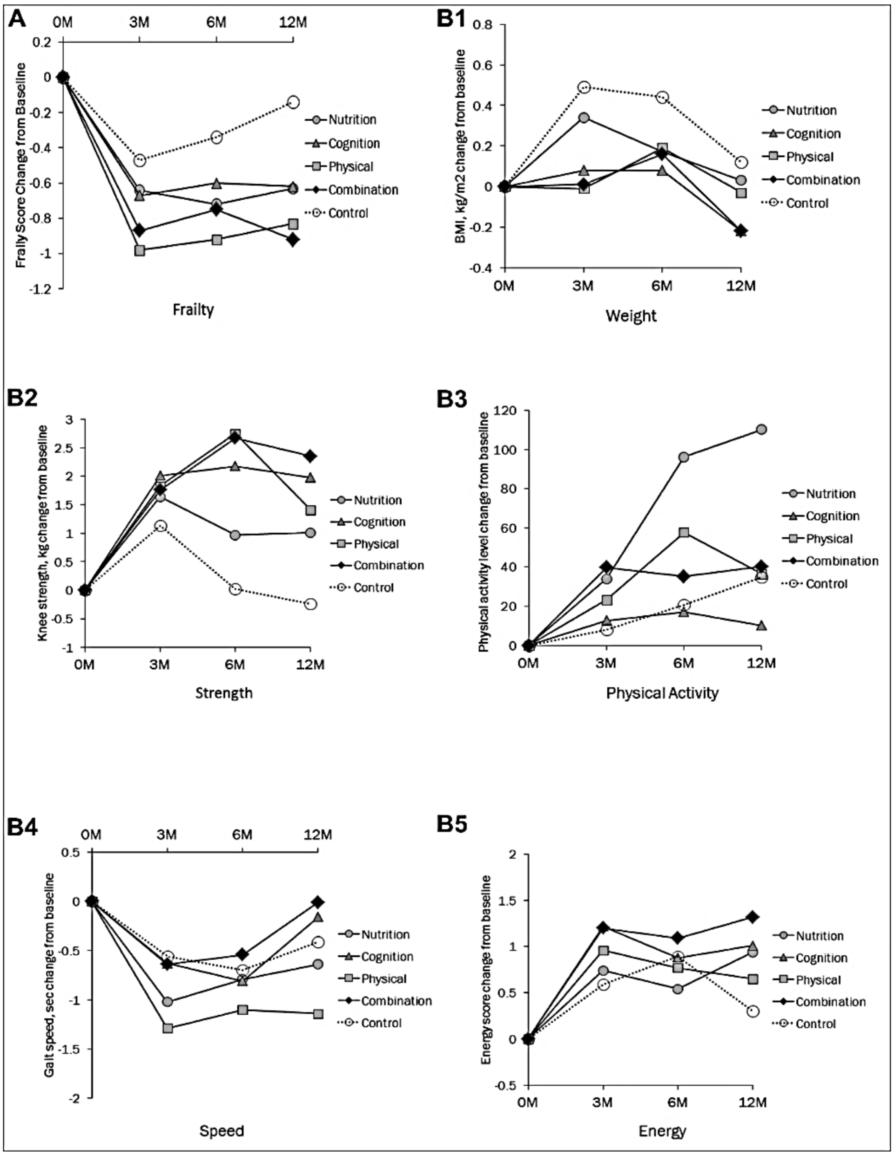


FIGURE 6. *Adapted from Ng et al.(2015)***.** *Experimental groups per intervention (i.e. Nutrition, Cognition, Physical, Combination) compared to a control group. The graph shows changes from baseline at 3, 6 and 12 months. The variables considered are: phenotype Frailty [A], weight (BMI) [B1], knee strength [B2], physical activity (Longitudinal Ageing Physical Activity Questionnaire (Voorrips et al., 1991)) [B3], gait speed [B4], energy level (exhaustion) [B5].*

Supporting the efficacy of this approach are studies showing that any type of intervention (physical exercise, nutrition supplements, cognitive training or a combination of the previous) leads to some degree of Frailty reduction in pre-frail and frail subjects (Ng et al., 2015). Figure 6 (adapted from Ng et al., 2015) shows the effects of different treatment modalities on phenotype Frailty and its five components measured as: body mass index (BMI), knee strength, self-reported physical activity, gait speed and exhaustion. Similarly, the Malaysian WE-RISE protocol (Murukesu et al., 2020) delivered a six month intervention program targeting multiple domains by combining resistance and balance training in group sessions, cognitive training, dietary counselling, and psychosocial support activities, resulting in improvements in both cognitive and physical function.

Overall, although more consistent evidence is needed, current research suggests cognitive and physical Frailty can be partly reversed or delayed through early targeted and, above all combined, interventions.

Interestingly, when focusing on the cognitive functions, it emerges that an integrated approach may be effective in slowing cognitive decline in some domains, but not in others, as shown by the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) (Ngandu et al., 2015), a randomized controlled trial involving older adults aged 60–77 with high dementia risk scores. Participants underwent a two-year combined intervention encompassing nutritional advice, physical and cognitive training, social activity, and vascular risk monitoring. Compared with a control group, the experimental group showed significant improvements in global cognition, processing speed and executive functions, but not on memory performances over 2 years, suggesting targeted benefits across specific cognitive domains rather than memory, that may require different strategies or longer timeframes. Thus, the combined approaches must be better studied to target all the cognitive domains.

1.1.1.4 Frailty and Cardiovascular Risk

Frailty is characterized by a decrease in physiological reserves that leads to increased vulnerability to stressors. This vulnerability in older adults often coexists with cardiovascular diseases (CVD): Frailty prevalence is noticeably higher in cardiac patients than in age-matched healthy subjects (Damluji et al., 2021; Ijaz et al., 2022). On average frail cardiac patients suffer worse medical outcomes than robust individuals (Uchmanowicz et al., 2023). CVD and Frailty share indeed common risks factors such as hypertension, diabetes, obesity, smoking and a sedentary lifestyle (Piotrowicz & Gąsowski, 2020). Frailty affects commonly heart failure patients significantly predicting their hospitalization, poor recovery and mortality outcome (Afilalo et al., 2014; Ijaz et al., 2022; Uchmanowicz et al., 2023). Pre-Frailty also seems to correlate with a greater risk of developing cardiac diseases, and especially slow gait as a marker of phenotype Frailty seems to be a positive candidate marker of CVD (Sergi et al., 2015). Each step up the Frailty spectrum (from robust to pre-frail to frail) carries an incrementally higher risk for CVD-related events (Ijaz et al., 2022). Moreover, studies show that on average older heart failure patients score poorly on different cognitive tasks (Bauer et al., 2011), highlighting the physiological connections between the performance of the cardiovascular system, physical health and cognitive Frailty.

Notably, the relationship between CVD and Frailty seems to be bidirectional (Ijaz et al., 2022): the occurrence of either one is intertwined whit the other, leading to its progression or worsening.

1.1.2 INTRINSIC CAPACITY

As a general concept, *ageing* is characterized by a decrease in physiological reserves, the question being whether there is an objective methodology to define and comprehensively assess the "physiological reserves". The World Report on Ageing and Health (WHO, 2015) provided the concept of "Intrinsic Capacity, IC" as <u>the composite of all the physical and mental capacities that an individual can draw on at any point in time.</u> It is a key concept in the WHO framework for *healthy ageing* and it highlights the importance of person-centred care. Cesari and colleagues, pointing out the need for an integrated care approach, identified five key domains of IC, specifically cognitive, psychological, sensory, locomotor, and vitality, grounding the individual's functional potential, and considering domains as crucial pillars for maintaining functional ability and overall well-being in older adults (Cesari et al., 2018, 2022). These domains interact dynamically (e.g. older adults often show coupled declines: declining mobility may be due to poor nutrition which could be a risk for cognitive decline), thus, a deficit in one domain may set off a cascade affecting other apparently unrelated domains.

The domains comprising individual resources are:

- Locomotor Capacity: accounts for motor function, balance, gait, and muscular strength. This domain is fundamental to mobility, the prevention of falls and physical independence.
- Vitality: represents physiological resilience and homeostasis. It grounds on nutritional state, endurance and the organism's capacity to recover and maintain energy balance.
- Cognitive Capacity: encompasses higher-order neurocognitive functions critical for adaptive behaviour and autonomy, including attention, memory, executive function, learning, and decision-making.
- Psychological well-being: evaluates emotion regulation and overall mental well-being as the absence of significant psychopathology such as depressive or anxiety disorders.
- Sensory Capacity: estimates the functionality of sensory systems, primarily visual and auditory, essential for environmental interaction, communication, and prevention of social isolation.

The concept of IC shifts the focus from the disease/symptoms to the functional resources of the individual, aligning with WHO's vision of healthy ageing.

While the concepts of Frailty and Intrinsic Capacity (IC) may appear similar, they must be rather considered as complementary frameworks for assessing an individual's functional health. Frailty reflects a state of vulnerability and estimates the degree of impairment of the homeostatic reserves, whereas Intrinsic Capacity represents the sum of physical and mental capacities available to the individual. In this light, Frailty and Intrinsic Capacity (IC) can be seen as “two sides of the same coin” (Belloni & Cesari, 2019): not mutually exclusive, but rather interrelated.

Tracking changes in IC over time may allow for the early detection of functional decline along the trajectory toward Frailty, even before clinical signs become evident. Although Frailty assessments are currently more widely used in clinical settings - often leading to tailored interventions - the IC framework provides a more proactive and capacity-oriented perspective.

In summary, Frailty focuses on risk and deficit accumulation, while IC emphasizes retained abilities and potential. Both models share the goal of shifting from a disease-centred to a function-centred approach in the care of older adults. However, further research is needed to fully clarify their respective roles, overlaps, and distinctions.

1.1.2.1 How is IC calculated?

Given its multidimensional nature, IC is a composite measure of the functional capacities measured across the five domains.

Each domain of IC is assessed through validated clinical instruments or performance and physiological measures, selected based on resources availability and context (Gonzalez-Bautista et al., 2020; López-Ortiz et al., 2022):

- Locomotor capacity is typically assessed through either gait speed tests, repeated chair stands, the Short Physical Perfomance Battery (SPPB) (Guralnik et al., 1994), and/or balance assessments (López-Ortiz et al., 2022).
- Vitality is measured with indicators such as nutritional status (usually the Mini Nutritional Assessment (MNA)) and body mass index (BMI) (López-Ortiz et al., 2022).
- Cognitive functions are mostly evaluated using cognitive screening tools including the Mini-Mental State Examination (MMSE), the Montreal Cognitive Assessment (MoCA) (López-Ortiz et al., 2022).
- Psychological well-being is usually assessed through self-reported mental health scales such as the Geriatric Depression Scale (GDS) or the Hospital Anxiety and Depression Scale (HADS) (López-Ortiz et al., 2022).
- Sensory capacity is assessed through tests for visual and auditory impairments, such as Snellen visual acuity charts and the Whisper test.

The Integrated Care for Older People (ICOPE), developed by WHO (2017), provides different guidelines for assessing and managing IC’s decline. ICOPE prioritizes prevention through early identification of impairments across the five domains of

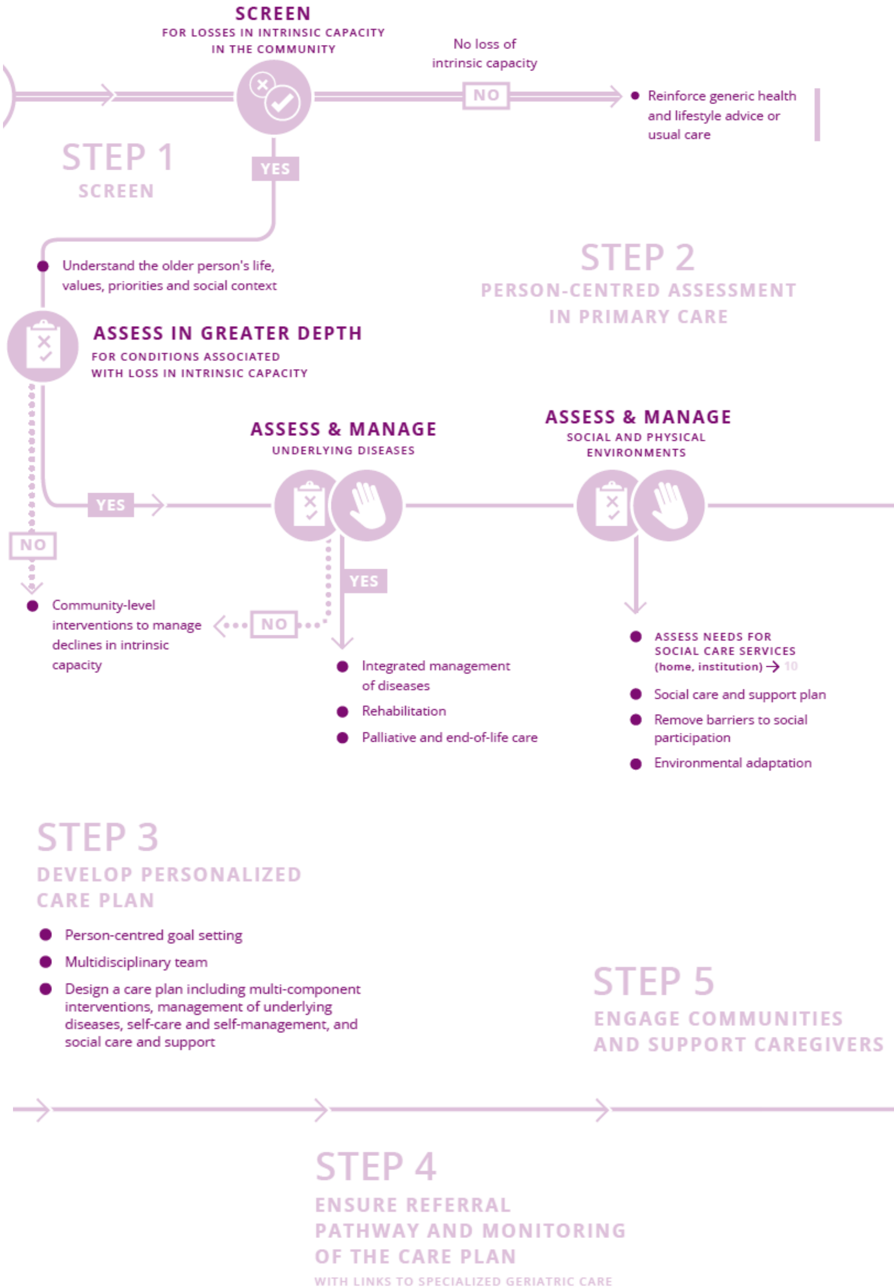


FIGURE 7. *ICOPE's steps for an integrated care and assessment of Intrinsic Capacity.*

IC. Aimed at being applied to the largest possible population, the ICOPE screening tool is designed to be as simple and applicable as possible. It employs a step-by-step approach starting with screening questions or tests (step 1), followed by a more comprehensive assessment if needed (step 2), and a personalized intervention plan, involving communities and caregivers (steps 3–5) (Fig.7). The screening phase includes standardized simple measurement such as gait speed for locomotion, weight loss and appetite questions for vitality, orientation questions for cognition, mood screening questions for the psychological domain, and basic vision and hearing tests for sensory capacity.

Despite the general agreement on the importance of the IC, a relevant issue regards the lack of scientific consensus on how to operationalize and express the global Intrinsic Capacity (IC) score. Figure 8 shows the percentages of applied measures across ten WHO studies (reported by Gonzalez-Bautista et al., 2020). Several simplified and accessible methods have been suggested to represent global Intrinsic Capacity. Among these, the most commonly used approach involves standardizing each domain using Z-scores and then calculating the global IC index as the average of these Z-scores across the five domains (López-Ortiz et al., 2022).

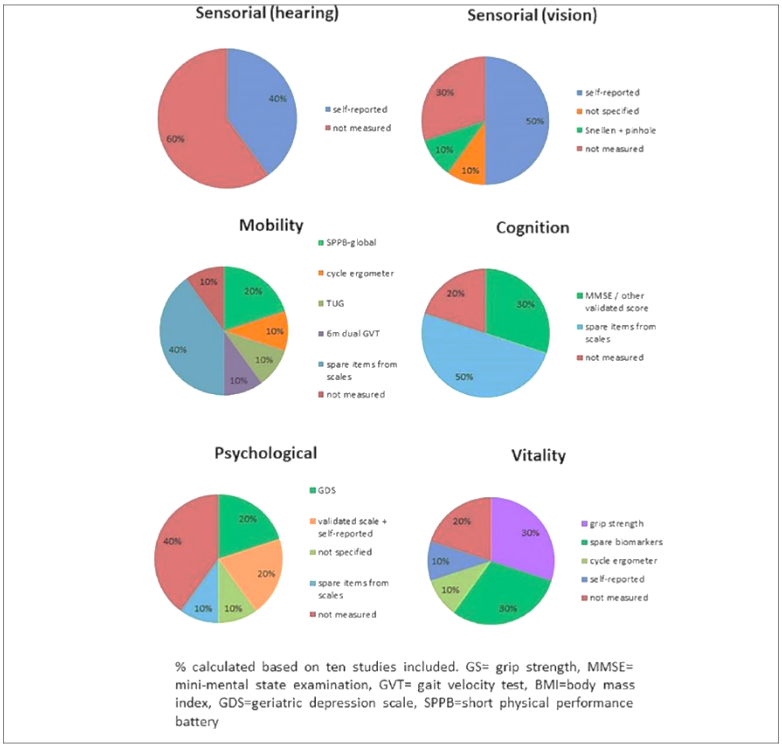


FIGURE 8. *Adapted from Gonzalez-Bautista et. al. (2020). Most studies utilize self-reported scale or spare items from different scales to compute IC composite scores. The sensorial domain is mostly measured through self-reported scales; spare items and the Short Physical Performance Battery* ***(Guralnik et al., 1994)*** *are the most common used parameters for the locomotor domain; the cognitive domain is mostly measured trough spare items and the Mini-Mental State of Examination* ***(Magni et al., 1996)****; the psychological domain is not always considered in the analysis or it is measure through the Geriatric Depression Scale* ***(Montorio & Izal, 1996)****; the most common parameter to represent the vitality domain is the grip strength.*

1.1.2.2 Interventions to Enhance Intrinsic Capacity

A growing body of evidence shows that targeted interventions can slow or reverse declines in IC. WHO's ICOPE guidelines (2017) explicitly recommend *physical activity to prevent sarcopenia and to preserve motor abilities and IC*. On this note, research shows the efficacy of Multicomponent Physical Exercise (MCE) integrated with cognitive training, nutritional supplements, and social strategies for older adults (Izquierdo et al., 2021). An example of MCE training is the *Vivifrail* multicomponent exercise program (Izquierdo et al., 2016), designed to improve strength, balance and gait trough a tailored physical program based on Frailty level. This approach produced significant gains in IC in frail older adults showing better performance in locomotion, cognition and vitality domains compared to controls (Sánchez-Sánchez et al., 2022). Notably, the program turned out to have greater effect among frail individuals than pre-frail ones, an unexpected result considered the literature reported above related to interventions aimed at reversing Frailty condition. MCE positively affects not only locomotor capabilities but other different IC's domains such as cognition and vitality (Huang et al., 2021; Sánchez-Sánchez et al., 2022)

Cognitive training also show promise for the prevention of physiological decline in IC's domains. One recent study found that combining physical exercise with Cognitive Stimulation Therapy (CST) significantly improved global IC scores in pre-frail older adults (Merchant et al., 2024); adding CST to physical training yielded specific improvements in the cognitive and psychological domain.

Psychosocial and nutritional interventions are also investigated as possible approaches to support healthy ageing (Castro et al., 2023; Ngandu et al., 2015). Sensory aids (particularly hearing aids or cataract surgery) and prevention of sensory domain decline, may be used to support cognitive performance (Levett et al., 2025; Maharani et al., 2018). Promoting social engagement and psychological support may help sustain executive functioning, sleep and physical wellbeing (Cacioppo & Cacioppo, 2014). WHO's recommendations explicitly include managing depressive symptoms and social support (2019).

Finally, early evidence suggests that targeted, multi-domain interventions, combining multicomponent physical exercise with cognitive or psychosocial support, can fortify older adults' Intrinsic Capacity and thereby promote an healthier ageing (Cesari et al., 2022; Merchant et al., 2024; Sánchez-Sánchez et al., 2022).

CONCLUDING REMARKS

Interventions targeting Frailty typically focus on mitigating risk and preventing adverse outcomes through the management of deficits, such as improving nutrition, enhancing mobility, or reducing polypharmacy, often in response to an already evident decline. In contrast, strategies aimed at restoring or maintaining Intrinsic Capacity adopt a more proactive and holistic approach, emphasizing the preservation and enhancement of functional abilities across multiple domains (e.g., locomotion, cognition, vitality, sensory function, and psychological well-being). While Frailty interventions are often "reactive" and centred on vulnerability, Intrinsic Capacity interventions are preventive and capacity-building, aiming to sustain autonomy and delay the onset of dependency.

1.2 BRAIN-HEART INTERACTIONS

Studying ageing through multi-domain constructs like IC and Frailty aims to capture the complexity of the system, highlighting the interplay of cognitive, psychological, locomotor, sensory, and vitality related functions (Cesari et al., 2018; Beard et al., 2019). This perspective relies on the concepts *of functional reserve and resilience*, i.e. the capacity to adapt and sustain activity despite external or internal stressors. Brain-heart interactions operating in cognitive performance control, emotional regulation and stress responsiveness, play a pivotal role in this adaptability (Forte et al., 2019; Smith et al., 2017; Thayer, Hansen, et al., 2009). Disruption to this bi-directional axis can influence different domains, possibly playing a role in the multi-domain decline that IC and Frailty frameworks seek to address, as suggested by the interdependence between Frailty and Cardiovascular diseases.

The French physiologist Claude Bernard (1813-1878) is considered the most authoritative pioneer in the investigation of the interplay between peripheral organs and the brain (Thayer & Lane, 2009). In 1872 Darwin wrote:

> *"Claude Bernard also repeatedly insists, and this deserves especial notice, that when the heart is affected it reacts on the brain; and the state of the brain again reacts through the pneumo-gastric (vagus) nerve on the heart; so that under any excitement there will be much mutual action and reaction between these, the two most important organs of the body''(Darwin, 1872).*

This and other early acknowledgments opened the way to contemporary studies of the autonomic nervous system (ANS), which regulates involuntary physiological functions and maintains homeostasis through continuous communication between the central nervous system (CNS) and the peripheral organs (Berntson et al., 1991). The ANS is responsible for the regulation of physiological functions such as cardiovascular performance, respiration, digestion, thermoregulation, and glandular secretion. It is classically subdivided into the sympathetic (SNS) and the parasympathetic (PNS) systems. The SNS and PNS, both always active in a dynamic balance to maintain homeostasis, typically exert antagonistic and/or complementary effects to flexibly regulate physiological functions according to environmental and internal demands (Cacioppo et al., 2017; McCorry, 2007).

The sympathetic preganglionic neurons originate in the cell column of the thoracolumbar spinal cord (T1-L2~L3) and project to the paravertebral sympathetic chain ganglia. Preganglionic neurons synapse with postganglionic neurons releasing acetylcholine (ACh) and activating nicotinic Ach receptors. Postganglionic neurons in response release norepinephrine (NE) activating adrenergic receptors in target tissues (Brodal, 2004). The sympathetic outflow orchestrates the classic “fight-or-flight” response to physical or psychological stressors. In the cardiovascular domain, sympathetic activation increases heart rate, myocardial contractility, and accelerates atrioventricular nodal conduction (Coote & Chauhan, 2016) (Fig. 9).

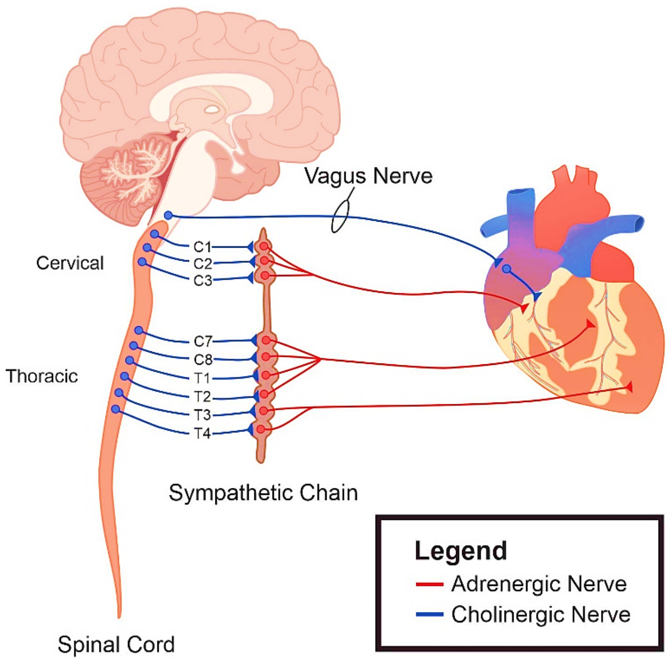


FIGURE 9. *Picture adapted from Espinoza and colleagues (Espinoza et al., 2021). The autonomic nervous system and cardiovascular control. The sympathetic branch sends long projection to both the vascular system and cardiac tissue. The parasympathetic branch, through the Vagus nerve originating in the brainstem projects to cardiac tissue.*

The parasympathetic preganglionic neurons origin in the brainstem and in the sacral spinal cord (S2-S4). Contrary to the sympathetic system, parasympathetic preganglionic fibers are longer and synapse in ganglia near or within target organs (Fig. 9). Regarding cardiac control, the Vagus nerve (cranial nerve X) serves as primary parasympathetic innervation pathway, connecting the brainstem, particularly the nucleus ambiguus (NA) and the dorsal motor nucleus of the Vagus (DMNV), to the heart. It acts like a break on the sinoatrial node by slowing the pacemaker firing rate and reducing atrioventricular conduction velocity. This supports “rest-and-digest” physiological states, counterbalancing sympathetic excitatory effects. It also provides continuous feedback to the brain about cardiac status, transmitting sensory information from cardiac baroreceptors and chemoreceptors to central autonomic nuclei. Overall, it reflects the brain's regulatory influence over bodily states, through a direct top-down control, and vice versa (Thayer & Lane, 2000).

Modern neurovisceral integration models built upon Bernard's and Darwin's foundational observations, include the SNS and PNS within the broader Central Autonomic Network (CAN), a distributed set of cortical, subcortical, and brainstem structures that integrates afferent feedback with descending control to regulate cardiovascular function in accordance to external stimuli, emotional status and cognitive processes (Benarroch, 1993; Thayer & Lane, 2009). The brain-heart axis is therefore a fundamental neurophysiological network involved not only in basic autonomic regulation but also in emotional and cognitive processes (Thayer & Lane, 2009).

1.2.1 The Neurovisceral Integration Model

In the modern view, the activity of the sympathetic and parasympathetic systems is coordinated within the central nervous system by the Central Autonomic Network (CAN) (Benarroch, 1993). The CAN is a vast network integrating visceromotor, neuroendocrine, nociceptive and adaptive behavioural processes. It includes different cortical and subcortical structures: the insula, the anterior cingulate, orbitofrontal and ventromedial prefrontal cortexes, hypothalamic nuclei, the central nucleus of the amygdala (CeA), the paraventricular nuclei, and several brainstem structures, like the periaqueductal grey, parabrachial nucleus, nucleus of the solitary tract (NTS), and nucleus ambiguus (NA), as well as spinal cord regions such as the thoracic lateral horn and Onuf's nucleus in the sacral cord. These structures extensively connected with each other, form a functional network rather than working as isolated centres.

Two main frameworks underlying sympatho-vagal regulation are currently debated: the Polyvagal Theory (Porges, 2009) and the Neurovisceral Integration Model (Thayer et al., 2000). The Polyvagal Theory divides the Vagus nerve in two branches based on distinct evolutionary trajectories: a myelinated, more recent ventral branch originating from the nucleus ambiguus, and an unmyelinated dorsal branch projecting from the dorsal motor nucleus. In healthy conditions, the ventral branch exerts inhibitory control over the dorsal branch and over sympathetic activity; it supports states of social engagement, safety, and rest. While influential, the theory focuses on brainstem mechanisms and does not address how higher brain regions might govern these vagal branches upstream.

The Neurovisceral Integration Model (NVI), on the other hand, explicitly incorporates higher structures, and the Amygdala is depicted as a pivotal centre for the brain-heart network. The NVI model emphasises the importance of inhibitory pathways from the prefrontal cortex to subcortical and brainstem centres (Fig. 10), pointing out that cognitive, emotional, and autonomic regulation share overlapping neural substrates. Through a pharmacological inactivation of the prefrontal cortex evidence has been provided that its inhibitory influence on heart rate is not equal across the lifespan (Thayer, Sollers, et al., 2009). 73 patients (aged 13–65 years) underwent an intracarotid sodium amobarbital procedure -as part of epilepsy surgery- inactivating anterior cortical regions and variations in heart rate (HR) were recorded (Fig 10). Younger adults (13-27 y.o.) displayed significant increases in HR following prefrontal bilateral inactivation, while the second tertile of participants (aged 28-38 years) showed larger effects only when the right hemisphere was pharmacologically blocked. In older adults (39-65 y.o., with an average age of 47) however, the response was significantly attenuated in comparison with the other groups and limited to the right hemisphere blockade, with significantly lower increase in HR. These findings seem to suggest that ageing could be associated with a reduction of prefrontal inhibitory control over autonomic function, both in magnitude and in lateralization, possibly reflecting a physiological neural decline.

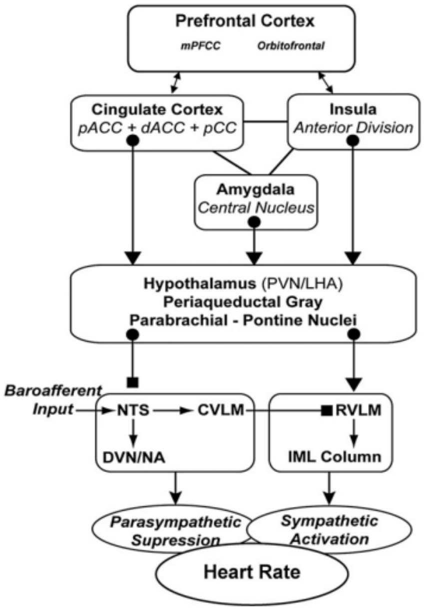


FIGURE 10. *Adapted from Thayer et al. (2009). Pharmacological blockade (sodium amobarbitol) of the prefrontal cortex. The prefrontal, cingulate, and insula cortices form an interconnected network with bi-directional communication with the amygdala. The activation of the central nucleus of the amygdala (CeA) inhibits the nucleus of the solitary tract (NTS) which in turn inhibits inhibitory caudal ventrolateral medullary (CVLM) inputs to the rostral ventrolateral medullary (RVLM) sympathoexcitatory neurons while simultaneously inhibiting vagal motor neurons in the nucleus ambiguus (NA) and the dorsal vagal motor nucleus (DVN). The CeA directly activates the sympathoexcitatory neurons in the RVLM. This leads to an increase in HR.*

In conclusion, the CAN and the Neurovisceral Integration Model provide a useful framework for exploring the interplay between brain, heart, and the adaptive potential of the system in a healthy ageing prospective. Measures such as Heart Rate Variability (HRV), reflecting the dynamic interplay of sympathetic and parasympathetic system, could serve as non-invasive biomarkers, and potentially also as targets for interventions designed for supporting cognitive and emotional health in older populations.

1.2.2 Heart Rate Variability

The term "heart rate variability" (HRV) refers to the inter-beat cardiac variability, that can be analysed in the time domain, in the frequency domain, or through nonlinear analyses (Berntson et al., 1997). It is a non-invasive and simple measure used to investigate the autonomic nervous system, as it reflects the influence of the parasympathetic and sympathetic systems on cardiac activity. Heart rate variability can be used as an indicator of psychophysical adaptability to environmental disturbances, as well as to "internal demands" of the system, as it is associated to motor, psychological and cognitive functions (Cattaneo et al., 2021; De Oliveira Matos et al., 2020; Matusik et al., 2023). An increase in HRV is observed when parasympathetic influence on cardiac activity increases. For example, low heart rate variability, and therefore a low parasympathetic activation, is associated with emotional dysregulation and with psychopathological dimensions linked to dysfunction of the prefrontal cortex (Cattaneo et al., 2021).

In the context of ageing, this index becomes especially relevant. Ageing is associated with structural and functional changes in several CAN nodes, such as thinning of the prefrontal and cingulate cortices, reduced connectivity between the amygdala and prefrontal regions, and altered white matter integrity in fronto-limbic tracts (Dotson et al., 2016; McGinnis et al., 2011; Raz et al., 2007; Sakaki et al., 2016). These changes can reduce autonomic flexibility, often reflected in lower HRV. In turn, lower HRV in older adults has been linked to poorer cognitive function, less effective emotional regulation, and higher cardiovascular risk. In other words, the same neural decline that affects cognitive and emotional control may also impair the brain's capacity to regulate the heart, with consequences for the overall resilience in later life.

In order to understand brain-heart interplay by using the HRV, a methodological background must be provided.

1.2.2.1 What is and how can we measure HRV

Heart rate variability is a non-invasive measure reflecting sympathovagal balance calculated between R-R intervals derived from an electrocardiogram (ECG) signal (Fig.11). The R peak, representing ventricular depolarization, provides a relevant reference point for measuring the timing of cardiac cycles, enabling a reliable assessment of temporal fluctuations in heart rate. From these inter-beat intervals, HRV can be extracted through time domain, frequency domain, and nonlinear methods. Non-linear approaches, such as Poincaré plots or entropy measures, reveal the complexity and unpredictability of heart rhythm dynamics.

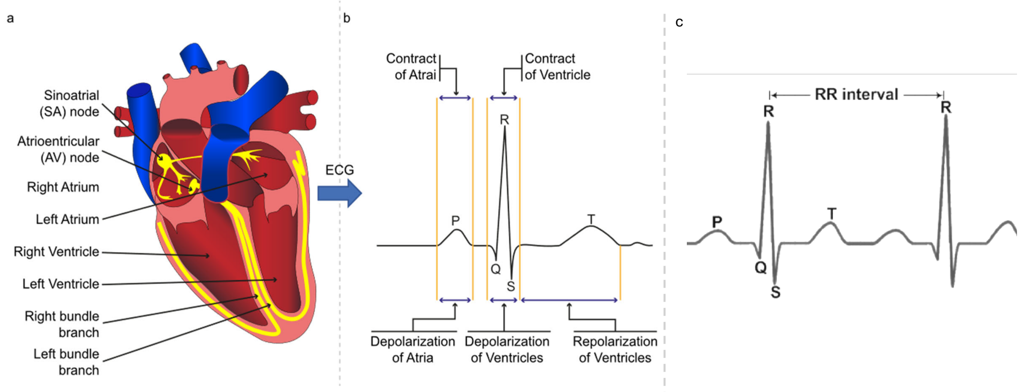


FIGURE 11. *Adapted from Abdullah Al et al. (2021). (a) electrical flow of the cardiac cycle depicted in yellow. (b) P,Q,R,S,T waves of the ECG signal: the R-wave reflects the depolarization and contraction of the ventricles. (c) the R-R interval representing the time difference between two consecutive heart beats.*

Time domain metrics, quantify the time variation between inter-beat intervals (IBIs); the most used measure are the standard deviation of normal-to-normal (NN: IBIs removed of possible artifacts) intervals (SDNN) and the root mean square of successive differences (RMSSD) (Shaffer & Ginsberg, 2017) (Table 1).

TABLE 1. *HRV time domain most used in literature indices (Shaffer & Ginsberg, 2017).*

Index	Unit	Description
SDNN	ms	Standard deviation of NN intervals
SDRR	ms	Standard deviation of RR intervals
pNN50	%	Percentage of successive RR intervals that differ by more than 50 ms
RMSSD	ms	Root mean square of successive RR interval differences

Frequency domain analysis quantifies the power distribution across specific frequency bands and is typically performed through Fast Fourier Transformation (FTT) or autoregressive (AR) analyses[1]. Four different spectral profiles emerge from the signal:

[1] *Fast Fourier Transform (FFT)* is a numerical algorithm that converts a time domain HRV signal into its constituent frequency components. It operates by decomposing complex waveforms into a sum of sinusoidal functions, providing a non-parametric estimate of the signal's spectral content (Li et al., 2019).
Autoregressive (AR) analysis is a parametric spectral estimation method in which HRV is modelled as a linear combination of its preceding values plus a stochastic term. It produces a continuous estimate of the power spectrum, often yielding improved frequency resolution compared to non-parametric approaches, especially for short data segments (Boardman et al., 2002; Malliani et al., 1994; Montano et al., 1994)

- *Ultra-low-frequency band, ULF* (≤ 0.003 Hz)
- *Very-low-frequency band, VLF* (0.0033–0.04Hz)
- *Low-frequency band, LF* (0.04–0.15 Hz)
- *High-frequency band, HF* (0.15–0.40 Hz) band.

The ULF and the VLF are best monitored using 24-hour ECG recordings, whereas LF and HF components are typically analysed over a 5-minute period.

The *power* of each frequency, indicating the strength or amplitude contribution of oscillations at that frequency, can be expressed in *absolute* values *(a)* or *normalized units (nu)* (Malliani et al., 1994; Shaffer & Ginsberg, 2017). Absolute power indices are reported in ms^2 or ms^2/Hz, while normalized units reflect the relative power of a specific component in relation to the sum of LF and HF absolute powers. Considered the significant intersubject variability in absolute power values between healthy age-matched individuals, normalized units allow to compare measurements across different subjects (Lucini et al., 2017; Montano et al., 1994; Shaffer & Ginsberg, 2017). Total power (TP; ≤ 0.40 Hz) is the sum in absolute power of the different frequency bands (Table 2).

TABLE 2. *HRV frequency domain most used in literature indices (Shaffer & Ginsberg, 2017).*

Index	Unit	Description
TP	ms^2	Total power or variance (≤0.4 Hz)
ULF	ms^2	Absolute power of the ultra-low-frequency band (≤0.003 Hz)
VLF	ms^2	Absolute power of the very-low-frequency band (0.0033–0.04 Hz)
LFa	ms^2	Absolute power of the low-frequency band (0.04–0.15 Hz)
LFnu	nu	Relative power of the low-frequency band (0.04–0.15 Hz) in normal units
HFa	ms^2	Absolute power of the high-frequency band (0.15–0.4 Hz)
HFnu	nu	Relative power of the high-frequency band (0.15–0.4 Hz) in normal units
LF/HF	%	Ratio of LF to HF absolute powers

Figure 12 illustrates the decomposition of the heart rate variability signal into its main frequency components using spectral analysis. The top trace represents the raw HRV over time, which contains oscillations arising from multiple underlying physiological rhythms. In fact, conceptually, HRV waveforms resemble sound waves as they are oscillatory signals which can be decomposed into frequency components. Just as a complex musical tone can be broken down into fundamental and harmonic frequencies, the HRV signal can be resolved into VLF, LF, and HF components. However, unlike sound, these oscillations are not mechanical vibrations of air molecules but rather fluctuations in heart rate driven by autonomic and physiological processes.

Overall, the HF band reflects parasympathetic activity, while the LF band is mainly associated with sympathetic activation, although the influence of the parasympathetic branch on this spectral component is still debated (Amekran et al., 2024; Billman, 2013; Malik, 1996; Malliani et al., 1994; Reyes del Paso et al., 2013). The ratio between LF and HF (LF/HF) is therefore considered a measure of sympathovagal balance (SVB), with higher values suggesting a predominance of LF band activity (mostly sympathetic) (Berntson et al., 1997; Billman, 2013; Malliani et al., 1994).

These spectral bands arise from distinct physiological oscillations: HF power corresponds to respiratory-linked inter-beat changes mediated by vagal efferent traffic, whereas LF power largely reflects baroreflex-mediated oscillations in heart period and blood pressure (Berntson et al., 1997; Montano et al., 1994; Shaffer & Ginsberg, 2017; Skytioti & Elstad, 2022).

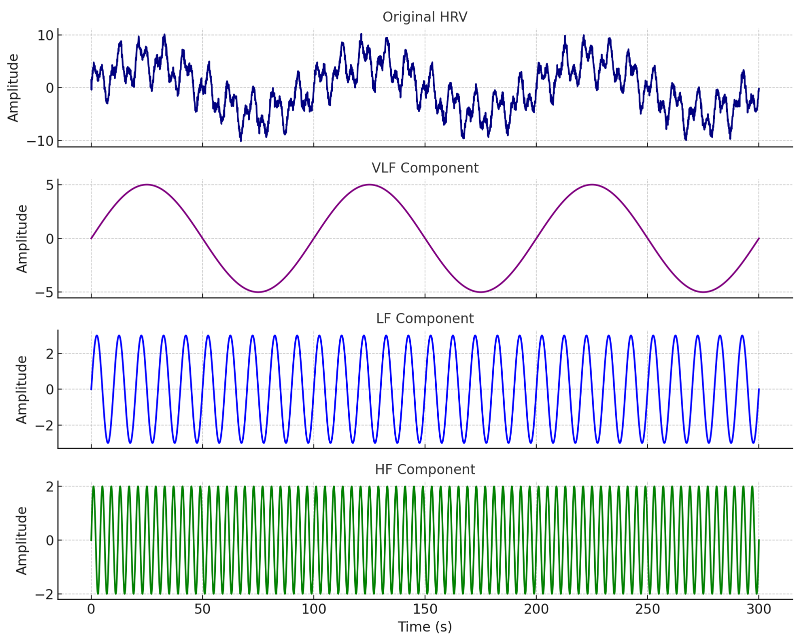


FIGURE 12. *Synthetic illustration of HRV decomposition. This representation is not based on real physiological data but was generated to illustrate the derivation of HRV components (VLF, LF, HF) from the raw HRV signal.*

Parasympathetic (vagal) efference to the sinoatrial node is both phasic and fast: it alters pacemaker currents on a beat-to-beat timescale and can produce almost instantaneous changes in heart rate (slower HR, greater HRV). By contrast, sympathetic effects have longer latencies, unfolding over seconds and accelerating the heart period (faster HR, lower HRV) (Berntson et al., 1997; Malik, 1996; Shaffer & Ginsberg, 2017; Skytioti & Elstad, 2022). This difference in latency explains the separation and characterization of high and low frequencies.

HF BAND. The HF band, also called "respiratory band" is dominated by *respiratory sinus arrhythmia (RSA)*, the phenomenon whereby heart rate rises during inspiration and falls during expiration (Fig. 13). Central respiratory networks modulate the firing of cardiac vagal motor neurons in the Nucleus Ambiguus so that vagal drive is inhibited during inspiration and enhanced during expiration. This produces rapid fluctuations in the RR interval that appear as HF power (fast) in the HRV spectrum (Berntson et al., 1997; Malik, 1996; Shaffer & Ginsberg, 2017; Skytioti & Elstad, 2022). The association between parasympathetic/ vagal activity and the HF band is highly supported by pharmacological studies, where vagal blockade (through atropine) virtually eliminates HF power, while β-adrenergic blockade (sympathetic blockade) has little effect on the HF band (Hayano et al., 1991; Maki et al., 2024; Skytioti & Elstad, 2022). Studies implementing respiration manipulations further demonstrate the mechanistic link between breathing, vagal timing, and HF power: paced breathing, with precise and regular vagal bursts, increases HF amplitude without necessarily changing mean heart rate or tonic vagal tone. Hence, RSA is the primary source of HF variability, that reflects how vagal activity is rhythmically modulated and not necessarily the absolute parasympathetic drive (Shaffer & Ginsberg, 2017; Skytioti & Elstad, 2022; Steffen et al., 2017). Overall HF power is a robust, grounded index of phasic vagal (parasympathetic) modulation of heart rate (Shaffer & Ginsberg, 2017).

LF BAND. Traditionally LF power has been associated to sympathetic activation (Berntson et al., 1997; Montano et al., 1994; Shaffer & Ginsberg, 2017), however more recent research shows that LF oscillations arise from interactions of both branches of the ANS (Billman, 2013; Goldstein et al., 2011; Reyes del Paso et al., 2013). Goldstein and colleagues (2011) argue that LF power is not directly associated to the SNS activity, but is rather a reflection of the arterial baroreflex, a rapid negative feedback loop through which the system buffers short-term compensatory adjustments to adapt to a blood pressure shift. Baroreceptors in the carotid sinus and aortic arch, by continuously monitoring the stretch of the arterial walls, detect a change in pressure (e.g. when we stand up) and correspondently their firing rate decreases or increases. From the baroreceptors the signal is sent to the nucleus of the tractus solitarius (NTS) via the Vagus and the Glossopharyngeal nerves. The NTS coordinates the autonomic responses: for example, upon standing, it increases sympathetic outflow to the heart and peripheral vessels by removing the parasympathetic brake in order to accelerate heart rate and thus restore blood pressure. The baroreflex is associated to an increase in LF power (reflecting mostly sympathetic activation) and a decrease in

HF power (reflecting parasympathetic withdrawal) (Montano et al., 1994; Solbiati & Caiani, 2025; Suarez-Roca et al., 2021) (Fig. 14).

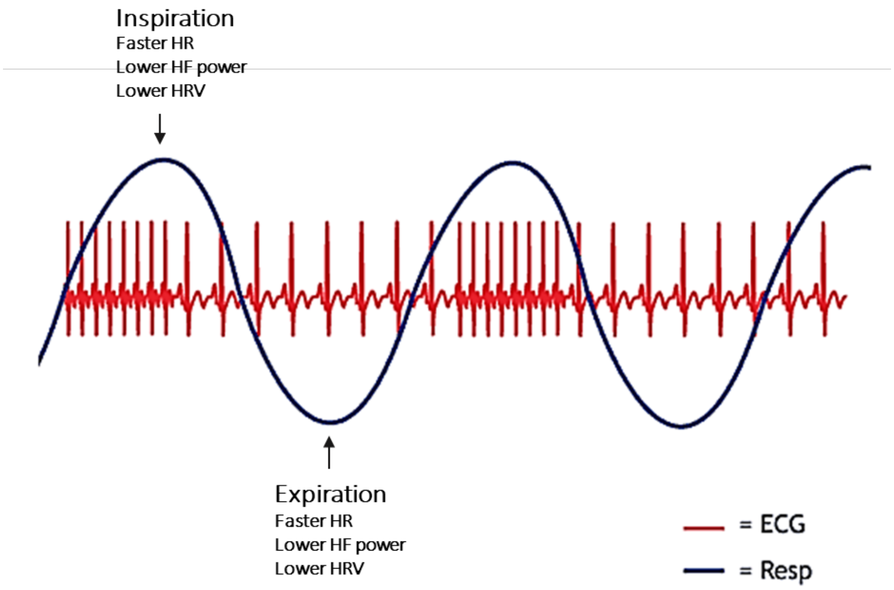


FIGURE 13. *Synthetic illustration of ECG and respiration connection. This representation is not based on real physiological data but was generated to illustrate the effects of respiratory sinus arrhythmia (RSA). During inspiration heart rate (HR) increases (vagal efferent activity to the sinoatrial node is inhibited during inspiration); with less vagal brake, the SA node speeds up (greater HR). Instantaneously HF power goes down: because vagal bursts are suppressed, the phasic modulation of heart period is reduced during inspiration, hence HRV is lower: R–R intervals become shorter and more uniform, so variability decreases. During expiration vagal activity resumes (slower HR), HF power increases and HRV is higher (with greater beat-to-beat variation, variability increases).*

The analysis of HRV during these manoeuvres (i.e. TILT test, active standing challenges) does not simply reflect raw heart rate changes but provides insight into how efficiently the autonomic system operates.

The difference in frequencies rebalance from a supine to a standing position is expressed as ΔHRV. In literature particular importance is given to the difference in low frequencies (nu) activity (ΔLF) between positions, as a measure of the response to the sympathetic excitatory challenge (Malliani et al., 1994; Mellingsæter et al., 2015; Montano et al., 1994; Nicolini et al., 2020; Park et al., 2019; Sala et al., 2017). A rise in low frequencies is associated to a proper and functioning baroreflex (increase of sympathetic activation and decrease of parasympathetic drive).

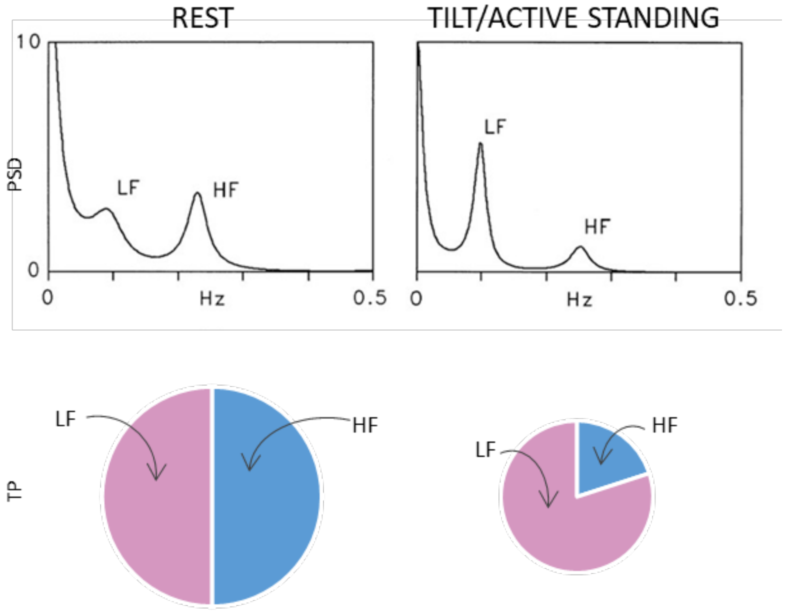


FIGURE 14. *Graphic illustration of the ANS response to the tilt challenge. A rise in low frequencies and a decrease in total power and high frequencies.TP: Total Power. LF: Low frequencies. HF: High frequencies. PSD: power spectral density.*

1.2.2.2 HRV AS A POSSIBLE MARKER OF COGNITIVE DECLINE

When investigating HRV in light of cognitive performance or emotional states, evidence has been provided that higher resting HRV, in particular vagal driven indices of HRV (e.g. RMSSD, HF), associates with better cognitive performance, more effective emotional regulation and better general physical health (Cattaneo et al., 2021; Forte et al., 2019; Jarczok et al., 2022; Magnon et al., 2022; Mahinrad et al., 2016).

When investigating the psychological domain, higher HRV has been associated with an improved capacity to modulate stress responses, maintain psychological resilience, and recover more quickly from negative affective states (Cattaneo et al., 2021; Thayer & Lane, 2000b). From a fitness and health perspective, elevated HRV often correlates with greater cardiovascular efficiency and superior aerobic capacity, contributing to better long-term health outcomes (Jarczok et al., 2022; Mahinrad et al., 2016; Routledge et al., 2010 ; Dorey et al., 2019).

In the cognitive domain, individuals with greater HRV tend to perform better on tasks requiring executive functions, sustained attention, working memory, and problem-solving, functions relying on prefrontal circuitry therefore possibly reflecting more adaptive NVI functioning and top-down control (Thayer, Hansen, et al., 2009; Forte et al., 2019; Magnon et al., 2022; Mahinrad et al., 2016).

Forte et al. (2019), in a systematic review and meta-analysis, showed that HRV is consistently associated with executive functions and other higher-order cognitive abilities across diverse populations. They proposed that HRV may serve as a proxy measure of top-down regulation, integrating autonomic, emotional, and cognitive domains. This aligns with the broader conceptualization of HRV as a biomarker of cognitive decline: reduced HRV not only signals autonomic dysregulation, but it also seems to reflect reduced cognitive functioning. Longitudinal studies summarized in Nicolini et al. (2024) strongly support this interpretation: in most studies lower HRV at baseline predicted future decline in global cognition, executive functions, and episodic memory.

Nonetheless, despite the growing interest in the relationship between resting sympathovagal balance, cognitive functioning and physiological ageing (Cheng et al., 2022; Forte et al., 2019; Liu et al., 2022; Magnon et al., 2022; Nicolini et al., 2024), further research is necessary to elucidate how this system operates in healthy adults, specifically in ageing individuals given that this population is underrepresented in current literature, predominantly focusing on either young healthy populations or clinical groups (Magnon et al., 2022; Nicolini et al., 2024).

The studies addressing healthy older individuals have yielded so far interesting results (Eggenberger et al., 2020; Forte et al., 2019; Mahinrad et al., 2016). For example, Eggenberger and colleagues (2020) found that in older adults (≥70 y.o.) 8-12% of variance in SDNN, RMSSD and HF parameters was explained by measures of executive functioning (Trail Making Test B), supporting a specific relationship between vagally-mediated HRV and higher-order cognitive control. In contrast, other measures, encompassing aerobic fitness, gait, and dual-task performance, failed to significantly predict HRV. These findings suggest that cognitive control mechanisms may be stronger associated to autonomic regulation, at least the parasympathetic branch, than many aspects of physical fitness.

Beyond static, resting measures, ΔHRV -estimated by monitoring the HRV when changing position from supine to the upright position and calculating the delta, i.e. the difference between the two conditions- may provide additional, relevant information. In this context "delta measures", maybe useful to quantify autonomic flexibility: the system's dynamism and its capacity to adapt in response to environmental demands are central aspects both for a healthy ageing and for the execution of complex, yet fundamental cognitive processes. Such dynamic responsiveness appears to map onto cognitive resilience. Interestingly, patients with Alzheimer's disease (AD) or amnestic mild cognitive impairment (aMCI) have been shown to exhibit blunted responses to such sympathetic challenges (lower LF gain) (Mellingsæter et al., 2015; Nicolini et al., 2020) suggesting a possible functional connection between cognitive demand and ANS adaptive reactivity. However, contradicting these results, a longitudinal study revealed that in MCI patients, a steeper decline in episodic memory was predicted by a greater response to a excitatory sympathetic challenge (greater LF gain), indicating complex and unexpected dynamics between sympathovagal balance and cognitive trajectories (Nicolini et al., 2022).

Overall, these findings support the proposal that HRV represents a feasible, non-invasive marker for the early detection of cognitive vulnerability and physiological or pathological decline.

CONCLUDING REMARKS

The presented background highlights the functional and structural interplay between high-order cognitive functions and non-voluntary basic hearth rhythms. Heart rate variability (HRV) is not merely a cardiac metric but an integrated, whole-person indicator of autonomic flexibility, neurovisceral health, and physiological resilience, central qualities for a healthy ageing perspective.

1.3 COGNITIVE AND PHYSICAL PERFORMANCE: DUAL-TASK

Cognitive functions and motor capabilities are tightly intertwined throughout adult life, and this coupling becomes increasingly important with age because the neural substrates that support both cognition and movement are vulnerable to age-related processes. Recent theoretical work even proposes that the entire prefrontal cortex functions as a premotor cortex, serving as a point of convergence in a functional hierarchy for action generation (Fine & Hayden, 2022). Moreover, anatomical evidence report associations between regional gray-matter volumes, including bilateral ventromedial prefrontal cortex, and muscle size, suggesting that variation in brain morphology co-varies with motor capacity (Kilgour et al., 2014).

During ageing, progressive morphological changes occur across the brain, leading to a progressive atrophy that starts in anterior regions; prefrontal areas are thereby the first and most affected by this process leading to declines in processing speed, executive functions and other higher-order cognitive functions (Deary et al., 2009; Lockhart & DeCarli, 2014). Nonetheless, despite the progressive loss of gray matter, the brain is still able to attenuate these structural and functional changes, by recruiting new pathways, in a process of neuronal plasticity (Deary et al., 2009). Longitudinal and interventional studies show that physical activity and fitness can attenuate regional atrophy and improve cognitive outcomes and sustain the preservation of prefrontal volumes (Cheval et al., 2020; Erickson et al., 2011; Ngandu et al., 2015; Voelcker-Rehage et al., 2011) .

Because prefrontal systems are central to both cognitive control and action planning, their decline may reasonably explain why gait and other motor functions predict cognitive outcomes. “Slow gait” phenotype has been investigated and associated with the insurgence of mild cognitive impairment, various forms of dementia and a general steeper cognitive functionality decrease (Verghese et al., 2002). It has been seen that motor impairment, defined on gait parameters, can incur up to 12 years before MCI onset (T. Buracchio et al., 2010). Complementary results show that a reduced level of executive functioning is a predictor of risk of falls and locomotor decline, consistent with the idea that diminished top-down control compromises safe and adaptable mobility in older adults (Al-Yahya et al., 2011; T. J. Buracchio et al., 2011; Mirelman et al., 2012; Verghese et al., 2008). Walking, in fact, particularly in complex or novel environments, is not purely automatic: it recruits attention and executive control functions (e.g. task switching, cognitive inhibition, planning) that undergo the age-related decline with age and with early neurodegeneration. When a secondary cognitive task, performed simultaneously, competes for these limited executive resources, gait control becomes more difficult (Nóbrega-Sousa et al., 2020; Ramírez & Gutiérrez, 2021a; Verghese et al., 2008; Watson et al., 2010; Yogev-Seligmann et al., 2008).

It is in this framework that Verghese and colleagues (2013) introduced the concept of *motoric cognitive risk (MCR) syndrome*, as a clinically useful reversible phenotype of dementia, and especially of vascular dementia (Verghese et al., 2013) (Fig. 15). Operationally, MCR diagnosis is established by four criteria:

1. Presence of slow gait, based on the normative parameters.
2. Subjective memory complaints, evaluated through the 15-item Consortium to Establish a Registry for Alzheimer's Disease (CERAD) questionnaire.
3. Absence of dementia.
4. Preserved ability to ambulate.

Dual-task paradigms probe the dependence of locomotion on cognitive resources and are therefore particularly revealing in older adults and for MCR patients. A cognitive-motor dual task combines a primary motor task (usually walking at comfortable/fast speed or standing/balance) with a secondary task that draws cognitive resources (e.g., verbal fluency, serial subtraction or an additional motor task) (Ramírez & Gutiérrez, 2021a; Verhaeghen et al., 2003).

A recent study implementing functional near-infrared spectroscopy (Nóbrega-Sousa et al., 2020) showed that older people recruit prefrontal cortex (PFC) activity increasingly as task complexity rises (usual walking → obstacle crossing → dual-task walking), consistent with a compensatory and increasing implementation of attentional and executive control when automatic gait control is insufficient. The authors suggested that this compensatory mechanism seems to occur up until the 70s years of age, when the worsening in executive functions limits it and overt gait impairments can be noted (Nóbrega-Sousa et al., 2020).

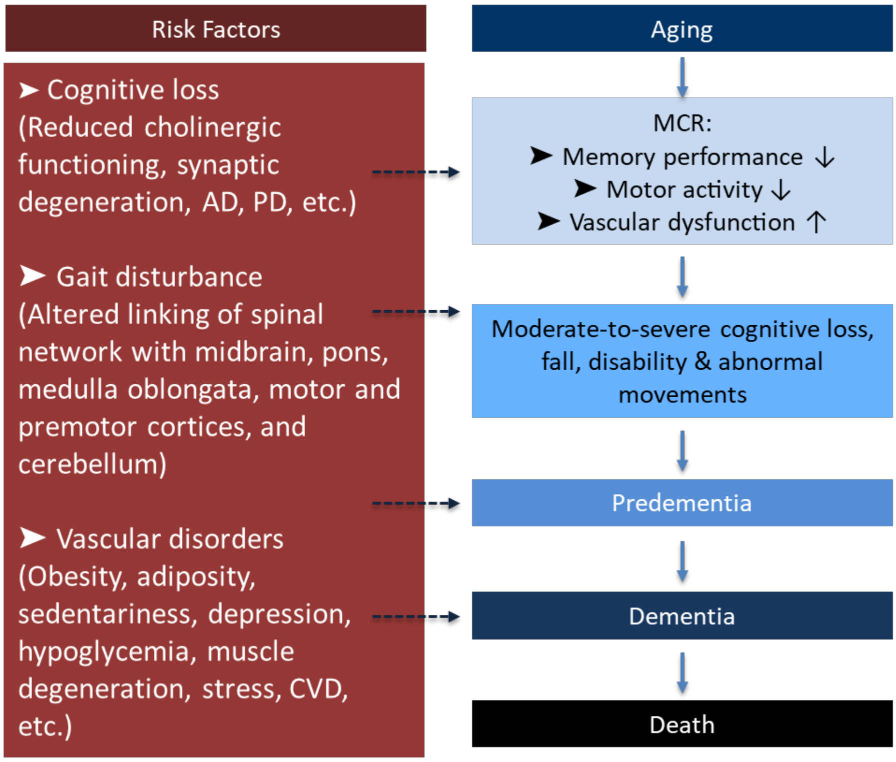


FIGURE 15. *Adapted from Xiang et al.(2022). Motoric cognitive risk (MCR), defined by reduced memory function and impaired gait, represents an intermediate stage between normal ageing and dementia. Cognitive decline may be linked to reduced cholinergic activity, synaptic degeneration, or conditions such as Alzheimer's disease (AD) and Parkinson's disease (PD). Gait disturbances often arise from disruptions in the spinal network's connections with the midbrain, pons, medulla oblongata, motor and premotor cortices, and cerebellum. Vascular disorders also contribute to MCR. As ageing progresses, moderate-to-severe cognitive decline, falls, disability, and abnormal movements can lead to pre-dementia, then dementia, and eventually death, often within a relatively short period following an MCR diagnosis. The risk factors driving this progression encompass vascular, muscular, cognitive, and psychological conditions.*

This pattern - structural frontally biased atrophy, compensatory PFC recruitment during complex gait tasks, and eventual failure of compensation- efficiently accounts for dual-task phenomena in ageing. When cognitive load competes with gait control, older adults typically show greater dual-task cost: gait speed reduces, stride variability increases, and cognitive errors arise (Blake, 2017; Casemiro et al., n.d.; Ross et al., 2021; San Martín Valenzuela et al., 2020; Verhaeghen et al., 2003)

Dual-task paradigms reveal how ageing affects the interface between cognition and mobility and have become a central tool for studying the risk of dementia and brain-body interactions, essential for independence in older people.

The most common outcome of these paradigms is the *dual-task cost (DTC),* the percentage change in (motor-cognitive) performance under dual-task (DT) in relation to single-task (ST) conditions. DTC captures interference between the two tasks as performance loss (e.g. slower gait in DT) (Bianchini et al., 2022; Pike et al., 2023; Ward et al., 2021).

For individuals meeting MCR criteria, dual-task assessment can refine risk stratification and help tailor interventions. In fact, the overlap between cognition and motor functions implies multiple possible training paradigms. Exercise and multimodal training (e.g. aerobic, resistance, balance) expand physical reserve and can improve executive function and gait, while task-specific dual-task training can reduce dual-task costs and improve functional mobility (J. A. Cohen et al., 2016; San Martín Valenzuela et al., 2020; Zhou et al., 2025). Recently exergames have attracted substantial research interest as motivating interventions that simultaneously challenge physical and cognitive systems implicated in age-related decline.

1.3.1 Exergames

Exergames (EG) are interactive, game-like exercise programs that combine motor activity with cognitively engaging virtual tasks. Exergames engage motor abilities (e.g. stepping, balance shifts, cycling) and cognitive capacities through visuospatial, attentional, working-memory, decision-making or executive challenges. They represent a controlled form of dual-tasking that maps well onto the cognitive-motor interplay that becomes fragile in older adults (Altorfer et al., 2021a; Eggenberger et al., 2020; Maggio et al., 2025).

Although only relatively recently implemented, randomized trials and meta-analyses indicate that exergaming can improve both motor and cognitive functions in older people. Systematic reviews and meta-analyses report that exergame training improves gait, static and dynamic balance, reduces fall risk factors compared with inactive controls, and, in some trials, outperforms conventional balance training in producing sustained functional gains (Fang et al., 2020; Pacheco et al., 2020). A recent study also suggests that exergames can improve, aside for the aforementioned motor abilities, cognitive functions such as processing speed, attention and executive control, across healthy older adults and clinical groups, although effect sizes and domain specificity vary between studies and more studies (especially longitudinal) are needed to investigate the relationship more precisely (Maggio et al., 2025). Functional studies showed reduced prefrontal and motor cortex hemodynamic activity during cognitive and motor tasks (Eggenberger et al., 2016; Kubica et al., 2019; Liao et al., 2021). Molecular findings included elevated brain-derived neurotrophic factor (BDNF) (Anderson-Hanley et al., 2012; Monteblanco Cavalcante et al., 2021) and increased cerebral blood flow and cerebrospinal fluid dynamics (Sakhare et al., 2021).

Exergame trainings likely operate through multiple, complementary neurobiological pathways. Attoh-Mensah and colleagues (2025) conducted a systematic review to investigate the neurobiological effects of exergame (EG) interventions in older adults with or without neurocognitive disorders. The study included ten studies on healthy older adults (mean age ≈72 y.o.), and two involving individuals with mild cognitive impairment (MCI; mean age ≈75 y.o.). Interventions lasted from 4 up to 24 weeks (with a mean of 10 weeks of training), with an average of 3 sessions peer week of 20-100 minutes each. EG formats included console-based systems and Virtual Reality (VR)-based setups. While cognitive improvements were consistently observed across domains such as executive function, attention, and memory, motor benefits were less consistent, with improvements reported only in gait speed, stride length, and balance in a few studies (Adcock et al., 2020; Attoh-Mensah et al., 2025; Eggenberger et al., 2016; Schättin et al., 2016; Yang et al., 2023). Notably, none of the studies examined included results of assessed dual-task performance, even though DT is a fundamental aspect of exergames and for the integration of cognitive and motor abilities. As for the neurobiological structural effects of EG, mixed and confounding findings were found, mostly due to methodological differences: in one MRI study no gray matter changes were found (Adcock et al., 2020), but another exploratory research reported increases in frontal and parietal volumes aside to cognitive improvements, suggesting that EG may help to preserve the cortical regions implicated in attention and executive control (Sakhare et al., 2021). A functional near-infrared spectroscopy (fNIRS) study showed a reduced prefrontal activation during tasks such as walking or stepping in exergame trained subjects and executive function gains (Eggenberger et al.2016). These results may appear contradictive; however, a reduced prefrontal activation is typically interpreted as a measure of greater neural efficiency, meaning that after training, participants can perform demanding tasks at lower cost. These effects are also observed, although to a lesser extent, in individuals with MCI, indicating that EG may help slow cognitive decline (Attoh-Mensah et al., 2025). Nevertheless, the heterogeneous methodologies, the lack of a dual-task assessment and small sample sizes limit possible conclusions.

Moreover, Eggenberger et al. (2020) investigated the effects of EG training on HRV and executive functions in healthy older adults and found that exergame training significantly improved HRV indices, including SDNN, RMSSD, and HF power, all indices of parasympathetic activity. The 89 participants were randomly assigned to one of three groups: a dance-based exergame group (DANCE), a memory treadmill walking group (MEMORY), and a physical treadmill walking group (PHYS). The intervention lasted for 10 weeks, with sessions held twice a week and follow-ups were performed at 3 and 6 months from T0. Both the DANCE and MEMORY groups showed greater HRV at 6 months compared to the PHYS group (SDNN and RMSSD), and the DANCE group exhibited an increase in all three HRV indices (RMSSD, SDNN, HF), suggesting that exergame training can preserve and also enhance the autonomic regulation in older adults.

In practical terms, exergames are a promising, evidence-backed adjunct to traditional rehabilitation and prevention strategies in ageing: they are particularly well-suited to target the intertwined deficits of executive function and gait and to engage older adults with motivating protocols.

CONCLUDING REMARKS

Dual-task assessment and exergame training represent innovative strategies to simultaneously challenge cognitive and motor domains in older adults. By integrating physical movement with cognitive demands, they rely on those neural networks that weakens with ageing. Exergames enhance engagement and motivation by providing interactive, gamified environments that challenge executive control, coordination, and balance. These approaches hold strong potential for reducing dual-task costs of daily life, supporting independence, and promoting healthy ageing.

CHAPTER 2

PRAISE: SCOPES AND METHODS

Healthy Ageing Current Scenario. In a fast-changing and increasingly ageing world, the WHO concept of *healthy ageing* is central to establish public health priorities for the coming decades. Conceptualizing ageing in terms of *residual functional capacities*, rather than as a *progressive accumulation of disease*, reorients the focus from pathology treatment to the preservation of functional resources that support autonomy and social participation. This paradigm shift underpins interventions aimed at enhancing the organism's adaptive capacity in response to everyday challenges and stressors. The WHO concept of *Intrinsic Capacity (IC)* operationalizes the individual functional resources as a product of five domains that collectively determine an individual's ability to function and participate in society. In this scenario the concept of *Frailty* represents the other side of the same coin, as it estimates the increased vulnerability of the individual to stressors and functional challenges and it is associated with adverse outcomes (disability, hospitalization, institutionalization). IC and Frailty should therefore be regarded as distinct but complementary constructs (Belloni & Cesari, 2019), as IC describes available functional reserves, whereas Frailty denotes vulnerability (a possible consequence of loss of functional reserves). Both IC and Frailty are dynamic conditions in a bidirectional perspective: IC declines and Frailty increases but, crucially, in the opposite direction Frailty is potentially reversable, especially when detected and treated through multi-domain interventions during its preceding condition: the *pre-Frail* stage. However, recent conceptual models propose that Frailty emerges when IC deteriorates beyond a critical threshold, triggering a physiological tipping point (Yu et al., 2025) leading to overt disability (Jia et al., 2023)and challenging the notion of absolute reversibility and highlights key uncertainties.

Lack of holistic interventional view. The main issue in this field is that the current literature lacks integrated multi-domain interventions that simultaneously target Frailty status, global functional reserves (i.e., IC) and autonomic regulation, all dimensions essential to assess and support the individual as a complex, multicomponent organism.

The PRAISE project. Aiming at bridging this gap, the *PRAISE* ("PRevenzione della disabilità nella persona Anziana Fragile attraverso un Innovativo programma di allenamento perSonale e Multidimensionale/ Prevention of disability in frail elderly people through an innovative personal and multidimensional training program") *project* addresses the challenge of healthy ageing by integrating concepts that are distinct yet intrinsically linked and complementary. Rather than focusing on single domains (e.g., balance training, aerobic training, or cognitive training), PRAISE focus on Frailty and IC as primary targets, encompassing locomotor abilities, sensory competence, cognitive reserve, psychological wellbeing and vitality status. It is a monocentric, randomized, controlled pilot trial designed to evaluate whether a personalized, multi-domain exergame training program delivered via the Dividat Senso platform (see 2.1) can slow or reverse decline in Intrinsic Capacity in pre-frail older adults and to investigate the relationship between IC, autonomic cardiac control (HRV) and dual-task performance. The early pre-Frail stage offers a critical window in which a targeted, multi-domain intervention can restore adaptability and prevent progression to Frailty and disability. Operationalizing adaptability and functional resources require measures that probe system dynamics rather than static snapshots. PRAISE, grounds on a dynamic holistic functional approach: rather than only measuring single-domain outcomes, it focuses on both the assessment of the adaptive responses of the whole system to ecological and experimental challenges/stressors (e.g. dual-tasking, actigraphic registration) and on the neurovegetative reaction needed to sustain adaptive responses (orthostatic challenge). PRAISE was designed to combine four complementary approaches. First, it measures *Frailty status* and global *IC* across its five domains with validated clinical tests to investigate how changes occurring in one or more domains translate into global functional outcomes. Second, it employs *dual-task paradigms* and *exergame training* challenging participants with concurrent cognitive and motor demands; the dual-task cost reveal how well the integrated system reallocates resources under stress. Third, it investigates *autonomic flexibility* by using standardized heart rate variability (HRV) protocols during an active standing challenge, in that HRV indexes moment-to-moment regulatory capacity and has been associated to cognitive performance and functional decline. Finally, it uses continuous activity monitoring (actigraphy) to capture real-world behaviour providing ecological measures that complement lab-based assessments.

PRAISE AND WHO GUIDELINES. Even if the WHO ICOPE (*Integrated Care for Older People (ICOPE)*, 2019) initiative shifted the field toward preserving Intrinsic Capacity, translational evidence on how to preserve or restore IC in order to prevent Frailty and disability remains limited. No study to our knowledge has so far combined the assessment of Frailty, IC, autonomic regulation, dual-task performance, and everyday activity within the same interventional framework. This limits our understanding of how all these constructs interact and how they may be modified through training. Moreover, while the ICOPE framework provides a conceptual foundation for multi-domain prevention, the heterogeneity of measurement and the predominance of single-domain interventions hinder firm conclusions about effective multisystem strategies (Cesari et al., 2018; Gonzalez-Bautista et al., 2020; Sánchez-Sánchez et al., 2022; Zhou & Ma, 2022). Finally, in most studies Frailty stratification is not specified, limiting possible conclusions on differences of trainings targeting pre-frail vs. frail subjects. This is relevant considering that, as stated in the Background section, while roughly 50% of older adults (> 50 years) are estimated to be pre-frail individuals (Rohrmann, 2020), already exhibiting functional decline in IC with comparable prevalence in European countries, Frailty's prevalence significantly varies across European countries (mean 17%, ranging from 5.8% to 23%). Based on these premises, training pre-frail individuals and enhancing functional resources by targeting different IC domains could lead to a significant reduction of Frailty incidence especially in high prevalence countries like Italy.

LACK OF KNOWLEDGE ON EXERGAMES. Given the multi-domain nature of IC, holistic approaches are needed. One promising strategy is cognitive-motor training using exergames (interactive video games requiring physical activity and cognitive engagement). Exergames embed dual-task challenges (e.g. stepping while performing cognitive tasks) and have been shown to yield broad neurobiological and functional benefits. Systematic reviews report that exergame interventions induce structural and functional brain changes, improving cognitive and motor performance (Adcock et al., 2020; Attoh-Mensah et al., 2025). Exergame training has also been found to improve neurovegetative flexibility (Eggenberger et al., 2020) and has therefore the potential to simultaneously train IC domains and autonomic balance. Although exergame programs have been shown to improve physical Frailty indicators such as gait speed, strength and activity performances comparably to conventional physical exercise interventions (Ho et al., 2025; Pacheco et al., 2020), it is unknown whether they also could enhance overall Intrinsic Capacity, especially the cognitive, psychological and sensorial domains. In other words, while exergaming reduces Frailty phenotypes, there is a lack of evidence on broader IC improvements and whether gains in one IC domain translate to others.

THE NEED OF ASSESSING THE NEUROVEGETATIVE FLEXIBILITY. The role of autonomic sympathovagal balance, indexed by heart rate variability, HRV, is also insufficiently characterized. Although lower parasympathetic activity and blunted autonomic reactivity have been associated with cognitive and physical decline, few interventional studies examined whether structured training can modify HRV. Even fewer explored how specific HRV patterns, such as parasympathetic modulation or orthostatic low-frequency responses, relate to cognitive and dual-task performances. Despite the growing interest in the relationship between resting sympathovagal balance, cognitive functioning and physiological ageing (Cheng et al., 2022; Forte et al., 2019; Liu et al., 2022; Magnon et al., 2022; Nicolini et al., 2024), further research is necessary to elucidate how this system operates in healthy ageing individuals given that this population is underrepresented in current literature, predominantly focusing on either young healthy populations or clinical groups (Magnon et al., 2022; Nicolini et al., 2024). Although dual-task paradigms are increasingly utilized to assess cognitive-motor interference, the integration of HRV as a physiological correlate is underexplored. Implementing resting HRV into dual-task paradigms could provide insights into the autonomic demands and resources required to execute ecologically relevant tasks such as walking while engaging in a cognitive challenge (Al-Yahya et al., 2011; Blake, 2017; Ramírez & Gutiérrez, 2021b). This is particularly relevant given the autonomic and motor impairments observed in various forms of dementia, and the increased risk of dementia in dual-decliners, exhibiting concurrent loss in memory and gait speed (Tian et al., 2021).

Conflicting evidence on HRV during an orthostatic challenge. Coupling the study of HRV reaction to a orthostatic challenge, i.e. during the tilt test, and the outcomes of cognitive tasks assessed in different separated session, allows for an evaluation of cardiovascular adaptability on one side, and of the activity of prefrontal neural networks underlying cognitive performance on the other, offering a more comprehensive view of the interplay between central autonomic regulation and its connection to higher-order brain functions. Interestingly, patients with Alzheimer's disease (AD) or amnestic Mild Cognitive Impairment (aMCI) have been shown to exhibit blunted responses to such sympathetic challenges (Mellingsæter et al., 2015; Nicolini et al., 2020) suggesting a possible functional connection between cognitive demand and ANS adaptive reactivity. However, a longitudinal study revealed that in MCI patients, a steeper decline in episodic memory was predicted by a greater response to a excitatory sympathetic challenge, indicating complex and unexpected dynamics between sympathovagal balance and cognitive trajectories (Nicolini et al., 2022). These conflicting evidence could be explained on one side by the intrinsic complexity and dynamic adaptability of the autonomic system itself and, on the other side, by the variability in the methodologies implemented to record ECG signals across studies, an issue that gains particular significance given the ongoing debate regarding the application and significance of the HRV indices (Magnon et al., 2022). Given the contradicting evidence, it has to be clarified if the association in either direction mainly relates to the cognitive disease rather than a functional interplay between the two systems. Studying these mechanisms in healthy subjects, with autonomic and cognitive functions presumably intact, could provide a clearer picture of the system's dynamic range, reveal baseline patterns of adaptability, and distinguish age-related or normal physiological variance from pathological alterations. Furthermore, there are only four studies to our knowledge directly investigating HRV in frail and pre-frail individuals, with contrasting results, and none of which utilized an orthostatic challenge to test the system level of adaptability (Chaves et al., 2008; Katayama et al., 2015; Samuel et al., 2025; Varadhan et al., 2009).

The dual-task paradigm. Similarly to autonomic balance, dual-task paradigms probe system adaptability by stressing the integrated cognitive-motor system through an imposed challenge. Dual-task costs (DTCs), i.e. the performance decrements under dual-task (DT) in relation to single-task (ST) conditions, estimate the system's capacity to allocate limited resources such attention and sensorimotor abilities when simultaneously engaged in a competing task (Verhaeghen et al., 2003). Everyday life functional performance in humans requires simultaneous handling of multiple demands (walking while talking, cleaning while trying to remember a name, avoiding obstacles while planning), thus dual-task performance is an ecologically valid indicator for the real-world adaptive capacity that IC attempts to quantify. Importantly, rather than isolating a single deficit, dual-task paradigms quantify the dynamic interplay between subsystems under stress, aligning closely with PRAISE's systems-oriented perspective. There is no universally accepted battery for dual-task assessment in older adults: this undermines cross-study comparisons and makes it difficult to derive clinically meaningful cutoffs for pre-Frailty or IC decline.

WHY INTEGRATING IC, FRAILTY AND HRV. Most studies have examined IC, Frailty, HRV or exergames in isolation. Few interventions targeted multiple IC domains simultaneously or measured integrated outcomes. In particular, the interplay between neurovegetative flexibility (HRV), dual-task ability, and IC/Frailty status is not well characterized in pre-frail older adults. Furthermore, although exergames can improve cognition and mobility, their impact on *global* function (IC composite) and autonomic health is underexplored. To our knowledge no study has combined a personalized, multidimensional exergame program with rigorous dual-task and HRV assessment in a pre-frail elderly population.

PRAISE project aims at filling these gaps in literature by implementing a thorough exploratory assessment and through an innovative, integrated exergame training protocol. Key research questions include:

- **IC-Frailty interplay:** How do Intrinsic Capacity domains relate to Frailty status in pre-frail subjects? Can changes in IC (composite score) or in IC domains be detected over time and are they informative about the pre-Frailty status?
- **HRV and Frailty/ IC:** Can HRV indices serve as early markers of IC decline or Frailty progression? How do baseline HRV measures relate to the IC domains and to a cognitive-motor training?
- **Dual-task assessment:** Does dual-tasking reflect IC and/or Frailty? Are dual-task costs sensitive/predictive indicators of early decline or of training effects?
- **Exergame training effects:** Does a tailored exergame intervention improve multiple IC domains and/or Frailty status in older adults? Does exergaming improve HRV measures?

- **Intervention gaps:** Can the intervention "drag" improvements across untrained domains, such as the psychological, the vitality or sensory domain?

In summary, PRAISE targets an under-investigated nexus: how autonomic health (HRV), cognitive-motor integration (dual tasks) and multidimensional training together influence the trajectory from pre-Frailty toward Frailty. Addressing these questions will advance understanding of healthy ageing and inform preventive strategies, potentially filling crucial gaps identified in the literature.

2.1 STUDY DESIGN AND METHODS

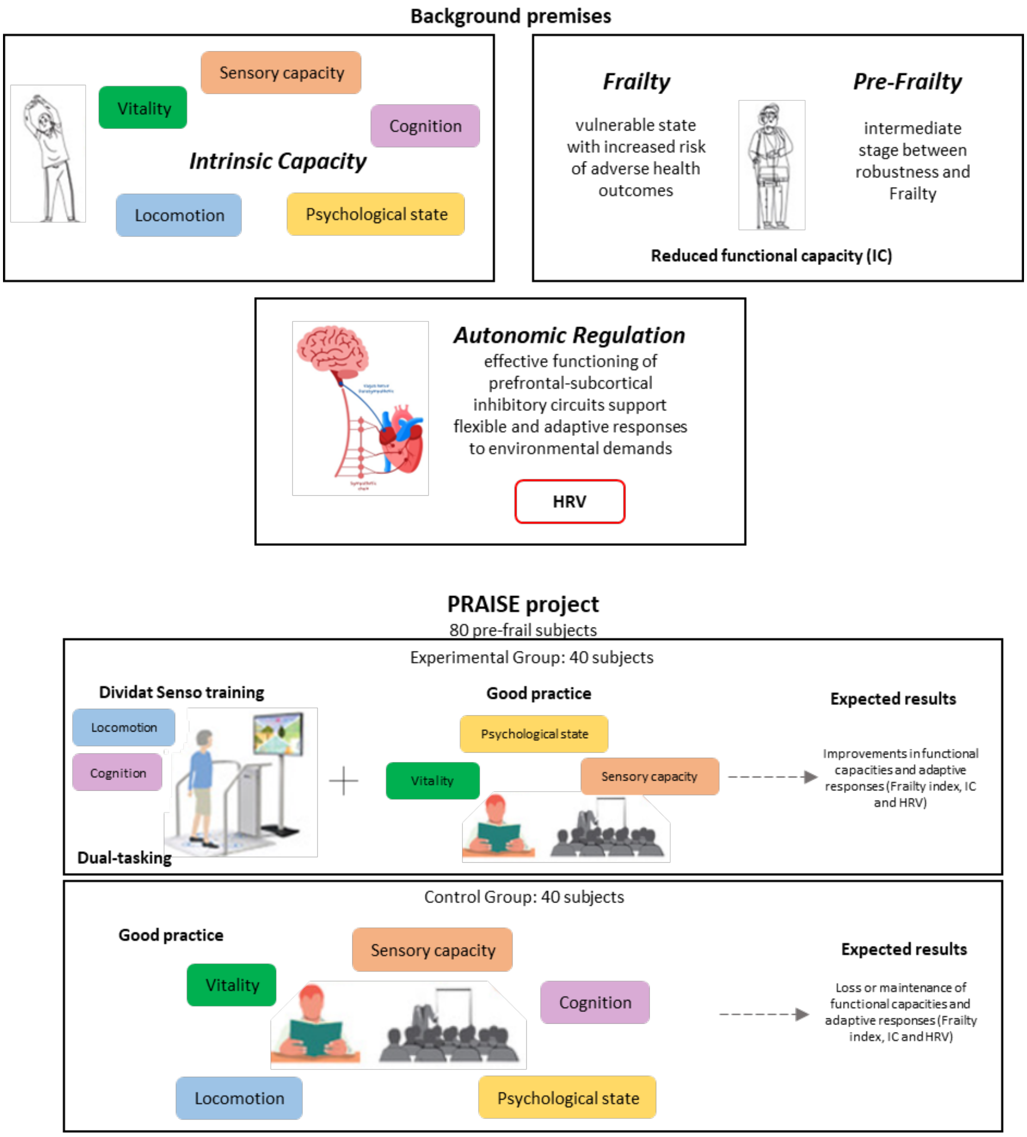


FIGURE 16. *Schematic representation of the Praise project. The background premises lay on the concepts of Intrinsic Capacity, Frailty and Heart Rate Variability, and their interplay in supporting adaptive behaviour. The project is a randomized controlled pilot study with a two-arm, parallel-group design. One group is trained throughout the year on the exergame platform Dividat Senso (focusing on dual-task abilities) while receiving*

usual-care good practices on the psychosocial, vitality and sensory domains. The other group receives usual-care good practices on all five domains of IC (vitality, sensory, locomotor, psychosocial, cognitive). The first group is expected to improve their functional resources (IC, Frailty, HRV), while the other group is expected to lose or maintain functionality.

GENERAL FRAME. The PRAISE project ("PRevenzione della disAbilità nella persona anziana Fragile attraverso un innovativo programma di allenamento perSonalizzato e Multidimensionale/ Prevention of disability in frail elderly people through an innovative personal and multidimensional training program") is a randomized controlled trial with a two-arm, parallel-group design funded by the Romeo and Enrica Invernizzi Foundation. Participants were randomly assigned to either an exergame intervention/study group (S) or a usual-care control group (C). Assessments were conducted at baseline (T0) and after approximately 12 months (12±1) of intervention (T1) (Fig. 16). The intervention group received a personalized multi-domain exergame training program using the Dividat Senso platform (Dividat AG, Switzerland). After a first month of practice to gain confidence with the device, training sessions were progressively adapted in difficulty; supervised sessions were scheduled 5 times every two weeks for approximately 30 minutes each. The control group continued with their usual activities and received general individually adapted health information but no structured training.

DIVIDAT SENSO. The Dividat Senso (Fig. 17) is a cognitive-motor training platform, providing exercises in interactive exergames. It is an evidence-based system designed in collaboration with ETH Zurich to provide therapeutic, preventive, and rehabilitative use and support people with neurological, geriatric, orthopaedic or cognitive-challenges (Altorfer et al., 2021b; Bakker et al., 2020). The system consists of a pressure-sensitive platform connected to a computer and display, where participants respond to visual stimuli by shifting their weight or stepping on designated areas of the platform. The platform includes a set of dual-task assessments that measure different cognitive functions and balance. Trainings difficulty is tailored to each individual automatically by the software that continuously evaluates performance and adapts the difficulty of the exercises in real time. Adjustments are based on accuracy, reaction time, and stability, ensuring that the tasks remain appropriately challenging and engaging without exceeding the participant's functional capacity provoking unnecessary frustration.

FIGURE 17. *Dividat Senso platform.*

Outcomes and Hypothesis. The primary outcomes were: changes in Frailty status and global Intrinsic Capacity (IC), with particular focus to the cognitive and locomotor domains. Secondary outcomes included: heart rate variability (HRV at rest and during active standing), dual-task performance (DCTs), and actigraphy-derived indices of daily physical activity, sedentary time, and sleep parameters.

The study was designed to test the hypothesis that exergame training enhances adaptability in a complex physiological system. Specifically, our expectation was to obtain improvements in IC and Frailty status, mediated or moderated by changes in HRV and dual-task performance, and to be reflected in ecological activity measures.

2.1.1 Sample characterization

PRAISE study is a University of Milan study (Proposing centre), based in the Motor Cognition and Action laboratory (MoCA LAB) directed by Prof Gabriella Cerri (PI of the study), BIOMETRA, UNIMI, affiliated with IRCCS Galeazzi–Sant'Ambrogio Hospital. Praise activity related were all based at IRCCS Galeazzi–Sant'Ambrogio Hospital (Recruiting centre). Eighty healthy volunteers aged 65 years or older were recruited between April 2023 and December 2024; recruitment took place in multiple settings, including recreational centres dedicated to older adults located in Milan and Rho (MI), as well as within clinical facilities of the IRCCS Galeazzi–Sant'Ambrogio Hospital.

Before enrolment, all potential participants were informed about the study objectives, procedures, and potential risks or benefits. Written informed consent was obtained from each participant prior to inclusion in the study and thus prior to any evaluation. The study protocol was reviewed and approved by the Ethics Committees of the University of Milano and "Vita e Salute San Raffaele" (n. 194/2022 in date 25/01/2023) and throughout the research process, strict measures were adopted to safeguard confidentiality and to ensure that all data were anonymized before analysis, in full compliance with ethical standards and data protection regulations as specified in the research agreement between Unimi and IRCCS Galeazzi Sant'Ambrogio. Classified as a Clinical interventional study, Insurance was stipulated by UNIMI and a Clinical monitor enrolled upon the law.

Eligibility criteria were established to guarantee the inclusion of individuals most likely to benefit from the intervention (pre-Frailty or light Frailty). The inclusion criteria were as follows:

1. Age of 65 years or older.
2. A Frailty Index (FI) ranging between 0.10 and 0.4.

Exclusion criteria were designed to avoid confounding conditions and to select participants who might be able to engage with the program. Individuals were excluded if they presented with any of the following:

1. Severe cognitive or motor impairments that significantly limited their ability to perform activities of daily living.
2. A diagnosis of dementia or a corrected score below 24 on the Mini-Mental State Examination (MMSE) (Magni et al., 1996).
3. Occurrence of progressive degenerative diseases affecting the locomotor, sensory, or cognitive systems, which could compromise participation or outcomes.

Of the 80 participants who provided informed consent, 9 were excluded due to a Frailty Index indicating robustness (<0.1), resulting in 71 eligible participants (mean age: 73.01±5.21, ranging from 65 to 88 years). During the baseline assessment (T0), 12 participants withdrew (of which 10 initially assigned to the intervention group and 2 to the control group). Between T0 and T1, 9 additional participants withdrew (3 from the intervention group for medical reasons, and 6 from the control group for medical and personal reasons including relocation to another city, caring for a sick family member, cerebrovascular event, orthopaedic surgery (e.g., hip replacement), and falls resulting in fractures) and 1 control participant died. As of August 2025, 36 participants have completed the T1 assessment (21 intervention, 15 control), while the remaining 13 participants are scheduled for evaluation between September and December 2025 (4 intervention, 9 control). The participant flow is summarized in Figure 18.

The sample at T0 included 23 men and 48 women with a mean Frailty Index of 0.195 ± 0.069, ranging from 0.10 to 0.38 (pre-frailty). The upper value, while marginally exceeding the operational threshold, lies within the light Frailty range (0.10–0.40) defined by the Italian Frailty Index and was therefore included. Group differences in continuous variables were tested by using independent samples t-tests; for non-normally distributed variables, Mann–Whitney U tests were additionally computed as robustness checks. Multiple comparisons were adjusted using the false discovery rate (FDR).

Compared with females, males had significantly higher grip strength ($t = –8.07$, $p < .001$, $d = –2.67$) and peak expiratory flow ($t = –6.39$, $p < .001$, $d = –2.15$), but no other variable was statistically different (Appendix C, Table C1). In Table 3 mean age, Frailty Index (FI), Body Mass Index (BMI), Mini-Mental State Examination (MMSE) outcomes (corrected for age and level of education) and Heart Rate (HR) are reported for the entire sample subdivided for the control and intervention groups.

TABLE 3. *Mean, median, range (max, min), standard deviation (SD) and standard error (SE) of age, Frailty Index, Body mass index (BMI), Mini-Mental State Examination (MMSE) outcomes and Heart Rate (HR) in supine and standing conditions. The entire sample at T0 was composed of 71 subjects, of which 33 allocated to the control group and 38 to the intervention group; the groups do not significantly differ in age, FI, BMI or MMSE.*

SAMPLE AT T0: N 71	**AGE**	**FRAILTY INDEX**	**BMI**	**MMSE**	**HR SUPINE**	**HR STANDING**
MEAN	73.014	0.195	24.965	27.37	62,75	70.07
MEDIAN	73	0.1875	24.84	27.4	61.02	69.87
MAX	88	0.38125	36.45	30.8	84.86	92.33
MIN	65	0.1	16.67	24.3	45.09	51.26
SD	5.211	0.069	3.840	1.365	9.94	9.79
SE	0.618	0.009	0.455	0.162	1.27	1.26
CONTROL GROUP: N 33						
MEAN	73.484	0.198	24.418	27.554	61,52	70.00
MEDIAN	73	0.1875	24.79	27.4	60.38	68.22
MAX	88	0.35	33.33	30.8	84.86	92.33
MIN	65	0.1	16.67	24.3	45.09	52.06
SD	5.585	0.070	4.101	1.54	9.75	9.93
SE	0.972	0.0149	0.714	0.268	1.81	1.88
INTERVENTION GROUP: N 38						
MEAN	72.605	0.192	25.44	27.21	63,87	70.13
MEDIAN	73	0.187	25.09	27.25	62.50	70.51
MAX	85	0.381	36.45	29.3	81.53	88.98
MIN	65	0.112	19.14	24.3	48.36	51.26
SD	4.901	0.069	3.585	1.191	10.14	9.84
SE	0.795	0.011	0.581	0.193	1.79	1.74

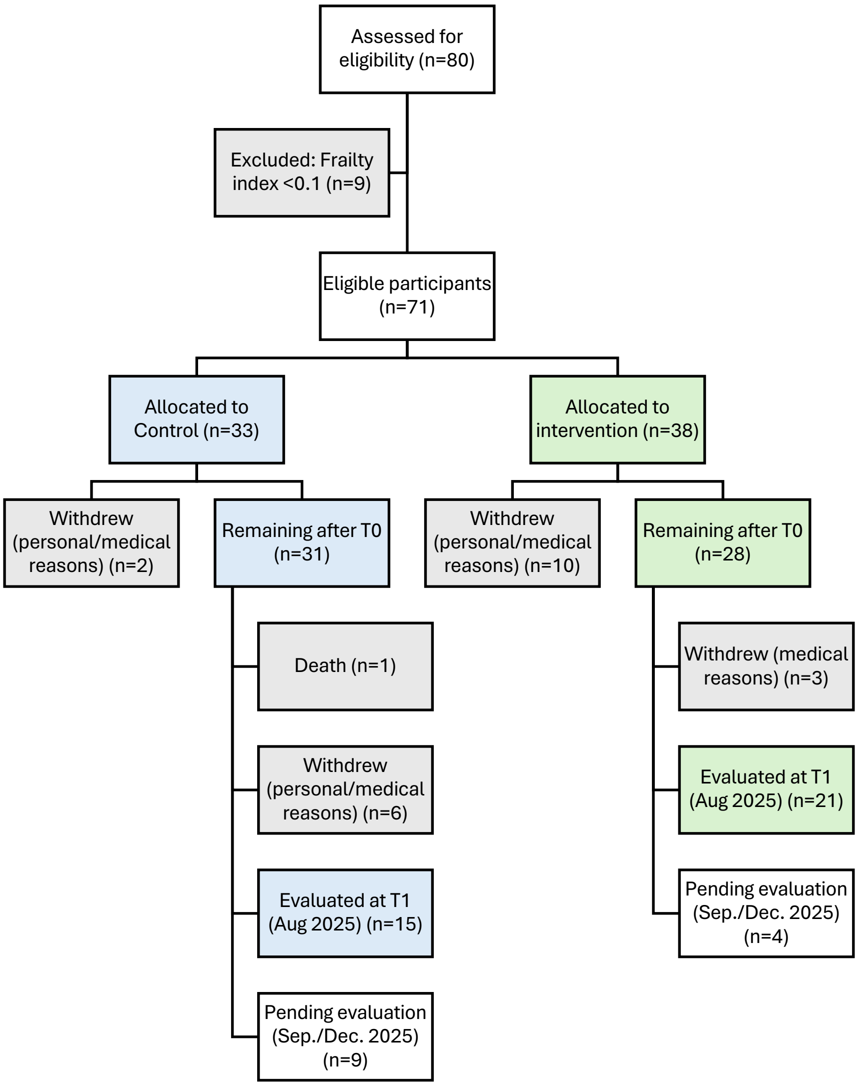


FIGURE 18. *Eighty individuals were assessed for eligibility, of whom nine were excluded due to a Frailty Index <0.1. Seventy-one participants were randomized to the intervention group (n = 38) or the control group (n = 33). At baseline (T0), 12 participants withdrew consent for personal or medical reasons (10 intervention, 2 control). Between T0 and T1, a further 9 participants withdrew (3 intervention, 6 control), and 1 participant in the control group died. At the first follow-up (T1, August 2025), 36 participants were evaluated (21 intervention, 15 control), while the remaining participants are scheduled for assessment between September and December 2025.*

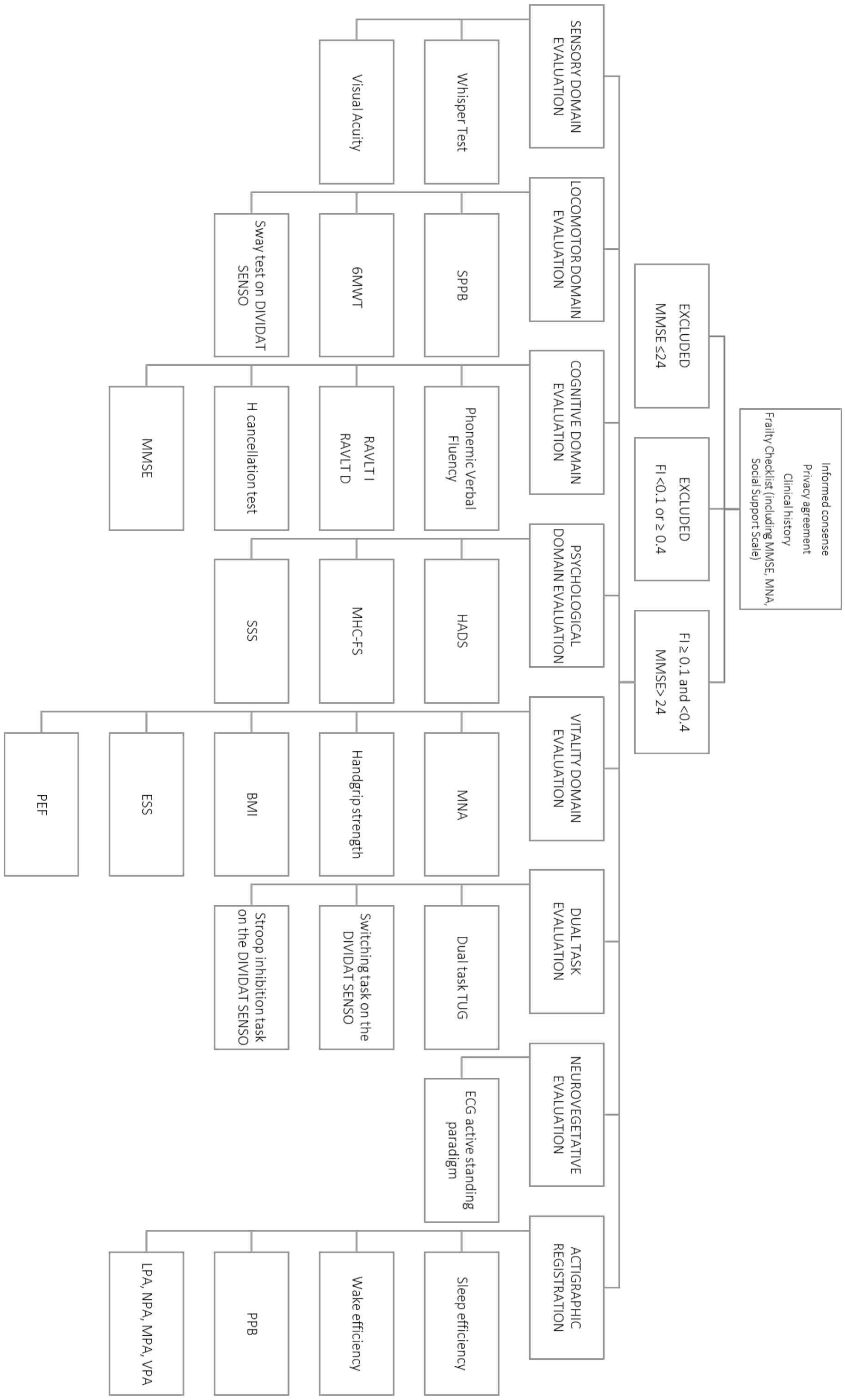


FIGURE 19. *Schematic representation of the tests conducted in the baseline assessment at T0 and T1. FI: Frailty Index. MMSE: Mini-Mental State examination. SPPB: Short Physical Performance Battery. 6MWT: Six minutes walking test. PEF: Peak Expiratory Flow. SSS: Social Support Scale. HADS: Hospital Anxiety and Depression Scale. MNA: Mini Nutritional Assessment. MHC-SF: The Mental Health Continuum–Short Form. RAVLT: Rey Auditory Verbal Learning Test, immediate (I) and delayed (D) recall. BMI: body mass index. ESS: Epworth Sleepiness Scale. TUG: Timed Up and Go. PPB: Pseudo-periodic Behaviour. LPA,NPA,MPA,VPA: light, no-, moderate, vigorous physical activity.*

2.1.2 Assessment and Data Collection

All participants (N=71) underwent a comprehensive baseline assessment (at T0) conducted over two separate sessions within a two-week window. Upon enrolment socio-demographic and clinical variables were collected, including age, sex, educational level, medical history and familiarity, medication use, body mass index (BMI), comorbidities, and lifestyle habits. All tests were administered according to a structured paper protocol (Appendix A) and reported to paper case report forms (CRFs) as the official record of each participant. Performance data from the Dividat Senso platform were automatically recorded by the device software during each evaluation. All paper and digital data were linked via a unique participant code to maintain confidentiality and only authorized members of the research team had access to the data, in compliance with institutional data protection policies and GDPR regulations.

The assessment encompassed the five domains of IC (cognition, locomotion, sensory abilities, vitality, psychological wellbeing), a neurovegetative evaluation through a standardized electrocardiogram (ECG) paradigm, a one week-long actigraphic registration and a thorough dual-task assessment (Fig. 19). All tests and parameters registrations were repeated at T1 for both groups.

In this section each test will be briefly explained, focusing on how it was performed and on the variables considered for the analysis.

Frailty Checklist

Frailty can be measured as the accumulation of deficits of an individual. The Italian ***Frailty Index*** (Abete et al., 2017) is stratified in light, moderate and severe Frailty; only subjects with a Frailty index between 0.1 and 0.4 - light Frailty, corresponding to pre-Frail stage (see Background section)- were included in the study. The index is calculated as a ratio between the number of deficits assessed in the subject and the total number of deficits considered (40 items). The different items of the checklist are visible in Appendix A and include:

- *Mini-Mental State Examination (MMSE)*: it is a screening tool for global cognition. The results were corrected for age and years of education (Magni et al., 1996).
- *Mini Nutritional Assessment (MNA)*: it is a screening and assessment tool, assessing anthropometric measures, general medical status, nutrition and dietary habits, and self-perceived health, implemented to evaluate the risk of malnutrition in an elderly population. The outcomes are divided in three categories: 1) normal nutritional state (scores above 24/30), 2) risk of malnutrition (scores between 17 and 23.5), 3) state of malnutrition (scores below 17/30) (Kaiser et al., 2010).
- *Social Support Scale (SSS)* (Abete et al., 2017; Mazzella et al., 2010): it is a questionnaire evaluating the presence and frequency of social networks,

social relationships and economic support. The score ranges from 0 to 17, with higher scores referring to lower social support.

- *Peak of Expiratory Flow (PEF):* it measures the volume of air, in L/min, expelled in a single fast exhalation. The measure was repeated three times, and the average of the responses was considered for the analysis.
- *Handgrip Strength (kgs) (Grip)*: it was measured three times with a handheld dynamometer. The subjects were asked to use their dominant hand, and the average of the outcomes was considered for the analysis.

COGNITIVE ASSESSMENT

- *Phonemic Verbal Fluency (PVF)* (Novelli et al., 1986): it investigates the capacity of generating words from three specific letters of the alphabet (F, P, L). Problems or difficulties in the execution of this test estimate executive functions possible deficits and capabilities. The results were corrected for age and years of education; higher scores indicate a good phonemic verbal fluency.
- *Rey Auditory Verbal Learning Test (RAVLT)* (Carlesimo et al., 2008): it is implemented as an assessment of immediate memory and verbal learning capacities. A list of 15 unrelated words (both common and less frequently used terms) is orally presented and repeated for five times to the subject; each time the subject is asked to recall as many words as he/she can remember (number of total words recalled-immediate recall- **RAVLT-I**). After a delay of 15-20 minutes participants are requested to freely recall as many words as possible of the same list (number of total words recalled- delayed recall- **RAVLT-D**). The results were corrected for age and years of education; higher scores reflect a better cognitive performance.
- *Letter Cancellation Test (H)* (Uttl & Pilkenton-Taylor, 2001): an often used assessment of visuospatial scanning abilities and visuospatial deficits. The participant is presented with six arrays of casual letter combinations and asked to cancel every letter "H" on the A3 paper as fast as possible.
    - H Reaction Time: time (s) needed to complete the task (Htime).
    - H missed: number of omission errors.
- *MMSE (see Frailty Checklist).*

PSYCHOLOGICAL ASSESSMENT

- *Hospital Anxiety and Depression Scale (HADS)* (Zigmond & Snaith, 1983): it is a 14 item scale assessing anxiety and depression states. Each item can be scored from 0 to 3 for a total of 42 (21 referring to anxious behaviour and 21 to depressive symptoms). Higher scores reflect self-reported presence of anxiety or depressive symptoms; the cut-off is established at 8-10/21. The outcomes are expressed as:
    - HADS A: referring to anxious symptoms
    - HADS D: referring to depressive symptoms

- HADS TOT: the sum of HADS A and HADS D, referring to the general anxious-depressive state

- *The Mental Health Continuum–Short Form (MHC–SF)* (Keyes, 2005): it consists in a 14 items test, measuring the level of Emotional Well Being -EWB-, Social Well Being -SWB-, and Psychological Well Being -PWB- (including degree of autonomy, environmental mastery, personal growth, relations with others, purpose in life and self-acceptance). The subjects are asked how often during the previous month they felt (or experienced) a certain state, and the answers options for all three categories (EWB, SWB, PWB) are "never"(0), "once or twice"(1), "about once a week"(2), "two or three times a week"(3), "almost every day"(4), and "every day"(5), so that higher scores relate to a better emotional/psychological/social well-being perception.

Locomotor Assessment

- *Short Physical Performance Battery (SPPB):* it is a brief accessible evaluation of legs strength, balance and pacing speed often applied in older adults' cohorts. The score ranges from 0 to 12, with higher scores referring to a better physical state (Guralnik et al., 1994).
- *Six Minute Walking Test (6MWT):* it assesses aerobic capacity and endurance. The subject is asked to walk in a straight 30 meters long hallway, turn around a cone and walk all the way back for a total of six minutes. Total meters walked was considered as outcome for the analysis. Due to hospital renovation works, no adequate space was available to perform the 6MWT at T1 and the variable was considered only for the analysis at T0.
- *Sway Test on DIVIDAT SENSO:* it measures postural control. The subjects were asked to stand with both feet hip-width apart, keep their arms crossed in front of their chest and try to stand as still as possible for 30 seconds; the measure was repeated 2 times for every subject, and an average of the results was considered for the analysis. The subjects were then asked to repeat the exercise while keeping their eyes closed. The test outcomes are synthetized in different indices, both in the open-eyes condition (SWAYO) and the eyes closed one (SWAYC):
    - Maximum deviation (*SWAY_O_maxDev*)
      The maximum deviation of the centre of pressure from the initial position.
    - Anterior/posterior sway (*SWAYO/C-AntPost*)
      The distance between the outermost points the centre of pressure reached on the anterior/posterior axis.
    - Medial/lateral sway (*SWAYO/C-Lateral*)
      The distance between the outermost points the centre of pressure reached on the medial/lateral axis.

- Sway path length (*SWAY_O/C_PL*)
  The total distance the centre of pressure moved during the test.
- Mean sway speed (*SWAY_O_Speed*)
  The average speed (mm/s) at which the centre of pressure moved during the test.

Vitality Assessment

- *Handgrip strength (see Frailty Index)*
- *Mini Nutritional Assessment -MNA- (see Frailty Index)*
- *Body Mass Index -BMI-:* measured as the ratio between weight (kg) and height^2 (cm). It is a measure of corpulence and leanness and is generally used to determine whether a person is underweight, in a normal range or overweight in relation to his/her height.
- *Epworth Sleepiness Scale -ESS-*: (Johns, 1991) it is a questionnaire used in clinical setting composed of 8 items, implemented to assess daytime sleepiness. Total score ranges from 0 to 24, with higher scores associated with a greater self-reported probability of dozing off.
- *Pittsburgh Sleep Quality Index -PSQI-* (Buysse et al., 1989): it is a 19 items questionnaire assessing sleep efficiency, sleep disturbances and daytime dysfunction; higher scores refer to a worse sleep quality.

Dual Task Assessment

- *Dual Task Timed Up and Go (DT TUG)* (Hofheinz & Mibs, 2016): the Timed Up and Go test is a common assessment for risk of falls and mobility both in clinical practice and research (Podsiadlo & Richardson, 1991). The subject starts in a seated position, at the experimenter's signal he/she is asked to stand up, walk in a straight line for 4 meters, turn around a cone on the ground, walk back to the chair and sit. The task was repeated twice, once asking the subject to walk at a normal habitual pace, once in a rapid fast pace.
  During the Dual Task TUG the participant was asked to perform a working memory task while executing the Tug (both in the normal-paced and in the fat-paced conditions); the subject had to count backwards, starting from 90 and subtracting 3. The instructions were to keep on walking even in case of a mistake.
  Dual Task Cost (TugDTC) was calculated as follows:

$$\frac{\text{RT dual task (normal or fast pace)} - \text{RT simple task (normal or fast pace)}}{\text{RT simple task (normal or fast pace)}}$$

  Dual Task Cost is needed to separate the result from its exclusively motor component. For the simple task, the timing of the normal TUG was used, as it represents a purely motor task. The dual-task cost (TugDTC) was calculated and expressed as a percentage both in the normal-paced condition (TugDTC) and in the fast-paced condition (TugDTC_fast). Higher scores represent a greater difficulty in executing the cognitive task while moving.

- *Go-NoGo on DIVIDAT SENSO*: in this task instructions were to look at a grey fixation dot at the centre of the screen; a x or + symbol would then appear to the right or left of it (Fig.20). In case of:
  x: the subject was asked to react by stepping into the direction of appearance as fast as possible.
  +: the subject was asked to not react.

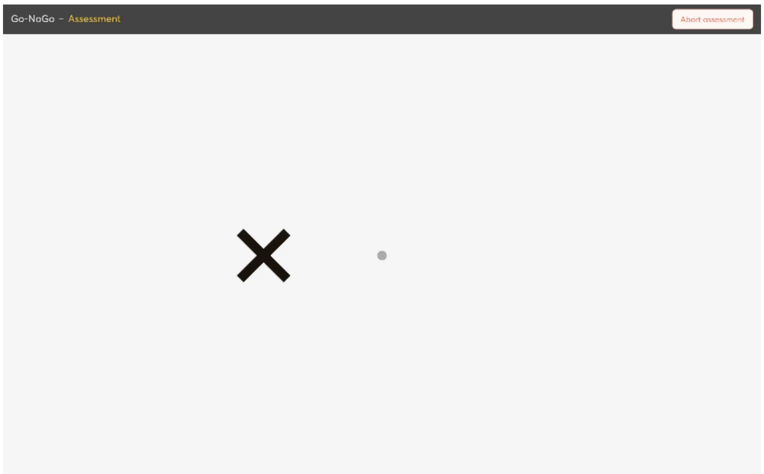


FIGURE 20. *Go-NoGo test on Dividat Senso*

The outcome considered for analysis was of the test average reaction time (GoNogo) i.e. the average time between stimulus and a correct response.

- *Switching task on DIVIDAT SENSO:* rounded and angular figures appear to the sides of the centre of the screen (Fig. 21). The subject must respond by alternating between stepping towards the rounded and angular figure

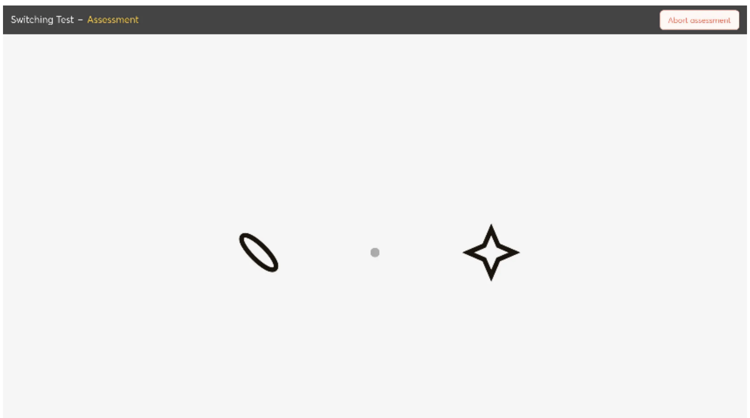


FIGURE 21. *Switching Test on Dividat Senso.*

(rounded-angular-rounded-angular and so on…). It is an assessment of cognitive flexibility and task switching capabilities.

Dual Task Cost (DTCSwitch) was calculated as follows:

$$\frac{RT\ cognitive\ switching\ task - RT\ simple\ task}{RT\ simple\ task}$$

to separate the result from its exclusively motor component. For the simple task, the average rection time of the Stroop Inhibition Test Phase 1 was used, as it represents a purely motor reaction to basic stimuli. Higher scores represent a greater difficulty in executing the cognitive task while moving.

- *Stroop Inhibition Test on DIVIDAT SENSO.*
  The test is divided in 4 phases:
  1. Assigning colours: a coloured square appears in the centre of the screen. The task requires to match the colour of the square to the matching circle with a step in the corresponding direction.
  2. Reading words: a word appears in the centre of the screen. The task requires to read the word and assign the colour to the matching circle with a step in the corresponding direction.
  3. Inhibition: a word written in coloured ink appears in the centre of the screen. The task requires to assign the colour in which the word is written to the matching circle with a step in the corresponding direction.
  4. Flexibility: a colour-inked word with or without a frame appears in the centre of the screen.
     - Word with frame: Read the word and match the colour you read to the appropriate circle.
     - Word without frame: Match the colour in which the word is written to the appropriate circle.

  Phase (1) measures the reaction time (RT) to simple coloured stimuli; (2) measures the RT needed to read the word and take a step in the direction of the written colour; (3) is a measure of cognitive inhibition, as the task requires for the subject to take a step in the direction of the colour of the ink in which the word is written, not the meaning of the word (Fig 22); (4) is a measure of cognitive flexibility as the subject is asked to switch between two different tasks.

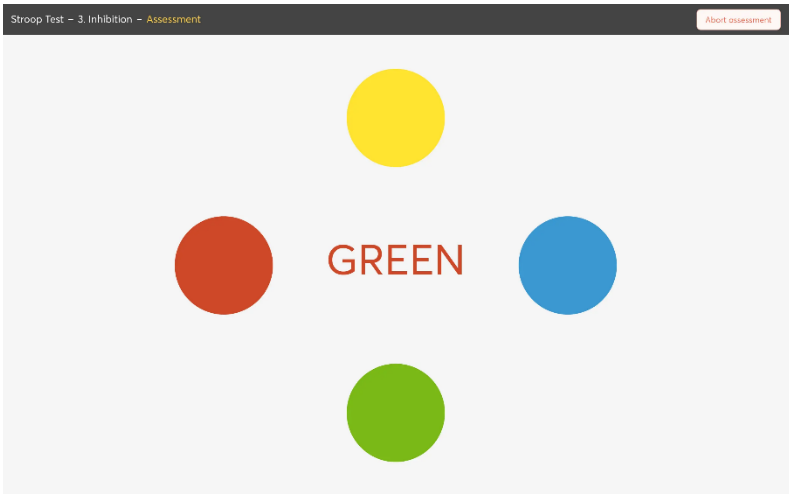


FIGURE 22. *Stroop Inhibition Test on Dividat Senso (phase 3).*

As for the other dual task assessment, the DTC was calculated as follows:

$$\frac{RT\ cognitive\ task\ [(3)\ ;(4)] - RT\ simple\ task\ [(1)\ ;(2)]}{RT\ simple\ task\ [(1)\ ;(2)]}$$

The variables considered for the analysis:

- StroopDTC_Inh_1: cognitive cost needed to inhibit the misleading reading of the word, compared to the RT of simple colour matching
- StroopDTC_Inh_2: cognitive cost needed to inhibit the misleading reading of the word, compared to the RT of words matching
- StroopDTC_Flex_1: cognitive cost needed to switch between the two tasks, compared to the RT of colours matching
- StroopDTC_Flex_2: cognitive cost needed to switch between the two tasks, compared to the RT of words matching

Sensory Assessment

- *Whisper Test* (Maguire et al., 1998): it is a brief and widely used screening test implemented to detect hearing impairment. Subjects were instructed to place a finger on the tragus of one ear; while standing behind them the experimenter whispered two numbers and asked the subject to repeat the numbers if heard. The test was administered twice for each ear and the scores were calculated as a percentage of correct answers over total stimuli (n=8). Lower scores reflect a worse hearing performance.
- *Visual acuity assessment* (Azzam & Ronquillo, 2024): Snellen chart for visual acuity was utilized for this measure. Results to the task were analysed as an average of visual acuity percentages of the eyes; higher scores reflect better visual acuity.

HRV Assessment

Fifthy-nine participants underwent the same protocol for signal acquisition of autonomic regulation.

ECG data were recorded in a quiet, temperature-controlled room with standardized lighting between 9 a.m. and 12 p.m. Participants were instructed to lie in a comfortable position without speaking and with closed eyes, while ECG signals were acquired at 500hz using a Cardioline Cubestress System HD+ for 5 minutes, considered a standard short-term recording period time (Malik, 1996). Subsequently participants were asked to stand upright with open eyes for 5 minutes while ECG signal was acquired.

At T0 twenty-eight subjects undergoing beta blockers (10 subjects), SSRI (4 subjects), Ace-inhibitors (7 subjects), or Benzodiazepine intake (7 subjects), medicines influencing HRV, were excluded from the statistical analyses. Although respiratory rate was not directly recorded, participants in the supine position whose spontaneous breathing frequency fell below 10 breaths per minute were instructed to increase their breathing rate to ensure that respiratory sinus arrhythmia remained within the HF band and did not encroach upon the LF range; HeartScope II was used to simulate the respiratory signal and confirm alignment of the respiratory waveform with the HF band. One participant was excluded on this basis, yielding a finale sample of 30 subjects.

The collected ECG data was analysed to extract heart rate variability (HRV) features, focusing on the frequency domain. The first 30 seconds of each recording were discarded to reduce possible initial artifacts. The signal was then visually inspected by a trained professional to ensure quality of the recording and for artifacts correction. Spectral analysis was conducted to estimate the power spectral density (PSD) of the HRV signal, and to quantify the magnitude of frequency components, including high frequencies (HF), low frequency (LF) and very low frequency (VLF) (Lucini et al., 2017).

Heart rate variability indices were computed with a dedicated software (Heartscope II) both in resting and in standing positions. Further analyses were conducted considering indices in absolute power and normalized unit. Normalized units (nu) were calculated as:

$$P[f]nu = (P[f]ms2 / P[tot]ms2 - VLFms2) * 100$$

where *f* indicates either LFa or HFa, and VLF (very low frequency) is the power under 0.03 Hz (Lucini et al., 2017).

HFa, HFnu, LFa, LFnu, Total Power (TP), and the ratio between low frequencies and high frequencies (LF/HF) were considered for the statistical analysis both in resting supine and active standing conditions. The dynamical change in sympathovagal balance was calculated as the difference in normalized units

(ΔLFnu, ΔHFnu and ΔLF/HF), and as a percentual difference (ΔHF%, ΔLF%) between positions (see Table 4).

The percentage change in absolute powers between conditions was retrieved using the following formula (Grant et al., 2012; Rani et al., 2022):

$$\Delta HF\% = [(HFa\ standing - HFa\ supine) / HFa\ supine] * 100$$

$$\Delta LF\% = [(LFa\ standing - LFa\ supine) / LFa\ supine] * 100$$

TABLE 4. *HRV indices considered for the analysis. LF: Low frequencies. HF: High frequencies. TP: Total power.*

Position	Absolute Power (ms^2)	Normalized Units (nu)	Description
Supine	LFa (0.04-0.15 Hz)	LFnu	Low frequencies: reflecting sympathetic and parasympathetic activity during resting in supine position.
	HFa (0.15-0.4 Hz)	HFnu	High frequencies: reflecting parasympathetic activity during resting in supine position.
		LF/HF	The ratio in nu between LF and HF: a measure of sympathovagal balance during resting in supine position.
	TP (≈≤0.4 Hz)		Total power: reflects total variance during resting in supine position.
Standing	LFa (0.04-0.15 Hz)	LFnu	Low frequencies: reflecting sympathetic and parasympathetic activity during active standing.
	HFa (0.15-0.4 Hz)	HFnu	High frequencies: reflecting parasympathetic activity during active standing.
		LF/HF	The ratio in nu between LF and HF: a measure of sympathovagal balance during active standing.
	TP (≈≤0.4 Hz)		Total power: reflects total variance during active standing.
Δ HRV		ΔLF	Difference in low frequencies (nu) activity between supine and standing.
		ΔLF/HF	Difference in the ratio between low and high frequencies (nu) activity between supine and standing.
	ΔHF%		Percentual difference in high frequencies (a) activity between supine and standing.
	ΔLF%		Percentual difference in low frequencies (a) activity between supine and standing.

ACTIGRAPHIC REGISTRATION

Actigraphy data were obtained using the GeneActiv system, which provided continuous monitoring of activity and sleep over the assigned periods.

In this test, participants are equipped with a wrist-worn actigraphy device for 7 consecutive days during T0 and T1 assessments. Data are used to derive physical activity intensity, sedentary behaviour, sleep efficiency and pseudo-periodic behaviour (Scalera et al., 2017). This provides ecologically valid information about behavioural patterns and circadian rhythms. Indices were computed on the 7-

days long recording. When the full-length recordings included a portion of scratch recording for any reason, for example because of participants dressing off the sensor, the scratch portion was removed from the recording and the remaining time duration was further reduced to the highest possible multiple of 24 hours. The previous algorithm allowed for the computation of the indexes on recordings whose length was a multiple of the basic 24-hour circadian cycle.
Indexes extracted were the following:

- *NPA, LPA, MPA* and *VPA*: the percentage duration of no-physical activity (NPA, 1 MET, MA<=10), light physical activity (LPA, 1 -3 MET, 10 <MA<=100), moderate physical activity (MPA, 3-6 MET, 100 <MA<=350) and vigorous physical activity (VPA, >6 MET, MA>350);
- *PPB*: the percentage duration of pseudo-periodic behaviour, whose occurrence was identified in 4-seconds epochs of the acceleration norm in which the autocorrelation coefficient was larger than 0.7;
- *S*leep efficiency (sleep_efficiency), the percentage of time between 11PM and 7AM in which MA was classified as NPA;
- *W*ake efficiency (wake_efficiency), the percentage of time between 9AM and 9PM in which MA was classified as LPA or MPA or VPA.

2.1.3 IMPLEMENTATION OF THE GOOD PRACTICE BOOKLET

As part of the study protocol, all participants received a good practice booklet at the end of their baseline (T0) assessment (Appendix B). The booklet was designed as an individualized guide to support healthy ageing, and its content was tailored to each participant's profile based on results from the T0 evaluation. The booklet was developed drawing on the WHO ICOPE (Integrated Care for Older People) guidelines (2017) and the ViviFrail passports (Izquierdo et al., 2016). Both resources emphasize multi-domain strategies to maintain or enhance intrinsic capacity (IC) and to prevent frailty and disability in older adults. The "PRAISE adaptation" incorporated practical recommendations and advice addressing the five domains of IC: locomotion, cognition, vitality, sensory, and psychological well-being. Specifically, the control group (C) received suggestions for all five domains of IC, while the intervention group (S) received booklets containing information on the sensory, vitality and psychological domains and trained the locomotor and cognitive domain on the Dividat Senso platform as part of the intervention. The booklet was handed to participants immediately after the T0 assessment with a brief explanation of the purpose and content. In both groups, the booklet served as a supportive tool to raise awareness of modifiable lifestyle factors and promote healthy behaviours. In the control group, it represented the main active component of the intervention, while in the intervention group, it played a complementary role alongside the supervised training program.

The following schematic figures aid comprehension of the tailoring process and provide domain-specific examples, illustrating how participant assessment data informed the selection of recommendations (Fig. 23. 24, 25, 26, 27, 28).

2.1.4 PRAISE Intervention: The Exergame Training

Participants randomized to the intervention group completed a one-year exergame training program on the Dividat Senso platform. Training was scheduled five times per month, following a structured pattern of two consecutive weeks of training, alternated with two weeks without training; this schedule was chosen to balance training intensity and feasibility for older adults.

Each training session lasted approximately 30 minutes and consisted of sensorimotor and cognitive tasks delivered through the Senso system. Exercises combined stepping, balance, and coordination challenges with simultaneous cognitive tasks (e.g., inhibition, memory, selective attention, cognitive flexibility), providing a multi-domain stimulation aligned with the study's purposes.

The first month was dedicated to assessment training, during which participants were familiarized with the platform and baseline performance was recorded. This phase ensured that subsequent progression and task adaptation were tailored to each individual's capacities (Tab. 5).

After this initial phase, participants rotated through three distinct training programs, each delivered once per month and repeated cyclically across the year. These training modules targeted different combinations of motor and cognitive domains, such as cognitive inhibition, attention, cognitive flexibility, goal directed behaviour and memory, therefore ensuring variety, engagement, progressive challenge, and multi-domain stimulation throughout the intervention (Tab. 6).

Sessions could be performed individually or in pairs, allowing participants to train alone or together with another participant (often a spouse or a friend). Training in couples was encouraged where possible, as it provided additional motivation and promoted social engagement, but participants were also able to complete sessions independently.

All sessions were supervised to ensure safety, adherence to the protocol, appropriate progression of difficulty, and comprehension of the exercises. The Dividat Senso system automatically adjusts task complexity based on individual performance, ensuring a personalized, motivating and progressively challenging training throughout the year. No serious adverse events related to the training were reported, and the intervention was well tolerated by the study population.

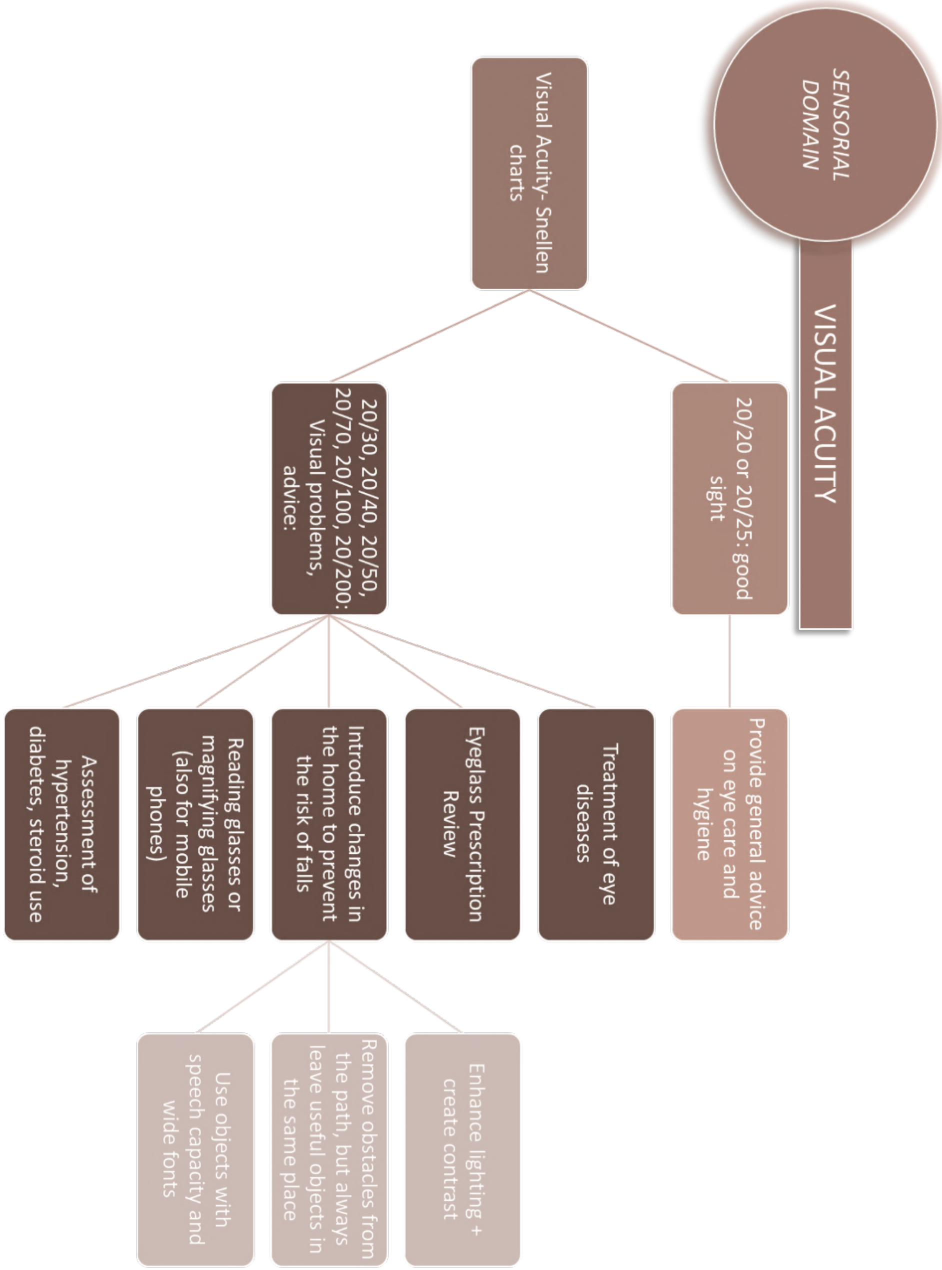


FIGURE 23. *Visual acuity assessment and recommendations within the sensorial domain. This diagram outlines the use of Snellen charts to determine visual acuity, distinguishing between normal vision (20/20 or 20/25) and visual impairments (20/30 to 20/200). It also presents advice and interventions, including eye care, eyeglass prescription review, treatment of eye diseases, home modifications to prevent falls, and the use of assistive tools like magnifying glasses, wide fonts, and speech-capable devices.*

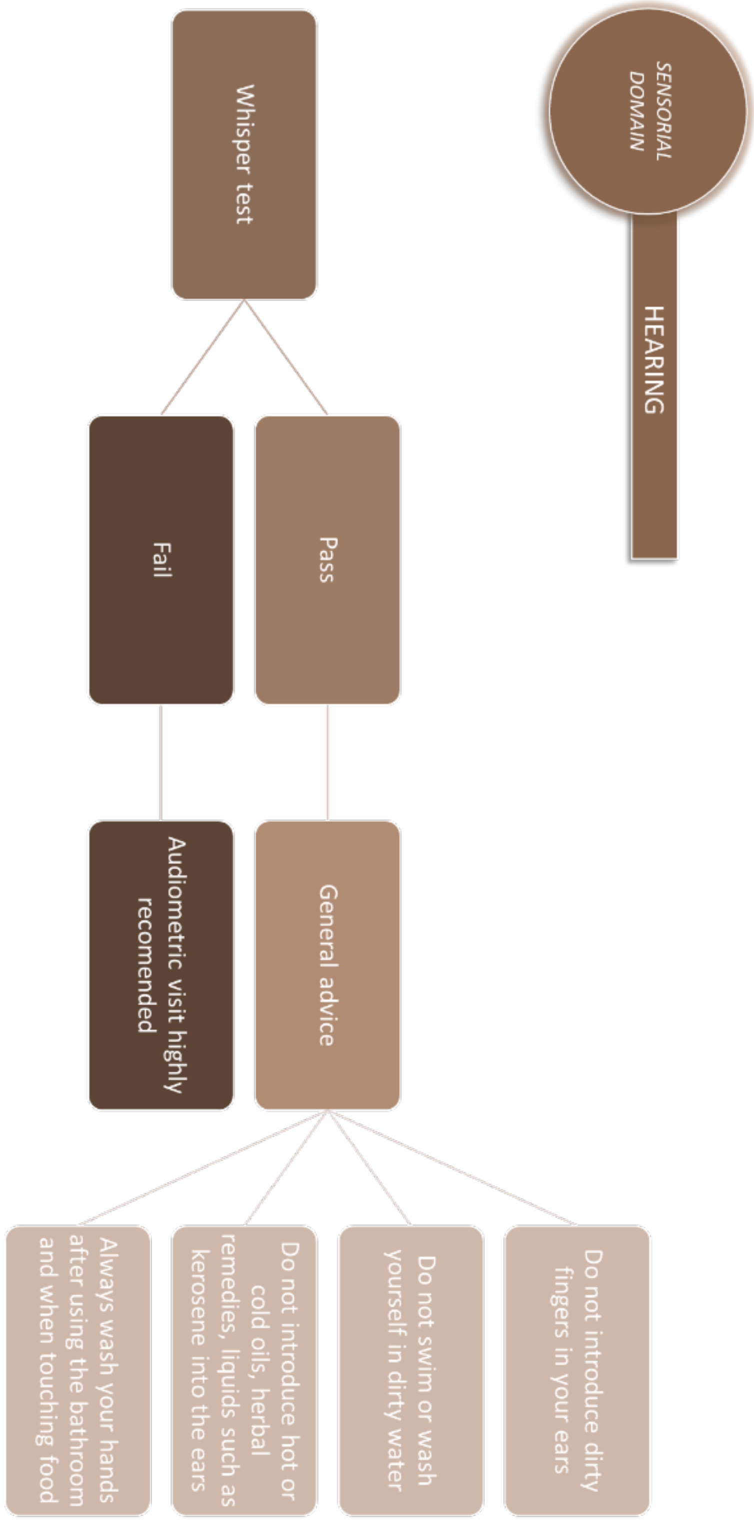


FIGURE 24. *Hearing assessment and recommendations within the sensorial domain. This diagram presents the whisper test as a screening tool for hearing. Outcomes (pass or fail) guide subsequent actions: general advice for ear hygiene and safety, or a recommended audiometric evaluation in case of failure. Preventive recommendations include avoiding dirty fingers or contaminated water in ears, refraining from harmful remedies (e.g., oils or kerosene), and maintaining proper hand hygiene.*

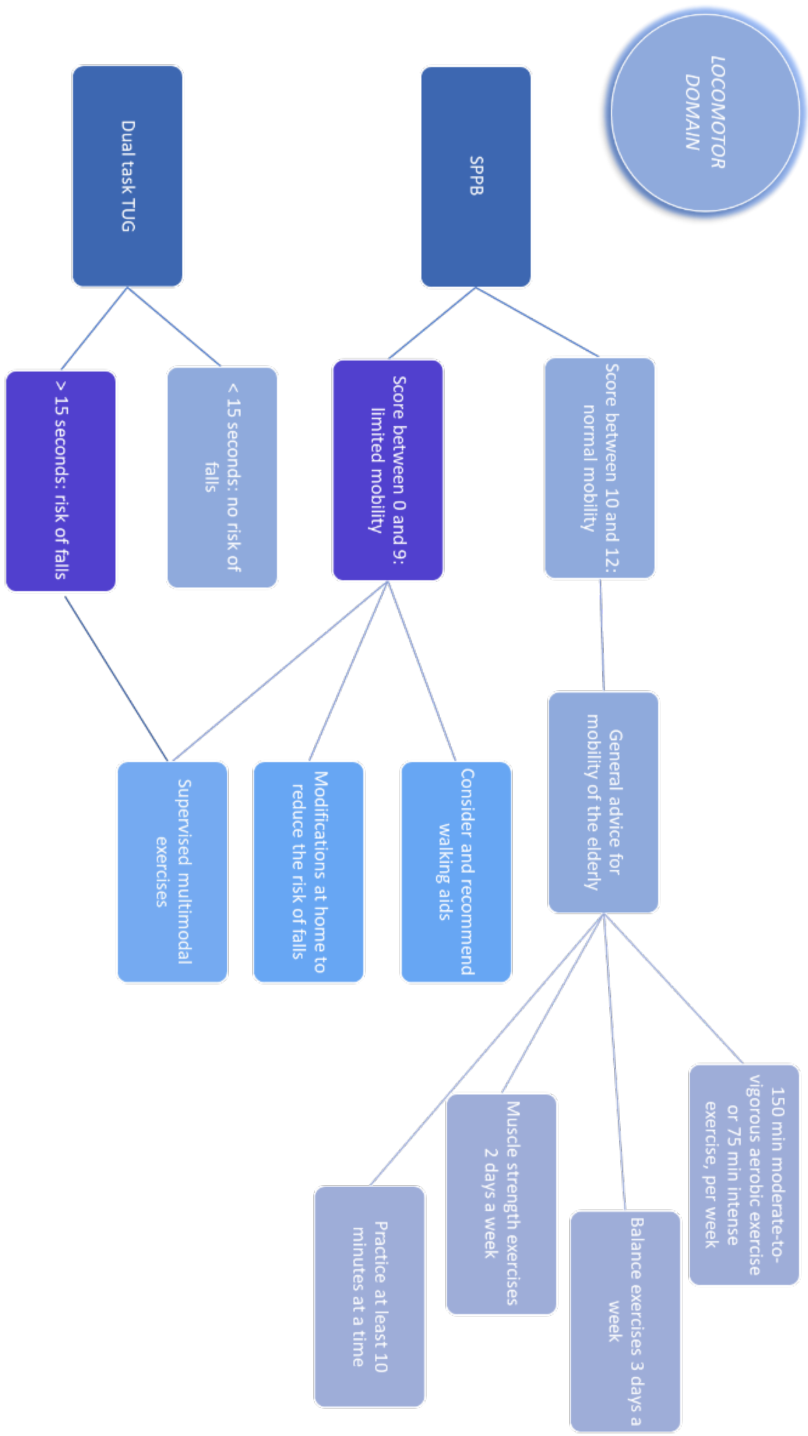


FIGURE 25. *Locomotor domain assessment and recommendations. This diagram presents the SPPB and the TUG tests as a screening tool for locomotion abilities. Outcomes guide subsequent actions: general advice for mobility, or recommended walking aids or supervised multimodal exercises. Preventive recommendations include multimodal exercises enhancing balance, strength and general mobility.*

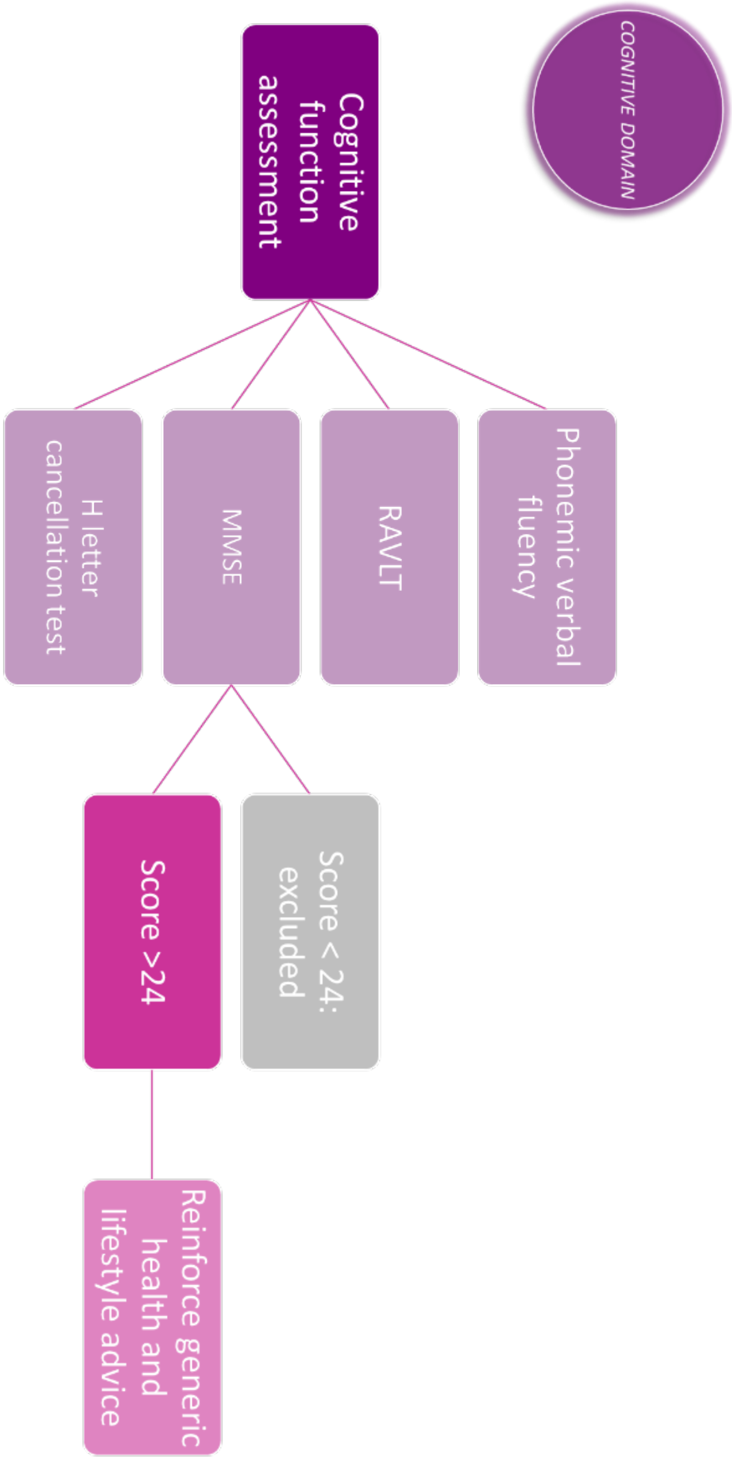


FIGURE 26. *Cognitive domain assessment and recommendations. This diagram presents the MMSE as a screening tool for cognitive abilities. Phonemic verbal fluency (PVF), Rey auditory verbal learning test (RAVLT) and H cancellation test are included as performed during the Praise assessment. Corrected MMSE outcomes guide subsequent actions: in this case the study did not include subject with a score <24, and according to the ICOPE guidelines the booklet pointed at reinforcing generic health and lifestyle recommendations.*

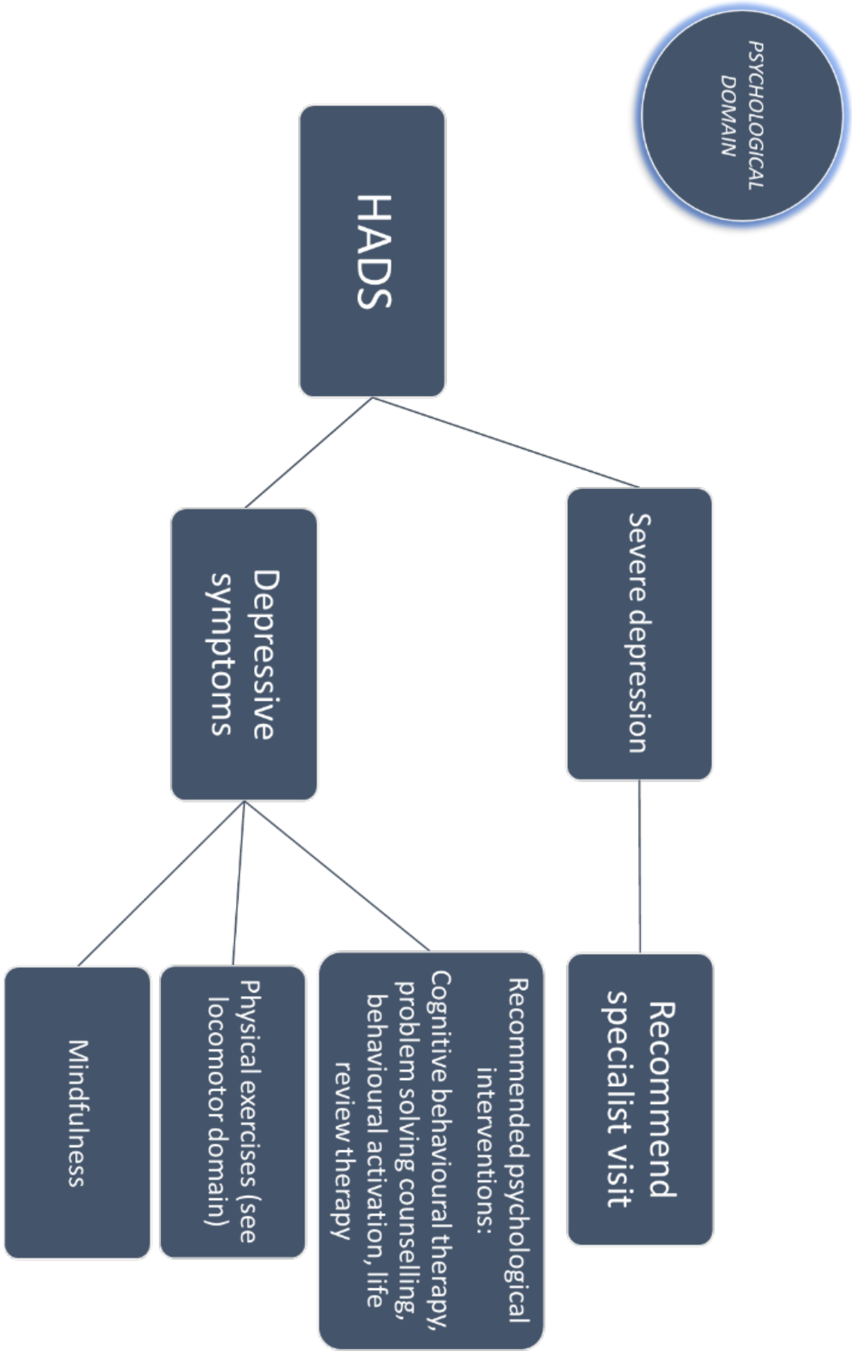


FIGURE 27. *Psychological domain assessment and recommendations. This diagram presents the HADS as a screening tool for psychological well-being. Outcomes guide subsequent actions: a specialist visit in case of depression, or recommended psychological interventions, physical exercises and mindfulness in case of depressive symptoms.*

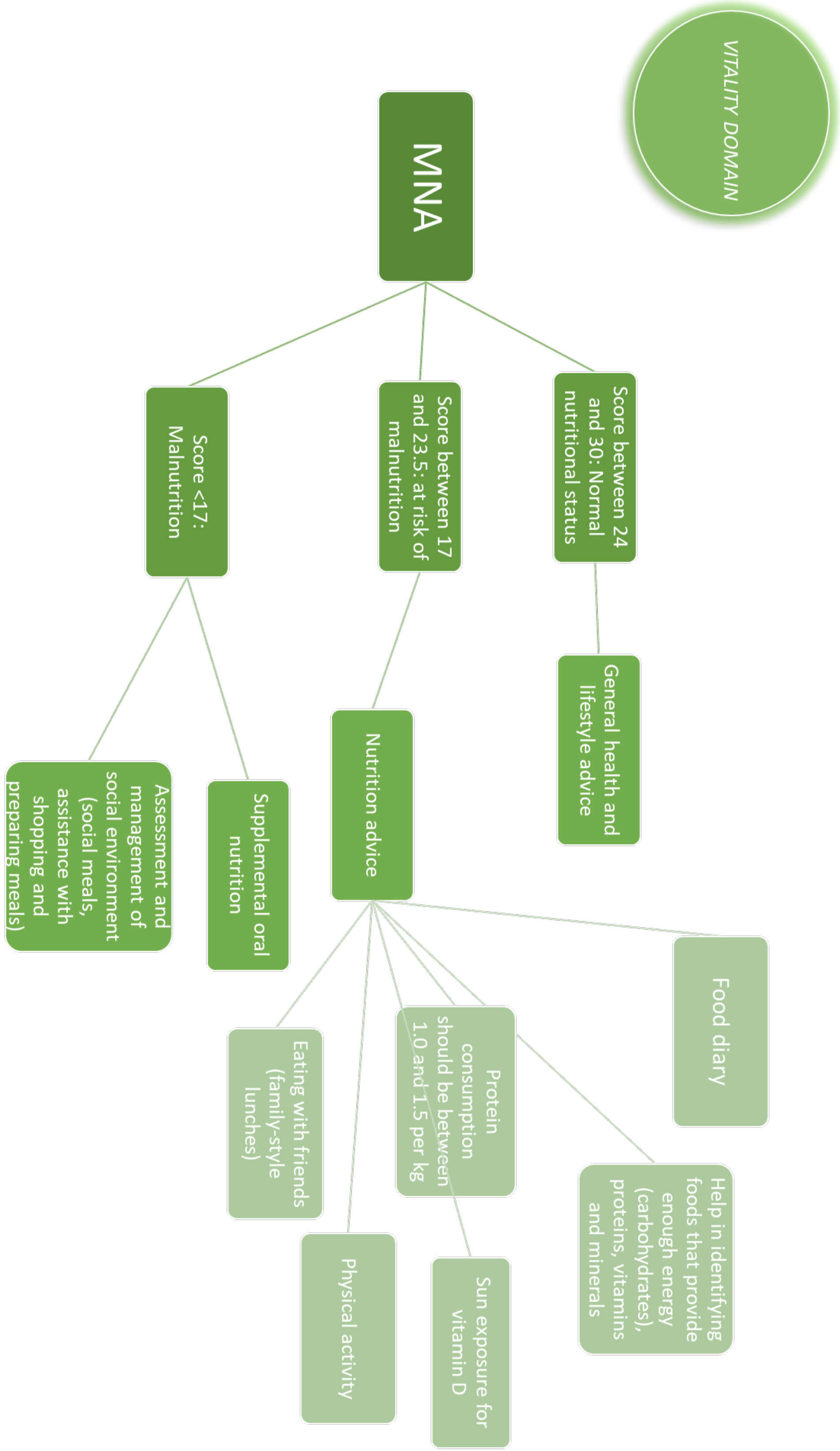


FIGURE 28. *Vitality domain assessment and recommendations. This diagram presents the Mini Nutritional Assessment (MNA) as a screening tool for the vitality domain. Outcomes guide subsequent actions: general*

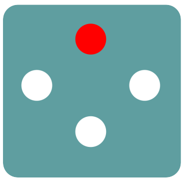
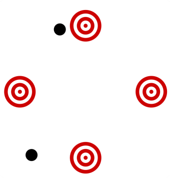
health and lifestyle advice, or nutritional advice in case of risk of malnutrition, and supplemental oral nutrition and management of the social environment in case of assessed state of malnutrition. Nutritional advice include writing a food diary, provide information on protein intake and nutritional needs, physical exercise, exposure to the sun and social eating habits.

Adherence to the intervention was carefully monitored throughout the 12-month training period. Attendance was recorded automatically by the Dividat Senso platform and verified by the supervising staff at each session. Training fidelity was considered satisfactory if participants completed at least 70% of the scheduled sessions across the intervention year.

Overall, adherence to the training protocol was high. All but one participant (excluded from final analysis) in the intervention group achieved the ≥70% attendance threshold, with most participants attending sessions consistently throughout the year. The final sample at T1 comprehended therefore 35 subjects.

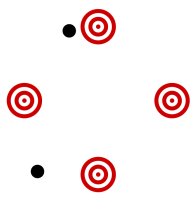
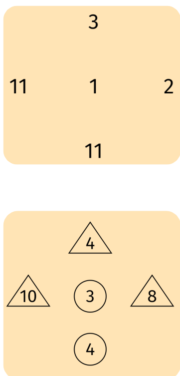
This high adherence rate suggests that the training protocol was feasible, acceptable, engaging and safe for pre-frail older adults.

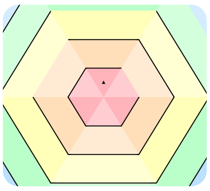
TABLE 5. *Instructions and main cognitive functions targeted by assessment exergames played on the Dividat Senso during the first month of training (PRAISE 1).*

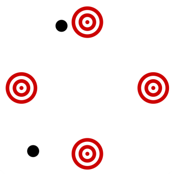
	Game	Instructions	Main cognitive function(s)
	Simple 	Four white dots are depicted on the screen. As soon as one dot turns red, the participant has to step in the right direction as quickly as possible.	Focused attention Psychomotor speed
PRAISE 1	**Targets** 	Four targets are depicted on the screen. Black dots "fly" randomly across the screen. The participant is asked to strike the balls exactly as they cross the centre.	Action planning Anticipatory reaction Goal-directed stepping
	Ladybug 	The participant is asked to stand still in the centre with the feet wider than hip-width apart and to steer the ladybug by leaning to his/her left and right. The goal is to collect the flowers and avoid the obstacles. Some flowers sparkle in the dew. The participant is asked to focus on them to achieve a bonus. 0% Difficulty level	Anticipatory reaction Inhibition Selective Attention Static balance Weight shift

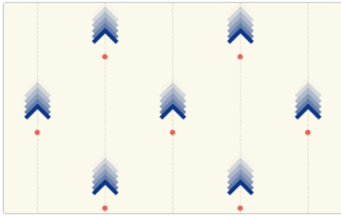
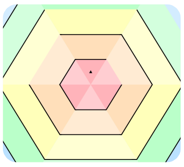
	Flaneur 	The participant is asked to take steps to explore the scenery.	Endurance Focus

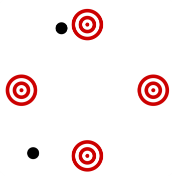
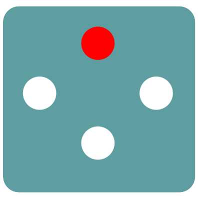
TABLE 6. *Instructions and main cognitive functions targeted by exergames played on the Dividat Senso during throughout the year of training. The training was divided in three programs, repeated cyclically: PRAISE 2, PRAISE 3 and PRAISE 4.*

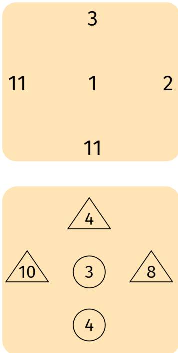
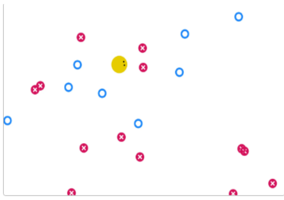
	Game	**Instructions**	**Main cognitive function(s)**
PRAISE 2	**Targets** 	Four targets are depicted on the screen. Black dots "fly" randomly across the screen. The participant is asked to strike the balls exactly as they cross the centre.	Action planning Anticipatory reaction Goal-directed stepping
	Flexi 	Flexi consists of two parts. In the middle of the screen a number appears and in **part A** it is required to execute a step in the direction of the next higher number as quickly as possible. In **part B** a figure around the number appears, and the task is to alternate between numbers in circles and numbers in triangles.	Task switching
	Drops 	Pairs of coloured drops fall down from the top of the screen. When a drop lands near a drop of the same colour, they connect into a group. The participant is asked to create four or more drops to make them burst and score points. Steps to the left or right move the pair sideways. Steps forwards rotate the pair. Steps	Action planning Strategic planning Mental rotation Visuo-spatial orientation

		backwards and hold to let it fall faster. You make more points when you clear multiple groups by landing a single pair of drops.	
	Habitats 	Animals are moving across four landscapes on the screen. The participant is asked to find the animals that have escaped from their natural habitat and make a step in their direction.	Selective attention Inhibition
	Hexagon 	The participant is asked to step to the left or right to rotate the hexagons and let the arrow pass through open edges.	Visual-spatial orientation Mental rotation
	Ladybug 	The participant is asked to stand still in the centre with the feet wider than hip-width apart and to steer the ladybug by leaning to his/her left and right. The goal is to collect the flowers and avoid the obstacles. Some flowers sparkle in the dew. The participant is asked to focus on them to achieve a bonus. 21% or 50% (after the first cycle of training) difficulty level	Anticipatory reaction Inhibition Selective Attention Static balance Weight shift

	Game	Instructions	Main cognitive function(s)
PRAISE 3	**Targets** 	Four targets are depicted on the screen. Black dots "fly" randomly across the screen. The participant is asked to strike the balls exactly as they cross the centre.	Action planning Anticipatory reaction Goal-directed stepping
	Simon 	A series of tones with a corresponding light is played, starting with one tone and continuously adding one. The task is to repeat the sequence of tones with steps.	Short-term memory

	Arrows 	Arrows move across the screen, sometimes leaving trails. When the moving arrows leave a trail, the participant is asked to step in the direction in which they move to. When there is no trail, the participant is asked to step in the direction the arrows point to.	Focus Inhibition Task switching
	Hexagon 	The participant is asked to step to the left or right to rotate the hexagons and let the arrow pass through open edges.	Visual-spatial orientation Mental rotation
	Ladybug 	The participant is asked to stand still in the centre with the feet wider than hip-width apart and to steer the ladybug by leaning to his/her left and right. The goal is to collect the flowers and avoid the obstacles. Some flowers sparkle in the dew. The participant is asked to focus on them to achieve a bonus. 50% Difficulty level	Anticipatory reaction Inhibition Selective Attention Static balance Weight shift

	Game	Instructions	Main cognitive function(s)
PRAISE 4	**Targets** 	Four targets are depicted on the screen. Black dots "fly" randomly across the screen. The participant is asked to strike the balls exactly as they cross the centre.	Action planning Anticipatory reaction Goal-directed stepping
	Divided 	There are four white circles on the screen. One of the circles changes its colour to red. The task is to react as quickly as possible with the execution of a step in the direction of the red circle. At random times one of two acoustic stimuli is played- either a higher or a deeper sound. With the higher tone the participant is asked to step forward, and with the deeper sound a step backward.	Divided attention

	Lumina 	The participant is asked to steer a firefly through a calming landscape standing in the centre with feet hip-width apart and shifting his/her balance to control the direction of flight. The subject can either collect the glowing lights or simply enjoy the journey.	Mindfulness Static balance Weight shift
	Flexi 	Flexi consists of two parts. In the middle of the screen a number appears and in **part A** it is required to execute a step in the direction of the next higher number as quickly as possible. In **part B** a figure around the number appears, and the task is to alternate between numbers in circles and numbers in triangles.	Task switching
	Evolve 	Stand in the centre with feet hip-width apart and shift your balance to catch hoops and avoid balls.	Anticipatory reaction Inhibition Selective Attention Static balance Weight shift
	Ladybug 	The participant is asked to stand still in the centre with the feet wider than hip-width apart and to steer the ladybug by leaning to his/her left and right. The goal is to collect the flowers and avoid the obstacles. Some flowers sparkle in the dew. The participant is asked to focus on them to achieve a bonus. 50% Difficulty level	Anticipatory reaction Inhibition Selective Attention Static balance Weight shift

2.1.5 STATISTICAL ANALYSIS

All statistical analyses were implemented using RStudio 2024.12.1+563 "Kousa Dogwood" and IBM SPSS Statistic version 29.

2.1.5.1 Construction of Intrinsic Capacity (IC) composites

Two Global Intrinsic Capacity (IC) composites were constructed, to highlight the possible role of a dual-task assessment in a healthy ageing framework (Fig 29).

- **IC**: a classic IC global composite score that followed the five WHO domains (locomotion, cognition, vitality, sensory, psychological);

- **DT IC**: a dual-task IC global composite score that included an additional dual-task domain to capture cognitive–motor integration.

The following measures were used to form the domain scores:

- **Sensory domain**
  - Visual acuity (Snellen chart)
  - Hearing loss (whisper test)
- **Psychological / Social domain**
  - HADS (total score, anxiety and depression subscales)
  - Social Support Scale (SSS)
  - MHC-SF
- **Vitality domain**
  - Mini Nutritional Assessment (MNA)
  - Grip strength
  - Peak expiratory flow (PEF)
- **Cognitive domain**
  - MMSE
  - Phonemic verbal fluency (PVF)
  - RAVLT I
  - RAVLT D
- **Locomotor domain**
  - Short Physical Performance Battery (SPPB)
  - Sway path length (PL)
  - PPB (actigraphy)
- **Dual-task (DT) domain**
  - Dual-task cost (DTC) Stroop - inhibition and cognitive flexibility
  - DTC Switching task
  - DTC TUG (normal and fast pace)

All component variables were inspected for distributional issues. Some component measures (i.e. reaction times (RTs), dual-task costs (DTCs), HADS outcomes, Sway indices, SSS) express with larger values poorer performance. To make all component z-scores align directionally (so that higher z = better capacity), the polarity of these variables was reversed after standardization. Concretely, at first the z-scores were computed by using mean and standard deviation of our sample and then multiplied the resulting z-score by −1 when necessary. The reversed z-scores were then used in the domain averages and in the computation of the IC and Dual-Task IC global composites.

Each component variable was standardized to a z-score using the baseline sample mean and standard deviation. The domain z-score was then computed as the arithmetic mean of its constituent variable z-scores, and global IC and DT IC were computed as the arithmetic mean of their constituent domain z-scores.

At T1, to ensure comparability in longitudinal analyses, IC composites at baseline were recalculated by using only the subset of participants who also completed the T1 assessment. In fact, while the initial baseline sample at T0 comprised 71 participants, only 36 subjects underwent reassessment at T1 (the remaining to be evaluated in October to December 2025). For this reason, baseline IC scores were recomputed on the reduced sample (n = 36), applying the same z-score standardization procedure. This approach allowed direct within-subject comparisons across timepoints.

FIGURE 29. *Overview of the variables included in each domain of Intrinsic Capacity (IC). The sensory domain comprised visual acuity (Snellen chart) and hearing loss (whisper test). The psychological/social domain included HADS, the Social Support Scale (SSS), and the Mental Health Continuum—Short Form (MHC-SF). The vitality domain comprised the Mini Nutritional Assessment (MNA), grip strength, and peak expiratory flow (PEF). The cognitive domain included MMSE, phonemic verbal fluency (PVF), Rey auditory verbal learning test immediate (RAVLT i), and DELAYED (RAVLT D) recall. The locomotor domain comprised the Short Physical Performance Battery (SPPB), sway path length (PL) acquired o Dividat Senso, and Pseudo periodic behaviour (PPB). An additional exploratory dual-task domain was constructed from dual-task cost (DTC) measures: Stroop (inhibition and flexibility), switching task on Dividat Senso, and Timed Up and Go (TUG) performed at normal and fast pace.*

2.1.5.2 Analysis of the Assessments at T0 and T1

Descriptive statistics were computed to summarize demographic characteristics, HRV parameters and cognitive outcomes of the sample. To ensure both inclusiveness and robustness, the baseline (T0) analyses were performed using two complementary datasets, which differed in the treatment of HRV measures and potential confounding factors, and consequently in the number of included subjects:

- PRAISE T0: all available data are reported in this dataset. HRV indices were considered for all subjects independently of medicine intake but excluding ECG signal not analysed for technical reasons (e.g. artifacts, breathing inconsistencies, arrhythmias). The total sample of PRAISE T0 consists in N=60 subjects.
- PRAISE HRV T0: thirty subjects were excluded from the statistical analyses in this dataset, yielding a finale clean sample of 30 subjects.

Analysis at T1, given the smaller sample size, where conducted on the entire sample (N=36), irrespectively to medications. After controlling for artifacts and heart rate arrhythmias, HRV data at T1 were available for 26 subjects. Six participants were excluded from ECG analysis due to the presence of extrasystoles (n = 4) or artefactual signal contamination (n = 3). Additionally, four participants withdrew from the study prior to ECG acquisition at T1 because of vacation or illness, and rescheduling was not possible. Of the 26 subjects remaining, 14 were not receiving pharmacological treatment. Eleven participants were receiving the same pharmacological treatment at both T0 and T1, and one participant initiated β-blocker therapy between T0 and T1.

In all three datasets variables were inspected and missing values were omitted from analyses as follows: for computation of pairwise correlations, we used pairwise-complete observations; for clustering and network construction any variable with unsupported missingness for a given analysis was excluded.

To assess the influence of age, all numeric variables (excluded cognitive variables already corrected for age i.e. RAVLT, Fluency, MMSE) were regressed on chronological age using simple linear models; the residuals from these models, representing variance unexplained by age, were used as age-adjusted values for correlation, clustering, and network analyses.

Pairwise Spearman's rank correlation was performed in order to explore the relationship between all variables and results from raw and age-adjusted data are reported. Multiple testing was controlled via the Benjamini–Hochberg false discovery rate (FDR).

A distance matrix was derived as

$$d_{ij}=1-|r_{ij}|$$

where d_{ij} is the distance matrix and $|r_{ij}|$ are the absolute correlation values between variable *i and variable j,* so that high (negative and positive) correlations imply small distance and small correlations mean large distance. Hierarchical agglomerative clustering was performed with Ward's D2 linkage. two complementary data-driven methods were used to choose the number of clusters: the elbow method (within-cluster sum of squares vs. k) and the average silhouette width (k = 2–10).

A dendrogram and a heatmap of the Euclidean distance matrix were generated to visualize the clustering hierarchy of subjects. This dual refiguration enabled both quantitative and visual assessment of cluster compactness and subject similarity.

Correlations were also represented as a network graph. Each variable was represented as a node, and edges were drawn between nodes when the absolute correlation exceeded a predefined threshold. Edge weights encoded the strength of the correlation while node colours denote community membership derived from network community detection (see below), and node size is proportional to node strength. Interactive visualizations were created with visNetwork package in R, providing an interactive interface for exploration; in this case edge color encoded the sign of the correlation (soft green = positive; dark blue = negative).

Analysis was conducted using the packages stats, cluster, igraph, qgraph, visNetwork, ggraph, RColorBrewer, and pheatmap of Rstudio. Exported HTML interactive plots are available in the project repository: The Adaptive Potential of a Multi-Domain System (https://lucia-pp.github.io/PRAISE/).

Standard network descriptors (nodes, edges, connected components, modularity, density) were computed from the network graphs. Community detection was performed using the Louvain algorithm on absolute weights and node-level statistics included the following measures:

- **Degree**: the number of direct connections (edges) a node has to other nodes;
- **Strength**: the sum of the absolute weights of edges connected to a node;
- **Betweenness centrality**: the proportion of shortest paths between all pairs of nodes in the network that pass through a given node;
- **Closeness**: the inverse of the average distance (shortest path length) from one node to all other nodes;
- **Eigenvector centrality**: measure of a node's importance based not only on the number of its connections but also on the centrality of the nodes it connects to.

For PRAISE HRV a secondary cluster analysis was computed at the subject level to identify subject's dissimilarities within a specific cluster of variables comprising HRV indices (ΔHF%, ΔHFnu, ΔLFnu, ΔLF/HF, LFnu stand, HFnu stand), cognitive performance (RAVLT I, RAVLT D, PVF, %DTC TUG in normal and fast pace, DTC Switch) and general physical fitness outcomes (SWAYC MaxDev, 6MWT). Subject level clusters were selected based on the average silhouette width.

Comparisons between the subject level clusters for the variables included in the primary cluster were conducted using non-parametric Wilcoxon rank-sum tests, with Benjamini–Hochberg (BH) correction applied to control for false discovery rate (FDR).

HRV indices in normalized units, absolute powers and ΔHRV measures were then further investigated and visually represented to determine differences between subject level clusters through Wilcoxon rank-sum tests with FDR correction.

2.1.5.3 Intervention effects

To evaluate group differences in longitudinal change across our set of clinical, cognitive, psychological, physical performance, and physiological measures, we employed linear mixed-effects models.

For each outcome variable, a model was fitted with fixed effects of group (S for intervention, C for control), time point, and their interaction, as well as a random intercept for participant ID to account for repeated measures. The interaction term represented the differential change between groups over time. Models were estimated using the *lmerTest* package in R.

Missing data were addressed in two ways. In the primary analysis, models were estimated using complete cases only (NA omission → “omit”). In a sensitivity analysis, missing values were imputed using median substitution within groups prior to analysis (→ “median”). Group sizes for each analysis were reported as the number of unique participants with valid data. Descriptive statistics (mean and standard deviation) were calculated separately for each group and time point to provide context for the model-based estimates.

To complement the group x time interaction tests, we also computed within-group contrasts estimating change from baseline to follow-up separately for each group. These contrasts were obtained from the fitted mixed-effects models using the *emmeans* Rstudio package. Within-group contrasts yield an estimate of the mean change over time for the control (C) and intervention/study (S) groups independently, together with standard error, degrees of freedom, t statistic, and associated p value. We performed these within-group analyses under the same two missing-data strategies described above (listwise deletion = “omit” and group-specific median substitution = “median”) to assess robustness and across raw and age-adjusted data.

CHAPTER 3

PRAISE: RESULTS

3.1 RESULTS AT T0

This section will report results related to the association between variables and the data at T0, i.e. before any intervention. This section reports the analysis of possible associations between variables of different domains selected, resulting in the picture of the population at baseline. This analysis is needed in that, as stated in Chapter 2, no studies are available at present considering Frailty, Intrinsic Capacity, neurovegetative flexibility, dual task and Exergame.

It will be divided in two main subsections, exploring different datasets (see Methods section):

- PRAISE T0: all available data are presented in this dataset. HRV indices are considered for all subjects independently of medicine intake but excluding ECG signal not analysed for technical reasons (e.g. artifacts, breathing inconsistencies, arrhythmias). The total sample of PRAISE T0 consists in N=60 subjects.
- PRAISE HRV T0: thirty subjects undergoing beta blockers, SSRI, Ace-inhibitors, or Benzodiazepine intake (medicines influencing HRV), or with irregular breathing were excluded from the statistical analyses in this dataset, yielding a finale clean sample of 30 subjects.

3.1.1 PRAISE T0

All reported results are presented for both the raw and age-adjusted datasets.

The comprehensive analysis of the possible correlations between all the variables considered in this study was performed with Spearman correlations that revealed several associated variables. After FDR correction ($q < 0.05$), 193 correlations remained significant in the raw data-set, and 173 in the age-adjusted one (Appendix C, Table C2). To explore the relationships among all the variables considered in PRAISE, we employed both hierarchical clustering and network analysis. *Hierarchical clustering* groups variables based on their overall similarity, producing a dendrogram that reveals clusters of closely related variables. In contrast, *network analysis* helps in visualizing partial correlations among variables, highlighting direct associations and their centrality within the network structure. While clustering emphasizes similarity-based grouping, network analysis uncovers complex interdependencies and the role of each variable within the system. Together, these methods provide complementary insights into the latent structure and interconnectedness of the variables.

3.1.1.1 Hierarchical clustering

Ward D2 dendrograms (distance = 1 − |ρ|) suggested a eight-cluster solution by the elbow method and a ten-cluster solution according to the silhouette criteria for the raw data (Fig 30). Considering both metrics, k = 8 was selected as the optimal number of clusters: this choice provides well-separated and cohesive clusters while also aligning with the structural balance identified by the elbow method.

The age-adjusted data provided similar results. The silhouette criteria suggested 10 clusters, while the elbow method reduced the number of clusters to k=7, avoiding unnecessary over-fragmentation and complexity (Fig. 31).

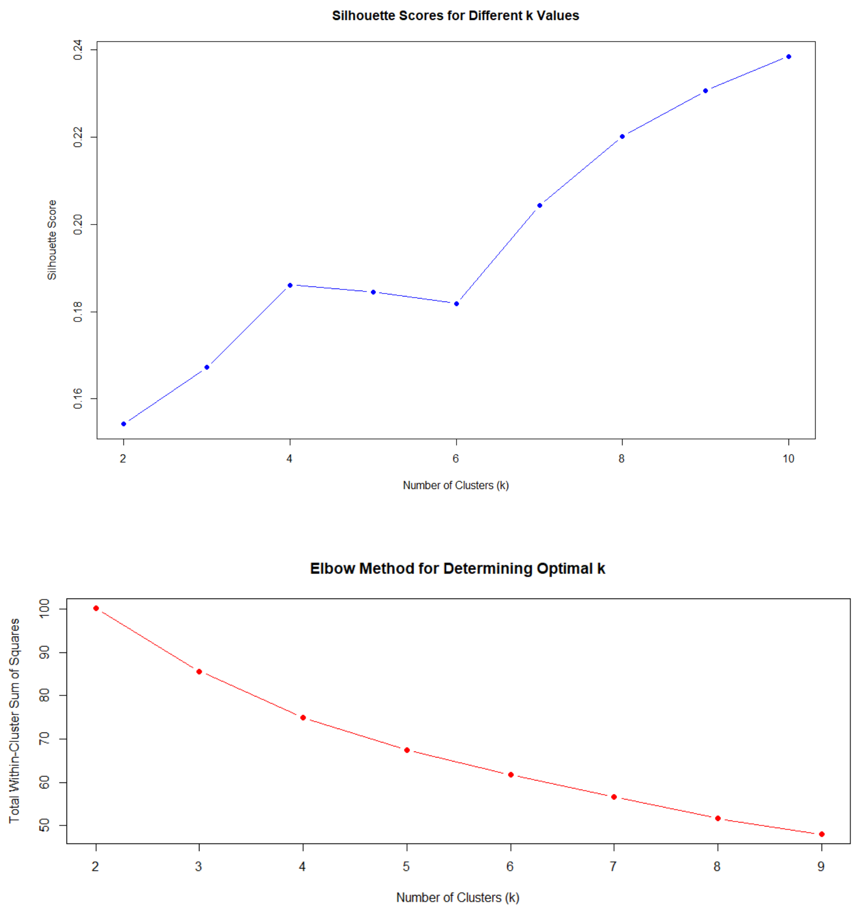


FIGURE 30. *Comparison of cluster validity metrics for the dataset PRAISE T0, raw data. While the silhouette analysis (above) shows increasing cohesion with higher values of k, the elbow method (below) suggested a solution for k=8, with a silhouette score of 0.26.*

The clusters are visualized in the dendrogram and in the correlation heatmaps for the raw data and the age adjusted data in Figure 32 and 33 respectively.

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The eight clusters for the raw data included: (1) a cognitive, dual-task, sleepiness (*ESS*) cluster; (2) normalized (nu) HRV measures in standing and ΔHRV indices; (3) absolute HRV indices; (4) nu HRV in supine (*rest*) and ΔHRV% of LFa (*Delat_LFa*); (5) a general health and functional cluster including Frailty and IC; (6) psychological domain; (7) physical fitness, cognition, and sensory capacities: (8) actigraphy-derived indices of mobility.

For the age-adjusted data, seven clusters emerged; the overall structure was qualitatively similar to the raw data clustering, with the main difference being that global IC and dual-task IC (IC_DT) clustered together with cognitive and dual-task outcomes. The detailed differences in cluster construction are illustrated in Fig. 34 (raw data) and Fig. 35 (age-adjusted data).

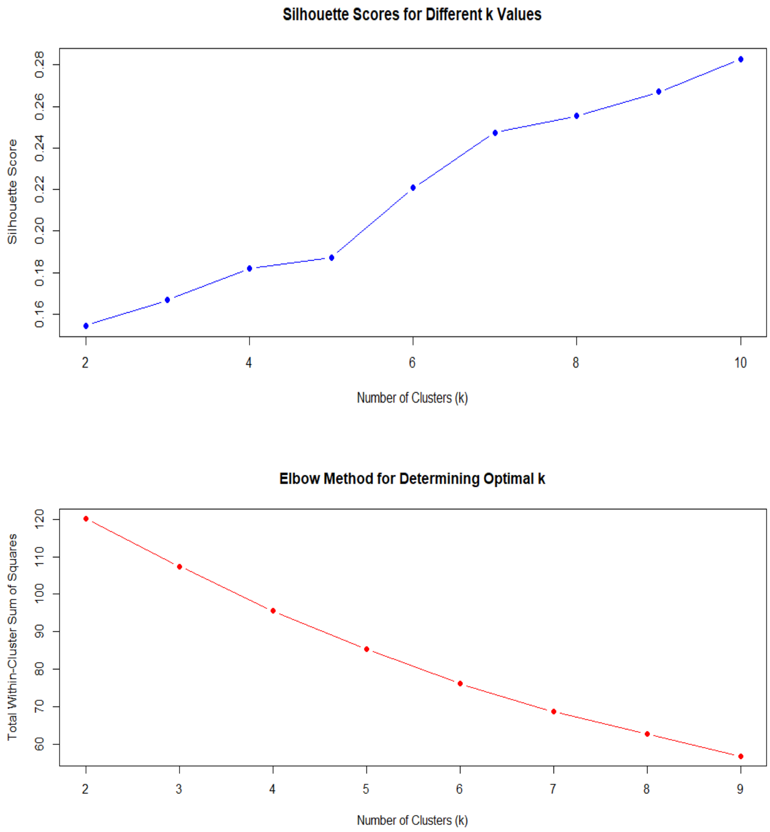


FIGURE 31.*Comparison of cluster validity metrics for the dataset PRAISE T0, age-adjusted data. While the silhouette analysis (above) shows increasing cohesion with higher values of k, the elbow method (below) suggested a solution for k=7, with a silhouette score of 0.20.*

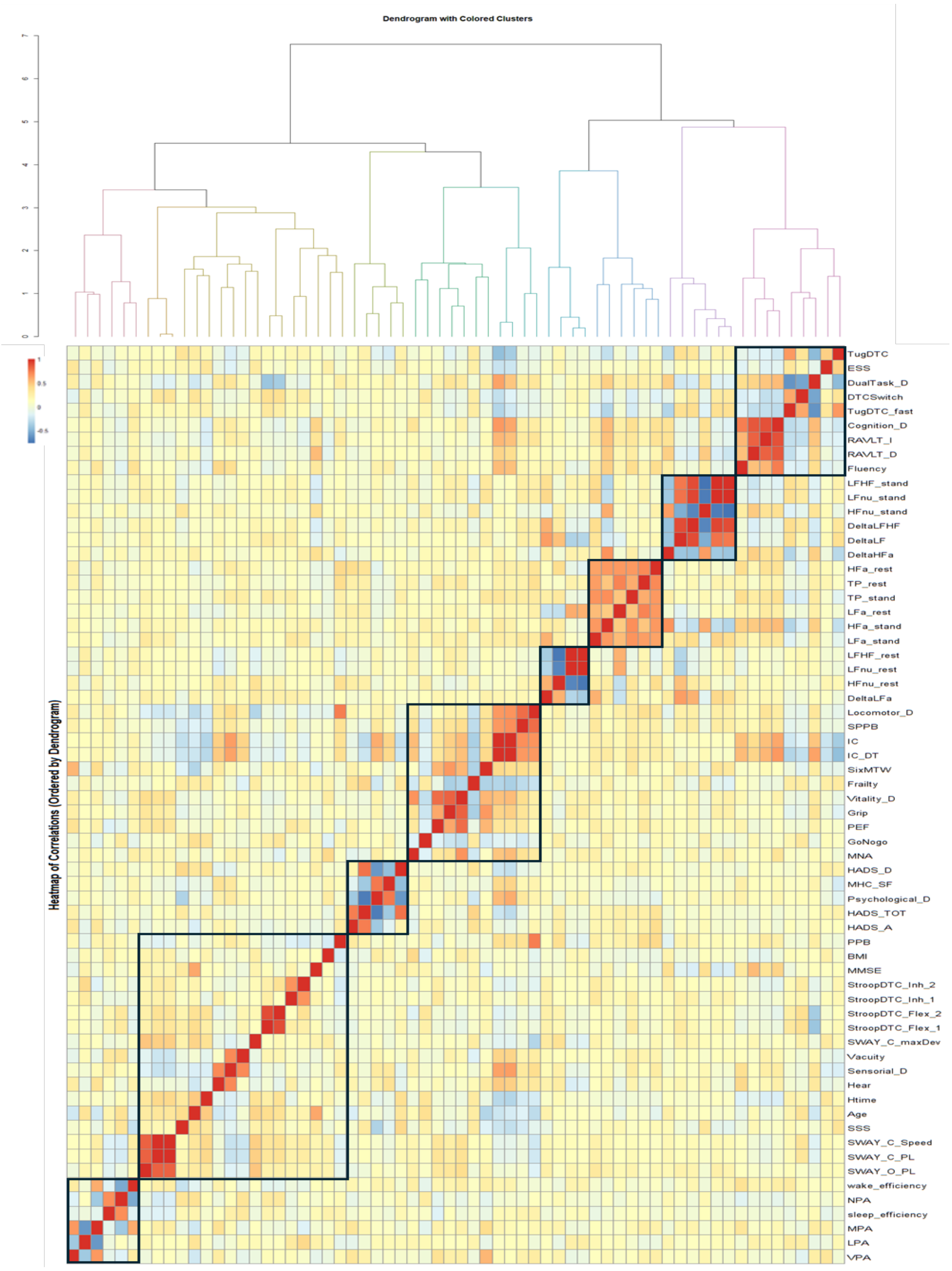


FIGURE 32. *Dendrogram with clusters (top) and corresponding heatmap of pairwise correlations (bottom) for the* ***raw*** *dataset of PRAISE T0. The heatmap highlights the correlation structure among variables, with blocks outlined to indicate clusters derived from hierarchical clustering. Warmer colours represent stronger positive correlations, while cooler colours indicate negative associations.*

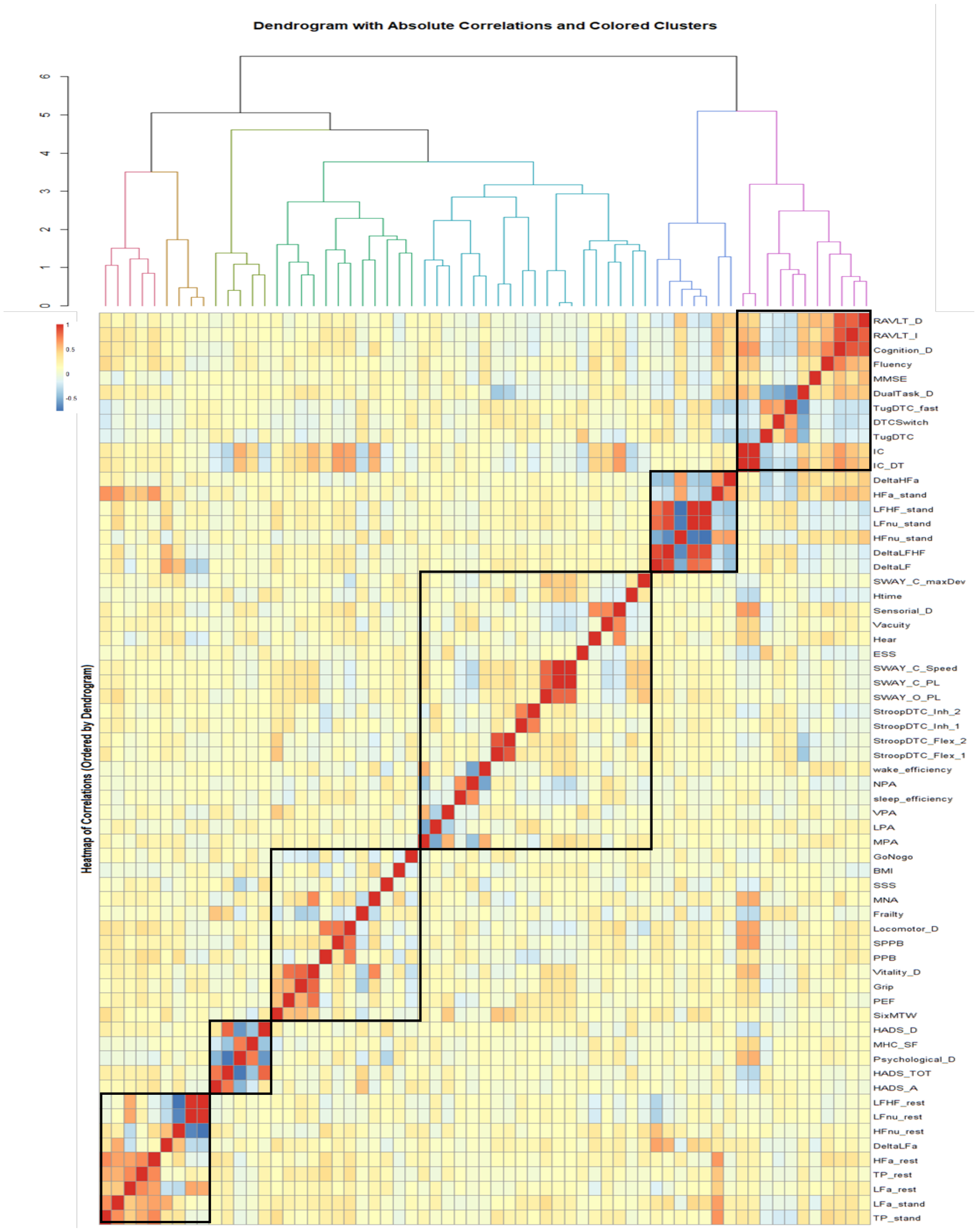


FIGURE 33. *Dendrogram with clusters (top) and corresponding heatmap of pairwise correlations (bottom) for the* ***age-adjusted*** *dataset of PRAISE T0. The heatmap highlights the correlation structure among variables, with blocks outlined to indicate clusters derived from hierarchical clustering. Warmer colours represent stronger positive correlations, while cooler colours indicate negative associations*

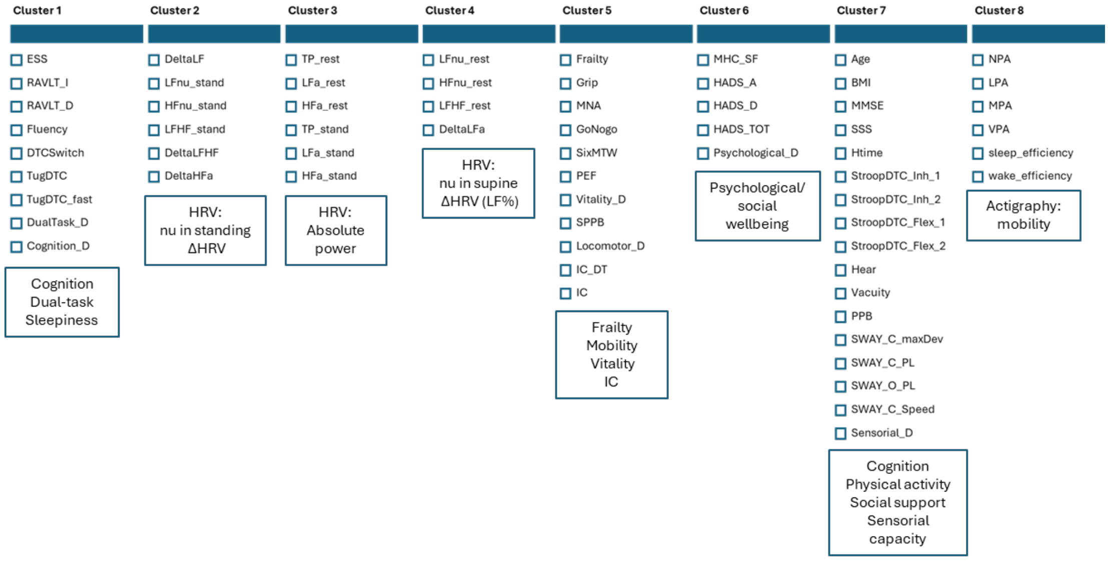


FIGURE 34. *Clusters derived from hierarchical Ward.D2 clustering of raw data. The variables are grouped into eight distinct clusters, consistent with the dendrogram and correlation heatmap.*

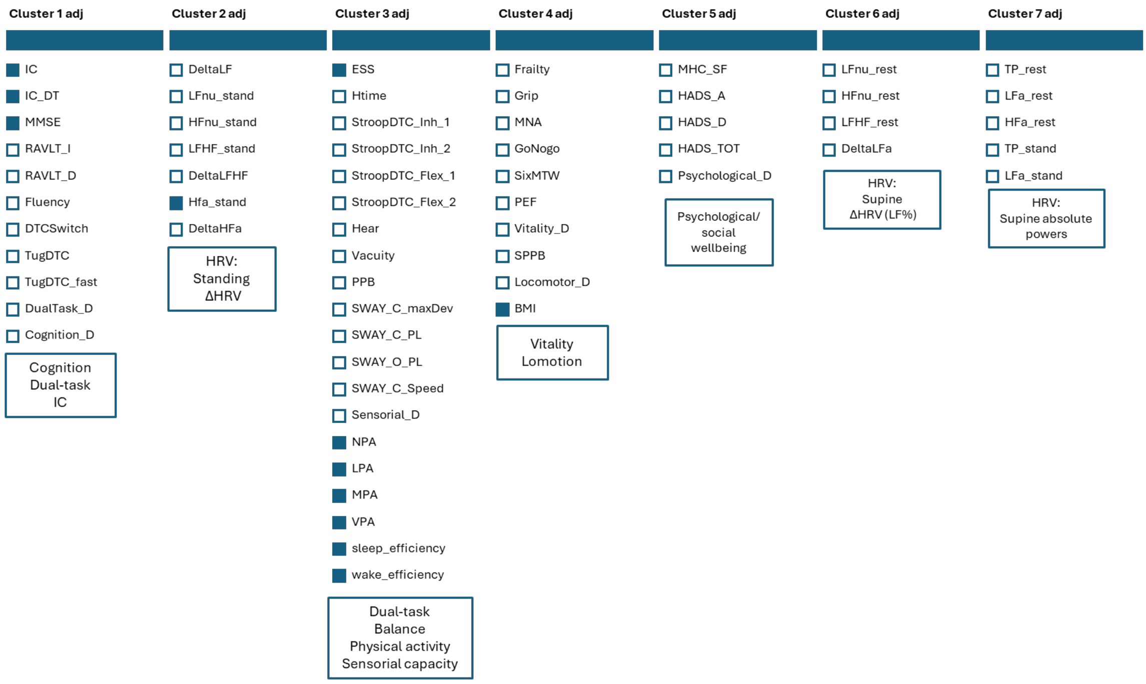


FIGURE 35. *Clusters derived from hierarchical Ward.D2 clustering of age-adjusted data. The variables are grouped into seven distinct clusters, consistent with the dendrogram and correlation heatmap. Variables highlighted with blue squares indicate those that changed cluster membership compared with the raw data clustering, illustrating the main differences introduced by age adjustment.*

3.1.1.2 Network communities and modularity

The correlation network was constructed using absolute pairwise Pearson correlations and a threshold of $|r| \geq 0.40$ applied to age-adjusted data (the network produced from raw data at the same threshold and an age-adjusted network at |r| ≥ 0.35 are available in the thesis appendix D - Fig. D1, Fig. D2). Nodes represent individual variables and edges connect node pairs with absolute correlation above the threshold; edge thickness encodes absolute correlation weight. Community detection was performed with the Louvain algorithm on absolute weights. Node size is proportional to node strength (sum of incident absolute weights); standard node-level centrality measures (degree, strength, betweenness using distances = 1/weight, closeness, harmonic centrality, and eigenvector centrality) were computed for all nodes. Interactive network plots (visNetwork) with edge colour encoding the sign of the relation (soft green = positive, dark blue = negative) are available at https://lucia-pp.github.io/PRAISE/ .

The network contains 63 nodes and 159 edges (sum of degrees = 318). The mean node degree is 5.05 and network density is 0.081 (2E / [N(N−1)] = 318 / (63×62)). The Louvain algorithm identified 8 communities with the following sizes:

- Community 1: 7 nodes
- Community 2: 1 node (BMI)
- Community 3: 12 nodes
- Community 4: 15 nodes
- Community 5: 2 nodes
- Community 6: 10 nodes
- Community 7: 10 nodes
- Community 8: 6 nodes

As visible in figure 36, only one variable (BMI) was isolated at this threshold (degree = 0) while the remaining 62 variables form the connected main component. Several variables were markedly more central than others according to degree, strength and betweenness, identifying them as hubs or potential integrators in this multivariate system (Table 7). The most relevant central nodes are:

- IC_DT (dual-task Intrinsic Capacity global composite): degree = 17, strength = 8.8826, eigenvector = 0.7513 (Community 4).
- HFa_stand (high frequency absolute power while standing): degree = 16, strength = 7.8488, eigenvector = 1.0000 (Community 7).
- IC (Intrinsic Capacity global composite): degree = 15, strength = 7.9567, eigenvector = 0.6043 (Community 4).
- Cognition_D (cognition domain composite): degree = 10, strength = 5.8467, eigenvector = 0.7319 (Community 3).
- RAVLT_D (RAVLT delayed recall): degree = 10, strength = 5.1435, eigenvector = 0.7232 (Community 3).

Other nodes with high overall strength included DeltaLF (ΔLF nu) (strength = 5.6973, eigenvector = 0.8455, Community 8), DeltaHFa (ΔHF%) (strength = 4.908

eigenvector = 0.875, Community 8), and TugDTC_fast (strength = 4.2105, Community 3). By contrast, several nodes had low degree and strength (for example, BMI: degree = 0, strength = 0; GoNogo, ESS, PPB, Hear, and several single-edge nodes), indicating limited pairwise correlations above the applied threshold.

To identify groups of closely related variables within the networks, the Louvain community detection algorithm was applied. This method partitions the network into communities by maximizing modularity, a measure of the density of connections within clusters compared to between them. The resulting communities reflect latent structures or functional groupings among the variables. The Louvain communities correspond to coherent domain clusters that are interpretable in clinical and physiological terms:

- **Community 1** (n = 7): Contains Frailty and related physical function measures (Frailty, Grip, MNA, PEF, SixMTW, Vitality_D, GoNogo) and represents a Frailty/functional domain that connects to IC and other domains but is less central than IC/HRV/cognition clusters.
- **Community 2** (n = 1): BMI is isolated at the chosen threshold (no absolute correlation > 0.40 with other variables after age adjustment).
- **Community 3** (n = 12): Cognitive and dual-task performance cluster (Cognition_D, RAVLT_I, RAVLT_D, Fluency, DTCSwitch, TugDTC, TugDTC_fast, Stroop_Flex_1 etc.). This community is cohesive; several cognitive measures (especially RAVLT_D) show high centrality within it.
- **Community 4** (n = 15): Includes IC and IC_DT together with locomotor variables (SPPB, PBB), sensorial impairments (Hear, visual acuity-Vacuity) and psychological measures (HADS, SSS, MHC_SF). IC and IC_DT are the highest degree/strength nodes in this community and also have the highest betweenness values in the whole network, indicating that the Intrinsic Capacity constructs are central connectors between psychological/clinical variables and other domains. Because IC and IC_DT are composite indices derived from multiple domain measures, their central role is expected and should be interpreted in light of their construction (they aggregate information and therefore tend to correlate with many domain-specific variables).
- **Community 6** (n = 10): Physical activity and postural sway metrics (NPA/LPA/MPA/VPA, SWAY measures) cluster together, representing an activity-balance domain that is relatively cohesive and partially peripheral to the cognition/IC/HRV hubs.
- **Community 5** (n = 2): Stroop dual-task inhibition measures (StroopDTC_Inh_1 and StroopDTC_Inh_2) form a small dyadic community with limited external connections.

- **Communities 7 and 8** (n = 10 and n = 6 respectively): Heart rate variability (HRV) metrics. Resting HRV variables (LFa_rest, HFa_rest, LFnu_rest, HFnu_rest, LFHF_rest, TP_rest) and standing HRV variables (LFa_stand, HFa_stand, LFnu_stand, HFnu_stand, LFHF_stand, TP_stand), with ΔHRV metrics, form two adjacent but distinguishable clusters. Community 8 indices in particular have very high eigenvector centrality, indicating they are embedded in a dense subnetwork of highly connected variables and likely influence or reflect a broad set of physiological and functional relations in this sample.

Similar results to the network and hierarchical analysis were obtained from the raw data and are visible in Appendix C (Tab. C3).

MAIN FINDINGS AT PRAISE T0.

- FRAILTY: it clusters and negatively correlates with variables related to the *locomotor* and the *vitality* domains of Intrinsic Capacities. It is connected to the psychological based community through a positive correlation with *anxiety* reported symptoms (HADS A): greater Frailty ↔ higher levels of anxiety.
- INTRINSIC CAPACITY: both composite measures, IC_DT and IC, are central to the network as expected and mainly cluster with cognitive and dual-task measures.
- Other variables central to the network and acting like bridges between communities are HFa_stand (high frequency absolute power while standing, reflecting parasympathetic activation) and RAVLT_D (verbal memory delayed recall).

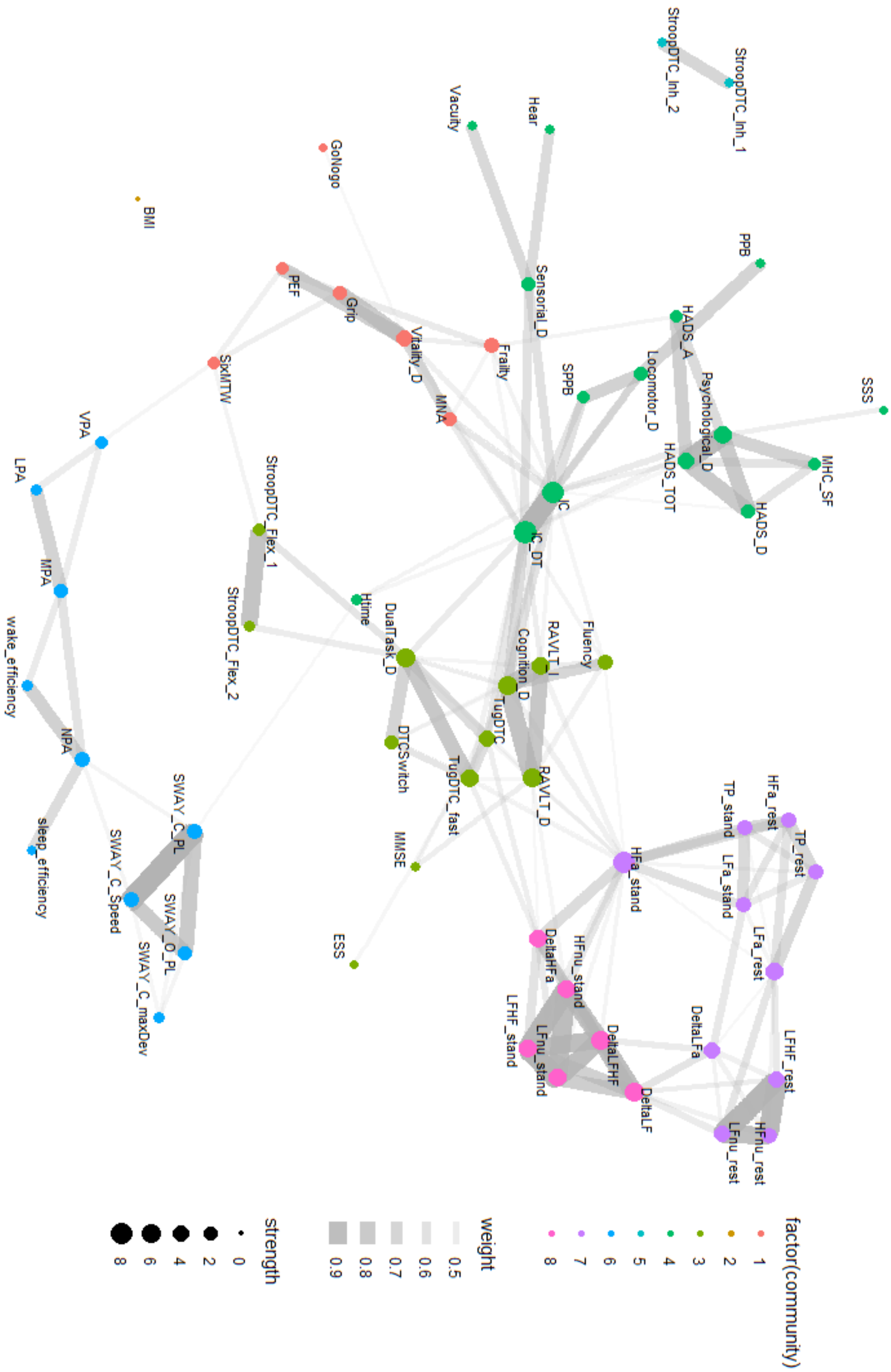


FIGURE 36. *Correlation network of* ***age-adjusted*** *variables at threshold* **|r| ≥ *0.40*** (PRAISE T0). *Each node represents a variable, with node size proportional to node strength (sum of absolute edge weights). Node colour indicates community membership as identified by the Louvain algorithm. Edges represent pairwise absolute correlations exceeding the threshold, with thickness proportional to the correlation strength. The network comprises 63 nodes and 159 edges, organized into 8 communities.*

TABLE 7. *Node-level centrality metrics for all variables in the thresholded age-adjusted correlation network (|r| ≥ 0.40). Degree = number of edges; Strength = sum of absolute edge weights; Betweenness = proportion of shortest paths passing through the node (using distance = 1/weight); Closeness = inverse of average path length to all other nodes; Eigenvector = importance based on connections to other central nodes; Community = Louvain cluster assignment.*

Variable	Degree	Strength	Betweenness	Closeness	Eigenvector	Community
Frailty	6	2.736	0.005	0.164	0.180	1
Grip	4	2.300	0.034	0.149	0.060	1
MNA	4	2.129	0.000	0.169	0.196	1
GoNogo (RT)	1	0.407	0.000	0.120	0.017	1
SixMWT	4	1.811	0.080	0.139	0.017	1
PEF	3	1.736	0.000	0.147	0.041	1
Vitality_D	7	4.035	0.103	0.170	0.200	1
BMI	0	0.000	0.000	NA	0.000	2
MMSE	2	0.928	0.000	0.146	0.145	3
ESS	1	0.413	0.000	0.136	0.043	3
RAVLT_I	8	4.390	0.000	0.193	0.612	3
RAVLT_D	**10**	**5.143**	**0.045**	**0.194**	**0.723**	3
Fluency	6	2.905	0.000	0.180	0.456	3
DTCSwitch	4	2.096	0.000	0.163	0.265	3
StroopDTC_Flex_1	3	1.847	0.059	0.159	0.075	3
StroopDTC_Flex_2	2	1.345	0.000	0.150	0.068	3
TugDTC	7	3.599	0.133	0.202	0.480	3
TugDTC_fast	**8**	**4.210**	**0.064**	**0.199**	**0.573**	3
DualTask_D	9	5.085	0.117	0.197	0.505	3
Cognition_D	10	5.847	0.134	0.207	0.732	3
SSS	1	0.480	0.000	0.123	0.024	4
MHC_SF	3	1.889	0.000	0.135	0.082	4
SPPB	3	1.903	0.000	0.167	0.201	4
Htime	3	1.268	0.177	0.168	0.126	4
HADS_A	3	1.835	0.002	0.138	0.086	4
HADS_D	4	2.583	0.000	0.149	0.141	4
HADS_TOT	6	3.942	0.014	0.159	0.224	4
Hear	1	0.653	0.000	0.135	0.025	4
Vacuity	1	0.670	0.000	0.135	0.026	4
PPB	1	0.708	0.000	0.134	0.030	4
Sensorial_D	4	2.509	0.061	0.169	0.180	4
Psychological_D	7	4.557	0.072	0.165	0.237	4
Locomotor_D	4	2.547	0.031	0.165	0.198	4
IC_DT	**17**	**8.883**	**0.332**	**0.224**	**0.751**	4
IC	**15**	**7.957**	**0.205**	**0.219**	**0.604**	4
StroopDTC_Inh_1	1	0.694	0.000	0.694	0.000	5

StroopDTC_Inh_2	1	0.694	0.000	0.694	0.000	5
NPA	5	2.829	0.072	0.108	0.002	6
LPA	2	1.221	0.000	0.097	0.000	6
MPA	4	2.325	0.021	0.101	0.000	6
VPA	3	1.433	0.056	0.114	0.002	6
sleep_efficiency	1	0.644	0.000	0.093	0.000	6
wake_efficiency	2	1.261	0.000	0.097	0.000	6
SWAY_C_PL	5	3.042	0.157	0.132	0.013	6
SWAY_O_PL	3	2.031	0.000	0.114	0.003	6
SWAY_O_maxDev	3	1.257	0.000	0.101	0.002	6
SWAY_O_Speed	4	2.648	0.007	0.119	0.003	6
TP_rest	5	2.844	0.000	0.134	0.247	7
LFa_rest	9	4.440	0.012	0.134	0.327	7
HFa_rest	5	3.125	0.000	0.146	0.286	7
LFnu_rest	5	3.366	0.001	0.118	0.268	7
HFnu_rest	5	3.191	0.000	0.115	0.253	7
LFHF_rest	5	3.397	0.000	0.117	0.267	7
TP_stand	5	2.891	0.000	0.145	0.275	7
LFa_stand	6	3.316	0.019	0.145	0.299	7
HFa_stand	**16**	**7.849**	**0.159**	**0.180**	**1.000**	7
DeltaLFa	7	3.380	0.003	0.122	0.344	7
DeltaLF	**9**	**5.697**	**0.080**	**0.143**	**0.845**	8
LFnu_stand	6	4.506	0.000	0.141	0.888	8
HFnu_stand	7	5.013	0.025	0.157	0.959	8
LFHF_stand	6	4.655	0.000	0.144	0.914	8
DeltaLFHF	7	5.109	0.002	0.145	0.933	8
DeltaHFa	**9**	**4.908**	**0.136**	**0.174**	**0.875**	8

3.1.2 PRAISE HRV T0

Participants taking beta blockers, SSRIs, ACE inhibitors, or benzodiazepines (i.e., medications known to influence HRV), as well as those presenting irregular breathing or cardiac rhythms, were excluded from the statistical analyses, yielding a final sample of 30 participants. In this dataset, the analyses focused mainly on HRV indices; IC domain variables were excluded from the analyses, as they are derived from single measures that were already included in the models. Including both would have introduced redundancy and collinearity, especially given the limited sample size. Same analysis adopted for the PRAISE T0 was applied here and Table C4 in Appendix C reports the results of the Spearman correlation among age-adjusted variables.

3.1.2.1 Hierarchical clustering

After correcting for age, a Spearman correlation matrix was computed among 57 age-adjusted behavioural, cognitive, motor, physiological, and functional variables (Fig.37). Hierarchical clustering grouped variables based on absolute pairwise correlation.

Both the elbow method and silhouette analysis were applied to guide cluster selection. While the silhouette scores peaked at k = 10 with a maximum average silhouette width of 0.226, the elbow method highlighted an inflection point at k = 5, which was selected to maintain interpretability and complexity in the clustering structure (Fig. 38).

The first cluster comprised psychological and social wellbeing outcomes (HADS, SSS, MHC-SF), general health and fitness level (PEF, SPPB, Visual acuity, actigraphic registration-VPA-, BMI).

The second cluster included a large set of variables encompassing physical fitness (actigraphic variables -MPA, LPA, NPA, wake and sleep efficiency-, balance outcomes from the Dividat Senso Sway assessment) and cognitive functions (MMSE, dual cost of the Stroop inhibition test on the Dividat Senso exergame platform).

The third cluster showed a connection between dual task capabilities (cognitive cost of dual task TUG, Switching task on Dividat Senso), cognitive performances (RAVLT immediate and delayed recall, phonemic verbal fluency), some measures of physical fitness (6MWT, SWAYC MaxDev) and the adaptive physiological response of the autonomic system to an excitatory challenge (ΔHRV indices and normalized HRV parameters during standing).

The fourth cluster was dominated by absolute HRV parameters, i.e. total power, LFa and HFa components, both in supine and in active standing conditions.

The fifth and last cluster comprised normalized HRV metrics, particularly LFnu, HFnu, and LF/HF in resting supine condition, the percentage gain in low frequencies in response to the orthostatic challenge (ΔLF%), general fitness and physical state measures (MNA, Frailty, grip strength, hearing loss).

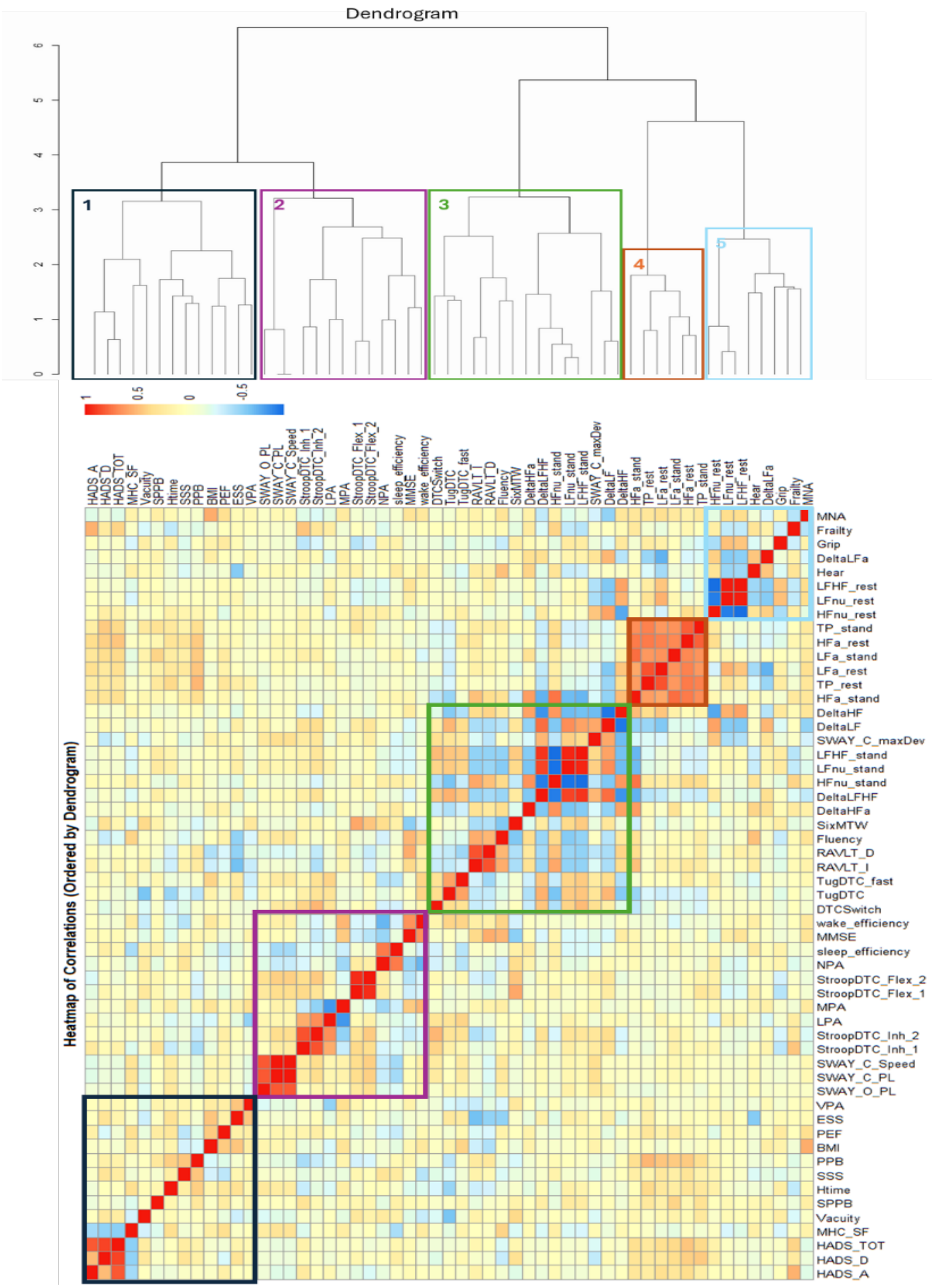


FIGURE 37. *Dendrogram with color-coded clusters (top) and corresponding heatmap of pairwise correlations (bottom) for the* ***age-adjusted*** *dataset of PRAISE HRV T0. The heatmap highlights the correlation structure among variables, with blocks outlined to indicate clusters derived from hierarchical clustering. Warmer colours represent stronger positive correlations, while cooler colours indicate negative associations.*

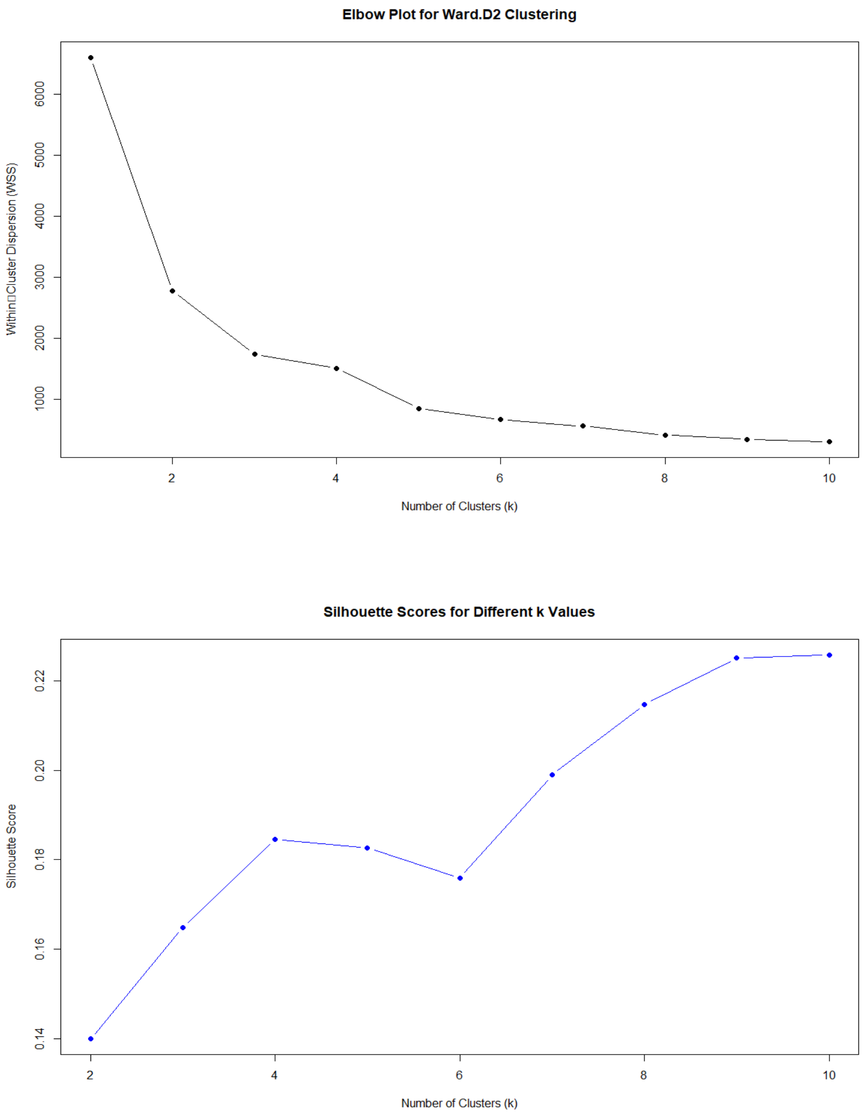


FIGURE 38. *Comparison of cluster validity metrics for the dataset PRAISE HRV T0, age-adjusted data. While the silhouette analysis (below) shows increasing cohesion with higher values of k, the elbow method (above) suggested a solution for k=5, corresponding to a silhouette score of 0.18.*

3.1.2.2 SUBJECT LEVEL CLUSTERING

To further explore the third cluster, due to its hybrid composition of HRV and cognitive features, a secondary cluster analysis was conducted at the subject level; participants were clustered based on the performances and indices of the variables included in the cluster, leading to the identification of two subgroups within our sample (maximum average silhouette width of 0.432 at k=2). Comparisons between groups were conducted using non-parametric Wilcoxon rank-sum tests and Benjamini–Hochberg (BH) correction for false discovery rate

(FDR); variables with corrected p-values < 0.05 were considered statistically significant (Table 8).

- **Heart Rate Variability parameters**

  Significant differences in HRV indices were observed between the two clusters.

  Cluster 1 exhibited significantly lower LFnu activity compared to Cluster 2 (W = 2, FDR-adjusted p < 0.001, d = –3.21), along with a significantly higher HFnu activation (W = 220, FDR-adjusted p <0.001, d = 3.25) while standing, suggesting a rise in parasympathetic outflow or a diminished sympathetic tone following the request to standing up. Similarly, the active standing LF/HF ratio was also significantly lower in Cluster 1 (W = 1, FDR-adjusted p < 0.001, d = –1.85), consistent with a lower sympathetic activation.

  Cluster 2 was characterized by a significantly greater ΔLF/HF (W = 1, FDR-adjusted p < 0.001, d = –1.98) and ΔLF (W = 29, FDR-adjusted p < 0.001, d = –1.43), indicating an enhanced sympathetic response to the orthostatic challenge. Complementarily, Cluster 2 exhibited a more negative ΔHF% (W = 199, FDR-adjusted p < 0.001, d = 1.10) and ΔHFnu (W = 192, FDR-adjusted p = 0.003, d = 1.48), consistent with a steeper parasympathetic withdrawal.

TABLE 8. *Comparison of HRV indices and cognitive-behavioural variables between the two clusters. The variables reported belong to the third cluster found in previous analysis. Mean values for each cluster are reported along with the Wilcoxon rank-sum test statistic (W), corresponding p-values, and False Discovery Rate (FDR) adjusted p-values.*

Variable	*Mean Cluster 1*	*Mean Cluster 2*	*W statistic*	*W p-value*	*FDR adjusted p*
LFnu stand	41.482	74.267	2	<0.001	**<0.001**
HFnu stand	43.911	18.760	220	<0.001	**<0.001**
LF/HF stand	1.008	4.971	1	<0.001	**<0.001**
ΔLF/HF	0.226	3.835	1	<0.001	**<0.001**
ΔHFnu	-11.865	-35.218	192	0.001	**0.002**
ΔLFnu	7.257	35.317	29	0.001	**0.002**
ΔHF%	-0.110	-70.264	199	<0.001	**0.001**
RAVLT I	57.653	51.221	160	0.017	**0.027**
PVF	45.933	36.571	160	0.017	**0.027**
RAVLT D	12.991	11.236	152	0.044	0.057
%DTC TUG normal pace	-3.360	12.849	27	0.013	**0.026**

DTC Switch	0.319	0.493	65	0.140	0.151
SWAYC MaxDev	15.630	17.393	79	0.266	0.286
%DTC TUG fast pace	5.279	26.725	33	0.033	**0.046**
6MWT	484.300	508.350	35	0.335	0.335

- **Neuropsychological Performance**

  Cluster 1 outperformed Cluster 2 on the RAVLT immediate recall task (W = 160, FDR-adjusted p = 0.027, d = 0.924) and on the phonemic verbal fluency test (W = 160, FDR-adjusted p = 0.027, d = 0.926). Furthermore, although no statistically significant difference was found for the RAVLT delayed recall (W = 152, FDR-adjusted p = 0.057, d = 0.786), a trend toward significance was observed.

- **Dual Task and Locomotor Performance**

  Significant group differences emerged also in regard to dual-task capabilities. Cluster 1 showed a reduced cognitive cost during the DTC TUG in both normal pace (W = 27, FDR-adjusted p = 0.026, d = –0.957) and fast pace (W = 33, FDR-adjusted p = 0.046, d = –0.734). However, no significant difference between groups was detected for the switching task performed on the Dividat Senso platform (W = 65, FDR-adjusted p = 0.151).

  No statistically significant difference between clusters was observed for the 6MWT (W = 35, FDR-adjusted p = 0.335), nor the SWAYC maximum deviation (W = 79, p = 0.286), indicating similar locomotor abilities between subjects.

Overall, Cluster 1 showed a significantly better cognitive and dual task performance, lower sympathetic (identified with Low Frequencies) activation (as indicated by lower LFnu in standing, ΔLFnu and ΔLF/HF) and reduced parasympathetic withdrawal (smaller ΔHF%, ΔHFnu). In contrast, Cluster 2 was characterized by poorer cognitive and dual task performance, a greater gain in normalized low frequencies (ΔLFnu, ΔLF/HF) upon standing and a greater parasympathetic withdrawal (ΔHF%, ΔHFnu).

In summary the difference between the two clusters reveals that cognitive performances (assessed in a separate session with respect to the ECG recording) seem actually related to the neurovegetative flexibility as measured with the adaptive sympathovagal balance changes due to the transition from supine to upright position. Based on this result a deeper analysis has been applied to the HRV different variables in the two clusters.

3.1.2.3 HRV INDICES

Heart rate variability (HRV) indices were further examined to characterize the autonomic dynamic response differentiating the two clusters. *Table 3* shows mean, standard deviation and median of the HRV indices for each cluster. Among the absolute power indices, HFa during active standing was the only parameter to significantly differ between groups. Regarding normalized units, HFnu and LFnu while standing were both found to significantly differ between clusters.

Interestingly, among the ΔHRV parameters, all but ΔLF% (FDR-adjusted $p = 0.69$) showed significant between-group differences, indicating that the proportional and relative gain in LF from supine to standing did not contribute meaningfully to group differentiation.

Fig.39 reports the mean percentual difference in each frequency band activation calculated as ΔHRV%: while ΔLF% does not vary significantly between clusters, ΔHF% (i.e. parasympathetic withdrawal) was significantly lower in cluster 1, i.e. more positive (W = 199, *FDR-adjusted p* < 0.001).

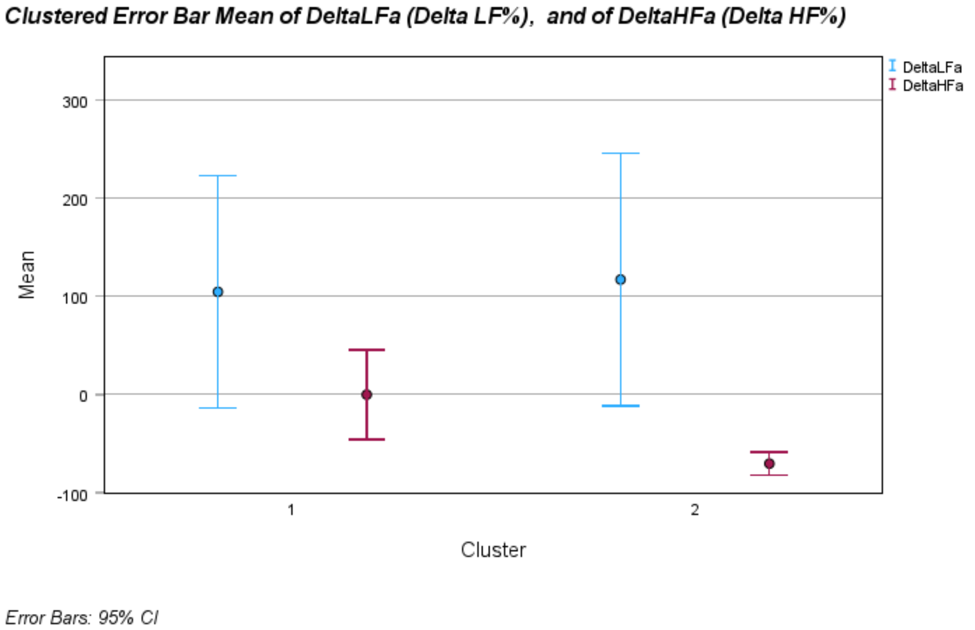


FIGURE 39. *Mean percentual difference in each frequency band activation calculated as ΔHRV%: while ΔLF% does not vary significantly between clusters, ΔHF% (i.e. parasympathetic withdrawal) was significantly lower in cluster 1 (W = 199, FDR-adjusted p < 0.001).*

Figure 40 illustrates ΔLFnu and ΔHFnu means by cluster, both of which differed significantly between groups. It is worth nothing that normalized measures are mathematically complementary and reciprocally influenced. This linkage arises from the normalization process itself, where LFnu and HFnu are expressed as relative proportions of the total power (excluding very-low-frequency components). Thus, an increase in one automatically corresponds to a decrease in the other. A reduction in HFa power (as observed in Cluster 2) can elevate LFnu even in the absence of an actual increase in LF absolute power.

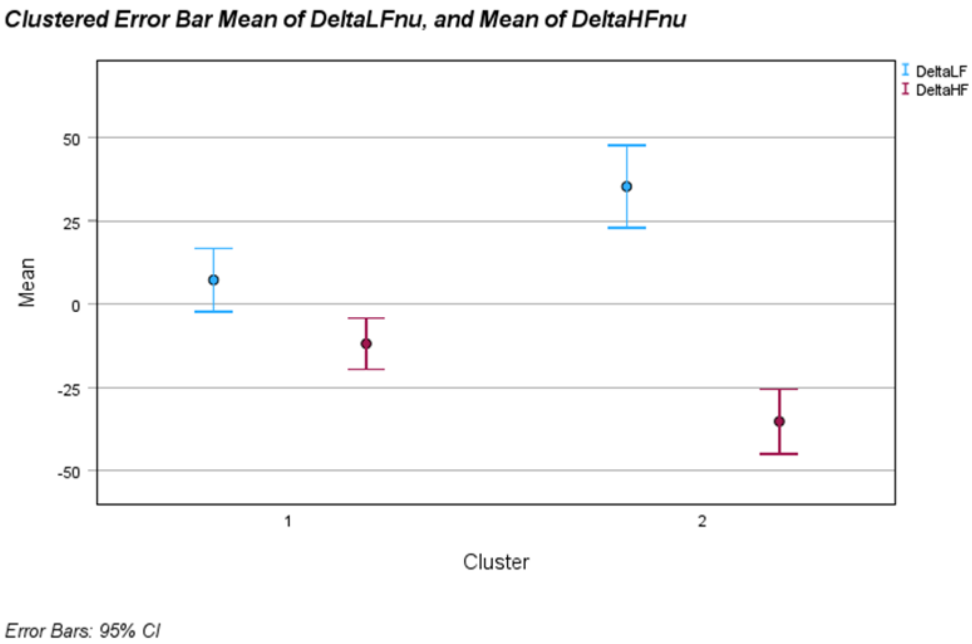


FIGURE 40. *Mean difference in each frequency band activation calculated as ΔHRVnu: both ΔHF and ΔLF vary significantly between clusters (ΔLFnu: W = 29, FDR-adjusted p <0.005; ΔHFnu: W = 192, FDR-adjusted p <0.005).*

TABLE 9. *Comparison of mean, median and standard deviation between the two clusters of HRV indices in absolute powers, normalized units and of ΔHRV measures. FDR-adjusted p values of the W statistic indicate significance. W statistics and t tests results for all variables are reported in Appendix C (Tab. C5).*

	VARIABLE	CLUSTER 1			CLUSTER 2			STATISTICALLY DIFFERENT?
		MEAN	SD ±	MEDIAN	MEAN	SD ±	MEDIAN	
Absolute powers	LFa supine	184.7969	179.10198	109.175	100.2436	93.31898	57.855	NO (FDR adj p= 0.55)
	HFa supine	279.6338	298.3077	148.23	149.2071	189.4639	83.305	NO (FDR adj p= 0.09)
	LFa standing	181.9381	140.13996	160.365	118.2593	95.90745	104.875	NO (FDR adj p= 0.45)
	HFa standing	197.36	184.016	138.56	31.85857	32.73007	18.34	YES (FDR adj p<0.001)
Normalized units	LFnu supine	34.225	16.54389	32.48	38.95	19.71083	38.835	NO (FDR adj p= 0.81)
	HFnu supine	55.77625	15.39574	56.125	53.97786	16.59826	55.75	NO (FDR adj p= 0.94)
	LFnu standing	41.48188	10.89962	45.04	74.26714	9.38976	73.27	YES (FDR adj p<0.001)
	HFnu standing	43.91125	8.094391	44.78	18.76	7.299455	19.74	YES (FDR adj p<0.001)
ΔHRV	ΔLFnu	7.256875	17.7786	7.3	35.31714	21.42307	32.26	YES (FDR adj p=0.002)
	ΔHFnu	-11.865	14.6392	-10.14	-35.2179	16.92928	-35.21	YES (FDR adj p=0.003)
	ΔLF%	104.4649	222.5481	-1.537216	116.9797	222.7048	42.95259	NO (FDR adj p= 0.69)
	ΔHF%	-0.1102327	85.34674	-24.84538	-70.264	20.29302	-76.4455	YES (FDR adj p=0.001)

As reported in Table 9, LFa measures do not significantly differ between clusters in either the supine or standing position. When the absolute powers are transformed in normalized units, HFa (that in the active standing condition is the only absolute measure significantly different between groups) is implemented in the calculus of LFnu. At the same time HFnu, and consequently also ΔHFnu, is mathematically influenced by LFa.

This relationship is further illustrated in Figure 41, depicting the changes in low-frequency (LF) and high-frequency (HF) components from supine to active standing, in both normalized units and absolute powers. Although Cluster 2 demonstrated a greater ΔLFnu, this was not paralleled by a greater increase in LFa but was instead a mathematical consequence of a greater reduction in HFa. Therefore, the sympathetic/LFnu dominance observed in Cluster 2 is more reflective of parasympathetic withdrawal rather than a true sympathetic gain.

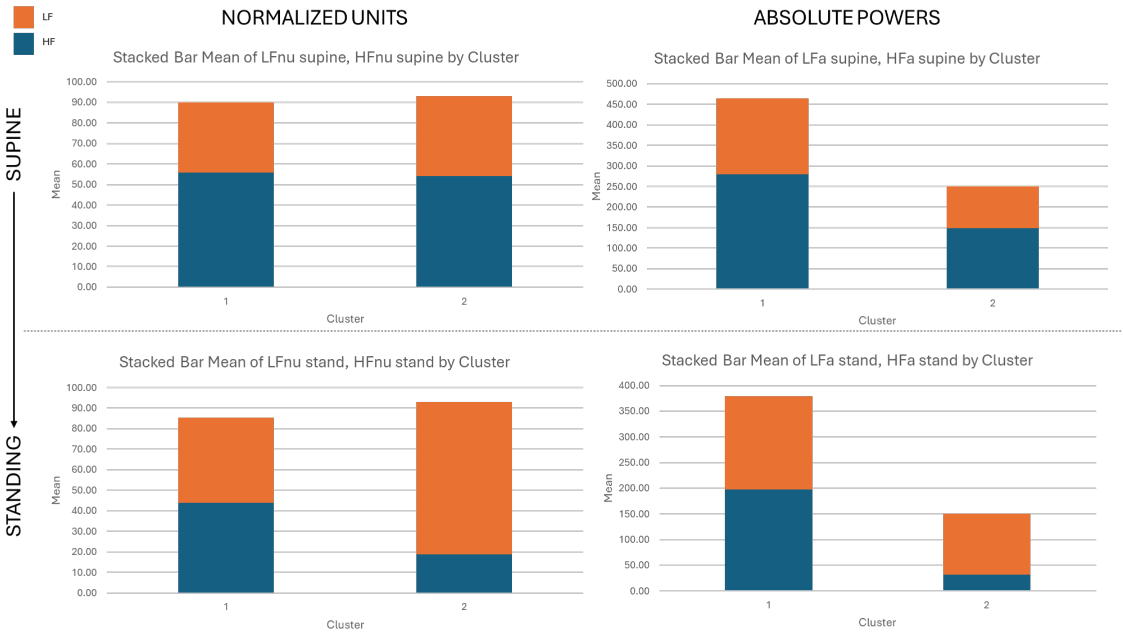


FIGURE 41. *Stacked bar means of LF and HF absolute powers (on the right) and normalized units (on the left), from a supine (above) to a standing (below) position. LF is represented in orange and HF in blue.*

3.1.2.4 HRV INDICES AND COGNITIVE PERFORMANCE

Spearman's rank-order correlations were performed between cognitive outcomes (PVF, RAVLT I, RAVLT D, DTC TUG normal pace, DTC TUG fast pace) and HRV indices.

As shown in Table 10, a greater ΔLFnu was associated with worse cognitive performance. No significant correlations were found between LFa (either in resting supine or in active standing) and cognitive performances.

In contrast, ΔHF% correlated positively with phonemic verbal fluency (PVF) (ρ = 0.435, p = 0.018) and RAVLT delayed recall (ρ = 0.385, p = 0.039) and negatively with the cognitive cost of the TUG in normal (ρ = –0.557, p = 0.005) and fast pace

(ρ = –0.470, p = 0.022). These findings suggest that steeper parasympathetic withdrawal (i.e., larger ΔHF%) is associated with reduced cognitive performance and increased dual-task cost.

TABLE 10. *Spearman's correlation coefficients (Rho) and corresponding p-values between heart rate variability (HRV) parameters (ΔHF%, ΔLF%, ΔHFnu, ΔLFnu, HFa supine, LFa supine, HFa standing, LFa standing) and cognitive/functional measures (PVF, RAVLT I, RAVLT D, dtTUG normal pace, dtTUG fast pace). Statistically significant correlations ($p < 0.05$) are highlighted in green.*

	ΔHF%		ΔLF%		ΔHFnu		ΔLFnu		HFa supine		LFa supine		HFa standing		LFa standing	
	Rho	*p value*	*Rho*	*p value*	*Rho*	*p value*	*Rho*	*p value*	*Rho*	*p value*	*Rho*	*p value*	*Rho*	*p value*	*Rho*	*p value*
PVF	0.435	**0.018**	0.029	0.883	0.254	0.184	-0.384	**0.040**	0.169	0.381	0.044	0.820	0.355	0.058	0.105	0.589
RAVLT I	0.325	0.085	-0.152	0.430	0.344	0.068	-0.444	**0.016**	0.319	0.092	0.194	0.314	0.406	**0.029**	0.122	0.529
RAVLT D	0.385	**0.039**	-0.020	0.918	0.350	0.063	-0.403	**0.030**	0.148	0.443	0.145	0.453	0.360	0.055	0.122	0.530
dtTUG normal pace	-0.557	**0.005**	0.010	0.963	-0.552	**0.006**	0.622	**0.001**	-0.254	0.230	-0.183	0.389	-0.426	**0.039**	-0.183	0.391
dtTUG fast pace	-0.470	**0.022**	-0.078	0.716	-0.423	**0.040**	0.419	**0.043**	0.083	0.700	0.032	0.882	-0.103	0.629	0.010	0.963

3.1.2.5 Network communities and modularity

As for PRAISE T0, the correlation network was constructed using absolute pairwise Pearson correlations and a threshold of |r| ≥ 0.40 applied to age-adjusted data (Fig. 42) (the network produced from raw data at the same threshold appendix D - Fig. D3). Figure 43 shows the correlational network of age-adjusted data at threshold |r| ≥ 0.35.

The thresholded (|r| ≥ 0.40) age-adjusted network contains 55 nodes and 185 unique edges. The average node degree is 6.73, indicating that on average each variable is directly connected to approximately five others at the chosen threshold. Network density, defined as the proportion of observed edges relative to all possible edges [2E/(N(N−1))], is 0.125. Interactive network plots (visNetwork) with edge colour encoding the sign of the relation (soft green = positive, dark blue = negative) are available at https://lucia-pp.github.io/PRAISE/ .

Louvain community detection partitioned the 55 nodes into 6 communities with sizes:

- Community 1: 5 nodes
- Community 2: 4 nodes
- Community 3: 6 nodes
- Community 4: 15 nodes
- Community 5: 10 nodes
- Community 6: 15 nodes

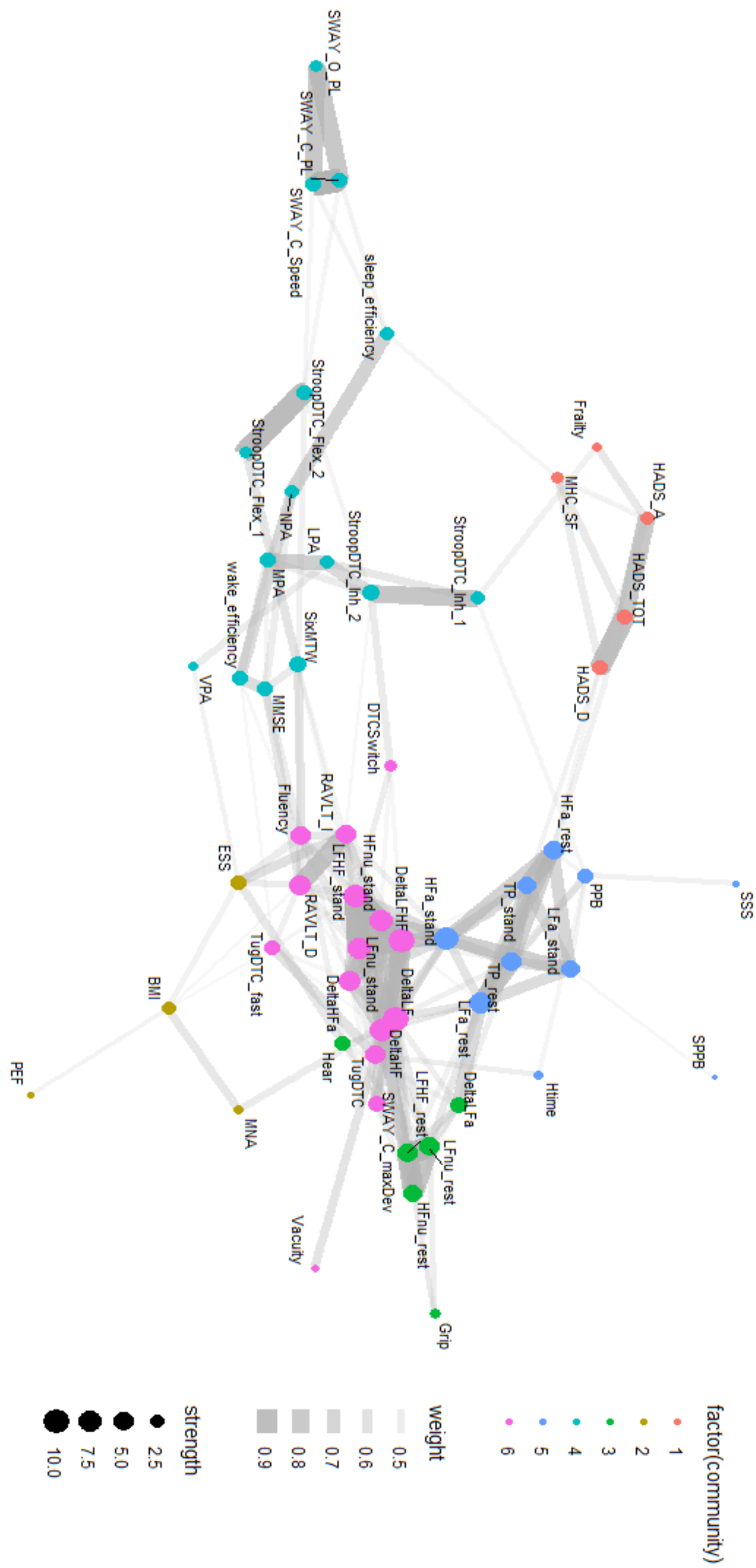


FIGURE 42. *Correlation network of age-adjusted variables at threshold |r| ≥ 0.40 in dataset PRAISE HRV T0. Each node represents a variable, with node size proportional to node strength (sum of absolute edge weights). Node colour indicates community membership as identified by the Louvain algorithm. Edges represent pairwise absolute correlations exceeding the threshold, with thickness proportional to the correlation strength. The network comprises 63 nodes and 159 edges, organized into 6 communities.*

Several HRV variables were markedly central according to degree, strength and betweenness, with also some cognitive variables, identifying them as hubs or potential integrators in this multivariate system (Table 7). The most central nodes, for the major part belonging to Community 6, are:

- DeltaLF (ΔLF in normalized units): degree = 18, strength = 10.179, eigenvector = 0.933 (Community 6);
- DeltaLFHF (ΔLF/HF): degree = 16, strength = 9.714, eigenvector = 1.000 (Community 6);
- DeltaHF (ΔHF in normalized units): degree = 15, strength = 8.860, eigenvector = 0.876 (Community 6);
- LFHF_stand (LF/HF in standing): degree = 14, strength = 8.486, eigenvector = 0.879 (Community 6);
- HFa_stand (HF absolute power in standing) degree = 14, strength = 8.679, eigenvector = 0.831 (Community 5);
- RAVLT_D (Rey Auditory Verbal Learning Test in delayed recall): degree = 13, strength = 6.352, eigenvector = 0.513 (Community 6);
- LFa_rest (LF in absolute power in supine resting position): degree = 13, strength = 7.354, eigenvector = 0.492 (Community 5);
- LFnu_stand (LF in normalized units while standing): degree = 12, strength = 7.670, eigenvector = 0.879 (Community 6);
- DeltaHFa (percentage of ΔHFa): degree = 11, strength = 6.235, eigenvector = 0.721 (Community 6);
- RAVLT_I (Rey Auditory Verbal Learning Test in immediate recall): degree = 11, strength = 5.796, eigenvector = 0.529 (Community 6);
- TugDTC (Dual task cost of the TUG in normal pace): degree = 11, strength = 5.622, eigenvector = 0.561 (Community 6).

All nodes' statistics are reported in Table 11. HFa in standing showed the highest betweenness (0.148), followed by 6MWT (0.103), LF/HF in stand (0.102), HFa in supine rest (0.092) and ΔLFnu (0.086). HFa in stand is frequently located on shortest paths connecting pairs of other nodes and therefore may act as an important bridge connecting different modules (physiological ↔ dual task/cognitive).

TABLE 11. *Node-level centrality metrics for all variables in the thresholded* ***age-adjusted*** *correlation network* ***(|r| ≥ 0.40)*** *– dataset PRAISE HRV T0. Degree = number of edges; Strength = sum of absolute edge weights; Betweenness = proportion of shortest paths passing through the node; Closeness = inverse of average path length to all other nodes; Eigenvector = importance based on connections to other central nodes; Community = Louvain cluster assignment.*

Variable	Degree	Strength	Betweenness	Closeness	Eigenvector	Community
Frailty	2	0.987	0.013	0.139	0.002	1
MHC_SF	4	1.904	0.034	0.147	0.006	1
HADS_A	4	2.298	0.021	0.151	0.007	1
HADS_D	5	2.737	0.008	0.163	0.041	1

HADS_TOT	4	2.684	0.066	0.169	0.025	1
BMI	5	2.234	0.043	0.163	0.063	2
ESS	6	3.043	0.030	0.194	0.133	2
MNA	2	1.054	0.027	0.170	0.078	2
PEF	1	0.434	0.000	0.119	0.004	2
Grip	3	1.365	0.000	0.140	0.068	3
Hear	6	2.853	0.027	0.196	0.136	3
LFnu_rest	9	5.326	0.033	0.193	0.334	3
HFnu_rest	7	4.294	0.016	0.186	0.308	3
LFHF_rest	9	5.296	0.002	0.192	0.336	3
DeltaLFa	7	3.576	0.000	0.188	0.230	3
MMSE	6	3.127	0.053	0.188	0.091	4
StroopDTC_Inh_1	4	2.251	0.068	0.181	0.014	4
StroopDTC_Inh_2	6	3.345	0.077	0.195	0.052	4
StroopDTC_Flex_1	2	1.494	0.000	0.162	0.017	4
StroopDTC_Flex_2	5	2.654	0.088	0.163	0.018	4
SixMTW	7	3.380	0.103	0.197	0.166	4
NPA	4	2.334	0.045	0.163	0.013	4
LPA	4	2.468	0.031	0.168	0.009	4
MPA	5	2.675	0.024	0.163	0.016	4
VPA	2	0.950	0.003	0.156	0.010	4
sleep_efficiency	4	2.033	0.048	0.149	0.002	4
wake_efficiency	5	2.612	0.013	0.180	0.050	4
SWAY_C_PL	4	2.673	0.020	0.130	0.002	4
SWAY_O_PL	2	1.632	0.000	0.113	0.000	4
SWAY_O_Speed	4	2.673	0.020	0.130	0.002	4
SSS	1	0.456	0.000	0.133	0.007	5
SPPB	1	0.405	0.000	0.136	0.015	5
Htime	2	0.909	0.006	0.162	0.048	5
PPB	7	3.138	0.075	0.187	0.102	5
TP_rest	**9**	**5.394**	**0.014**	**0.208**	**0.381**	**5**
LFa_rest	**13**	**7.354**	**0.073**	**0.216**	**0.492**	**5**
HFa_rest	8	4.961	0.092	0.212	0.259	5
TP_stand	7	4.280	0.020	0.202	0.292	5
LFa_stand	7	4.196	0.037	0.203	0.244	5
HFa_stand	**14**	**8.679**	**0.148**	**0.237**	**0.831**	**5**
RAVLT_I	**11**	**5.796**	**0.072**	**0.236**	**0.529**	**6**
RAVLT_D	**13**	**6.352**	**0.078**	**0.223**	**0.513**	**6**
Fluency	**11**	**5.409**	**0.045**	**0.216**	**0.380**	**6**
DTCSwitch	4	1.821	0.014	0.190	0.186	6
TugDTC	**11**	**5.622**	**0.066**	**0.209**	**0.561**	**6**
TugDTC_fast	7	3.097	0.022	0.198	0.249	6
Vacuity	1	0.574	0.000	0.154	0.049	6
SWAY_O_maxDev	8	3.862	0.000	0.182	0.412	6

DeltaHFa	**11**	**6.235**	**0.000**	**0.219**	**0.722**	**6**
DeltaLF	**18**	**10.179**	**0.086**	**0.236**	**0.933**	**6**
DeltaLFHF	**16**	**9.714**	**0.032**	**0.241**	**1.000**	**6**
DeltaHF	**15**	**8.860**	**0.067**	**0.226**	**0.876**	**6**
LFnu_stand	**12**	**7.670**	**0.015**	**0.234**	**0.879**	**6**
HFnu_stand	**11**	**7.333**	**0.015**	**0.236**	**0.853**	**6**
LFHF_stand	**14**	**8.486**	**0.102**	**0.244**	**0.879**	**6**

The Louvain communities correspond to coherent domain clusters, aligning with previous results, and are interpretable in behavioural and physiological terms:

- **Community 1**: Frailty; MHC_SF (Mental Health Continuum – Short Form); HADS_A (anxiety); HADS_D (depression); HADS_TOT (total HADS). This small module groups self-reported mental health scales and Frailty. HADS total and depression scores show relatively higher centrality (HADS_TOT has highest betweenness in the community; HADS_D highest eigenvector), indicating they are the most connected psychological indicators to the rest of the network.
- **Community 2**: BMI; ESS (Epworth Sleepiness Scale); MNA (Mini Nutritional Assessment); PEF (peak expiratory flow). This community groups subjective daytime sleepiness and basic physiological/nutritional measures. PEF is relatively peripheral within the module (low degree/strength); ESS on the other hand is well connected to cognitive, dual-task and HRV measures.
- **Community 3**: Grip strength; Hear (Whisper test); LFnu_rest (LFnu supine); HFnu_rest (HFnu supine); LFHF_rest (LF/HF supine); DeltaLFa (percentage gain in LFa from supine to standing). This community is dominated by resting HRV metrics (in particular LF indices) and includes peripheral measures. The high strength and eigenvector centralities of LF/HF and LFnu indicate that resting autonomic balance is a coherent subnetwork and is well-connected within the broader graph. The inclusion of hearing and grip may suggest modest links between resting autonomic tone and basic sensory/strength measures.
- **Community 4**: MMSE; StroopDTC_Inh_1; StroopDTC_Inh_2 (cognitive inhibition DTC); StroopDTC_Flex_1; StroopDTC_Flex_2 (cognitive flexibility DTC); 6MWT; NPA, LPA, MPA, VPA; sleep_efficiency; wake_efficiency (physical and actigraphic activity); SWAY_C_PL; SWAY_O_PL; SWAY_O_Speed (balance). Overall, Community 4 reflects physical and functional capacity, executive control and everyday activity patterns. 6MWT and Stroop indices show elevated betweenness, indicating bridging roles between Community 4 and other modules.
- **Community 5**: SSS (social support scale); SPPB (Short Physical Performance Battery); Htime (Execution timing of H cancellation Letter

test); PPB (Pseudo-periodic behaviour); TP_rest (Total Power in resting supine); LFa_rest (LF absolute power in supine); HFa_rest (HF absolute power in supine); TP_stand (Total Power in standing); LFa_stand (LF absolute power in standing); HFa_stand (HF absolute power in standing). This community groups a mixture of HRV absolute power measures (both supine and stand) along with functional physical indices (SPPB, PPB) and processing speed (Htime). Notably, HFa_stand is the single node with the highest betweenness in the entire network (0.148), and it has very high eigenvector centrality, indicating it sits at the intersection of multiple domains and is connected to other highly connected nodes.

- **Community 6**: RAVLT_I (RAVLT immediate recall); RAVLT_D (RAVLT deayed recall); Fluency (Phonemic Verbal Fluency); DTCSwitch (Switching task dual cost); TugDTC; TugDTC_fast; Vacuity (visual acuity); SWAY_O_maxDev (max deviation during SWAY); DeltaHFa (percentage change in HFa from supine to standing); DeltaLF (gain in LFnu); DeltaLFHF (gain in LF/HF from supine to stand); DeltaHF (change in HFnu); LFnu_stand; HFnu_stand; LFHF_stand. Community 6 is the autonomic reactivity and cognitive/dual-task core of the network. It is dominated by ΔHRV metrics that show the highest degrees, strengths and the very highest eigenvector centralities (DeltaLFHF = 1.000). This indicates these ΔHRV measures are not only strongly intercorrelated, but they are also connected to other highly central nodes. Cognitive performance (RAVLT immediate/delayed and phonemic verbal fluency) and dual-task costs (TugDTC) are tightly integrated into this module, supporting an empirical link between autonomic reactivity and cognitive/dual-task function in the sample.

When we change the absolute correlation threshold from $|r| \geq 0.40$ to $|r| \geq 0.35$ the network (Fig. 43), as expected, becomes substantially denser: the number of edges rises from 185 to 243 (an increase of 58 edges, ≈ +31%), average node degree increases from ~6.7 to ~8.8, and density increases from ~0.125 to ~0.164. The same variables remain the major hubs in both networks, but several variables acquire multiple new connections at the lower threshold (Table 12). In particular:

- DeltaLF: 18 → 21 (Δ = +3)
- DeltaHF: 15 → 18 (Δ = +3)
- LFnu_stand: 12 → 15 (Δ = +3)
- HFnu_stand: 11 → 17 (Δ = +6)
- RAVLT_D: 13 → 17 (Δ = +4)
- TugDTC: 11 → 15 (Δ = +4)
- RAVLT_I: 11 → 14 (Δ = +3)
- TugDTC_fast: 8 → 12 (Δ = +4)

These changes indicate that many more HRV–cognitive-functional connections are actually hidden in the data, but they fall in the correlation range 0.35–0.40 and are therefore visible only after lowering the threshold. Community structure is maintained in a broadly similar partition, but several resting and standing HRV absolute power measures and locomotor variables that were grouped in Community 5 at $|r| \geq 0.40$ (LFa_rest, HFa_rest, LFa_stand, HFa_stand, TP_rest, TP_stand, PPB, SPPB) were reassigned to Community 1 at $|r| \geq 0.35$, along with Frailty and psychological measures.

The autonomic-cognitive-DT relationship at $|r| \geq 0.35$ reinforces the main substantive finding that autonomic reactivity indices form a highly central physiological core that is empirically coupled to cognitive and dual-task performance in this sample. Because the sample size is small (N = 30), these threshold-dependent differences should be treated as sensitivity checks: the qualitative is robust, but the precise number of edges and the centrality measures depend on the chosen |r| threshold.

MAIN FINDINGS AT PRAISE HRV T0.

- Strong correlations between cognitive/dual-task measures and ΔHRV indices, that are the most central nodes in the network.
- ΔHRVnu indices derived from LFnu or HFnu changes should be considered with ΔHRV% measures, that better capture shifts in single frequencies.
- Worst cognitive/dual-task performance is associated to a steeper parasympathetic withdrawal in response to the orthostatic challenge (ΔHF%).
- FRAILTY: mainly associated to psychological distress, but, even if not directly associated to, it also clusters with HRV indices.

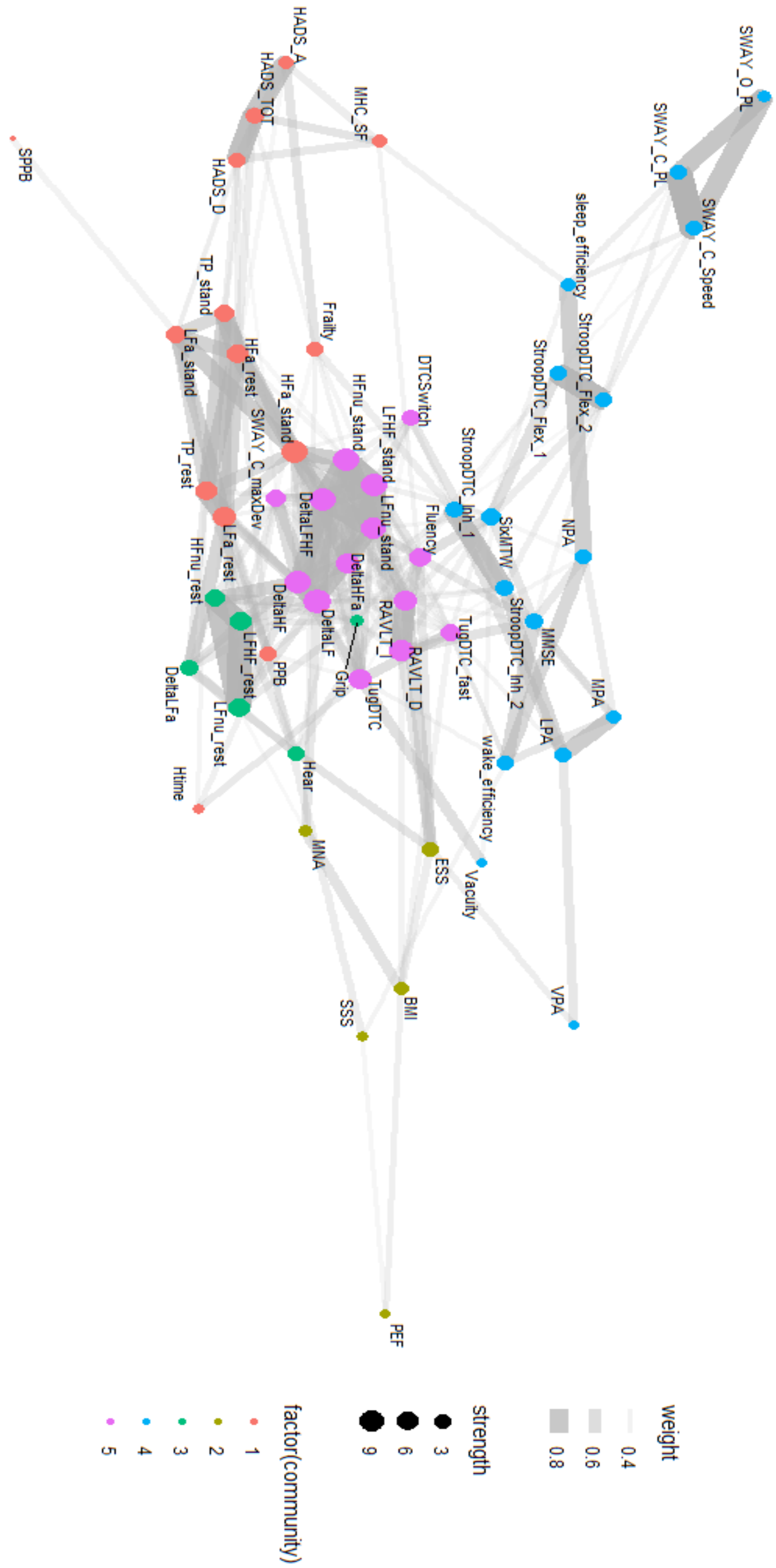


FIGURE 43. *Correlation network of age-adjusted variables at threshold |r| ≥ 0.35 in dataset PRAISE HRV T0. Each node represents a variable, with node size proportional to node strength (sum of absolute edge weights). Node colour indicates community membership as identified by the Louvain algorithm. Edges represent pairwise absolute correlations exceeding the threshold, with thickness proportional to the correlation strength. The network comprises 63 nodes and 159 edges, organized into 5 communities.*

TABLE 12. *Node-level centrality metrics for all variables in the thresholded* ***age-adjusted*** *correlation network* ***(|r| ≥ 0.35)*** *– dataset PRAISE HRV T0. Degree = number of edges; Strength = sum of absolute edge weights; Betweenness = proportion of shortest paths passing through the node; Closeness = inverse of average path length to all other nodes; Eigenvector = importance based on connections to other central nodes; Community = Louvain cluster assignment.*

Variable	Degree	Strength	Betweenness	Closeness	Eigenvector	Community
Frailty	7	2.91362	0.027254	0.206546	0.133712	1
MHC_SF	5	2.299848	0.039133	0.184608	0.043619	1
SPPB	1	0.404584	0	0.142029	0.013996	1
Htime	3	1.287395	0	0.179777	0.069488	1
HADS_A	5	2.663958	0.003494	0.180018	0.047234	1
HADS_D	7	3.44981	0.00559	0.179903	0.09553	1
HADS_TOT	7	3.824168	0.020266	0.185821	0.08142	1
PPB	8	3.507114	0.039133	0.206831	0.138171	1
TP_rest	11	6.138114	0.014675	0.219265	0.413135	1
LFa_rest	**13**	**7.354447**	**0.039133**	**0.229761**	**0.471136**	**1**
HFa_rest	12	6.443499	0.037736	0.221444	0.370837	1
TP_stand	9	5.017471	0.006289	0.20949	0.334724	1
LFa_stand	9	4.936622	0.037037	0.21669	0.249444	1
HFa_stand	**16**	**9.412191**	**0.102725**	**0.249555**	**0.839291**	**1**
BMI	5	2.233763	0.034941	0.18564	0.070744	2
SSS	3	1.21123	0.011181	0.166084	0.014372	2
ESS	6	3.043009	0.026555	0.204946	0.145345	2
MNA	4	1.80287	0.013976	0.196099	0.093207	2
PEF	2	0.800972	0.001398	0.13891	0.00499	2
Grip	5	2.126105	0.012579	0.18173	0.066635	3
Hear	7	3.248535	0.016073	0.208577	0.169684	3
LFnu_rest	10	5.676864	0.01747	0.221471	0.313771	3
HFnu_rest	8	4.650453	0.007687	0.21642	0.301207	3
LFHF_rest	10	5.653918	0.004892	0.219838	0.31752	3
DeltaLFa	8	3.975063	0	0.204395	0.256554	3
MMSE	8	3.888155	0.019567	0.209452	0.148957	4
StroopDTC_Inh_1	9	4.09128	0.044025	0.217814	0.109597	4
StroopDTC_Inh_2	**8**	**4.089448**	**0.05311**	**0.223669**	**0.160472**	**4**
StroopDTC_Flex_1	6	2.94945	0.01747	0.186029	0.037647	4
StroopDTC_Flex_2	7	3.387353	0.051013	0.183135	0.046167	4
SixMTW	**11**	**4.848682**	**0.058001**	**0.21916**	**0.275996**	**4**
Vacuity	2	0.952251	0.002795	0.183999	0.061337	4
NPA	6	3.075443	0.015374	0.186834	0.056673	4
LPA	5	2.86243	0.027952	0.193371	0.046755	4
MPA	5	2.675224	0.016073	0.181469	0.035963	4
VPA	2	0.95011	0.002096	0.161263	0.012248	4
sleep_efficiency	5	2.431226	0.054507	0.183098	0.028528	4
wake_efficiency	7	3.391919	0.025856	0.204355	0.099904	4

SWAY_C_PL	5	3.023207	0.019217	0.147939	0.007472	4
SWAY_O_PL	2	1.631527	0	0.125879	0.001691	4
SWAY_O_Speed	5	3.023207	0.019217	0.147939	0.007472	4
RAVLT_I	**14**	**6.885497**	**0.023061**	**0.247425**	**0.602118**	**5**
RAVLT_D	**17**	**7.817039**	**0.044025**	**0.245083**	**0.621697**	**5**
Fluency	**14**	**6.567779**	**0.052411**	**0.240814**	**0.480824**	**5**
DTCSwitch	9	3.68836	0.001398	0.206961	0.344447	5
TugDTC	**15**	**7.09415**	**0.078966**	**0.245192**	**0.5887**	**5**
TugDTC_fast	**12**	**5.036589**	**0.064291**	**0.233892**	**0.349488**	**5**
SWAY_O_maxDev	**12**	**5.338304**	**0.007687**	**0.212803**	**0.505076**	**5**
DeltaHFa	**14**	**7.3706**	**0.004892**	**0.244501**	**0.743921**	**5**
DeltaLF	**21**	**11.30328**	**0.097834**	**0.267227**	**0.919708**	**5**
DeltaLFHF	**18**	**10.47736**	**0.013277**	**0.262389**	**1**	**5**
DeltaHF	**18**	**9.981179**	**0.048218**	**0.253804**	**0.887446**	**5**
LFnu_stand	**15**	**8.823325**	**0.006289**	**0.25636**	**0.891226**	**5**
HFnu_stand	**17**	**9.572973**	**0.013976**	**0.258017**	**0.914725**	**5**
LFHF_stand	**16**	**9.258841**	**0.041929**	**0.261741**	**0.891188**	**5**

3.2 RESULTS AT T1

Baseline assessment analysis was repeated at T1 for 35 subjects. Overall structure and major findings were qualitatively similar between raw and age-adjusted analyses at T1; where age adjustment materially changed cluster membership or centrality metrics this is explicitly reported.

Spearman correlations revealed several associated variables. After FDR correction ($q < 0.05$), 109 correlations remained significant for the raw dataset and 64 for the age-adjusted one (Appendix C, Table C6).

3.2.1 HIERARCHICAL CLUSTERING

Ward D2 dendrograms (distance = $1 - |\rho|$) suggested a four-cluster solution by the elbow method and a ten-cluster solution according to the silhouette criteria for the raw data (Fig. 44). Considering both metrics, $k = 4$ was selected as the optimal number of clusters: this choice provides well-separated and cohesive clusters while also aligning with the structural balance identified by the elbow method.

As shown in Figure 45, the first cluster included cognitive and dual-task measures (RAVLT, DTC TUG), actigraphic registration indices, HRV measures in normalised units at rest and percentage of ΔHFa, and general health and fitness level (PEF, Visual acuity, Grip strength, BMI).

The second cluster included balance indices from the SWAY test an HRV absolute powers both in rest and in stand, while the third cluster included only few HRV variables, referring to normalized measures in standing and ΔHRVnu indices.

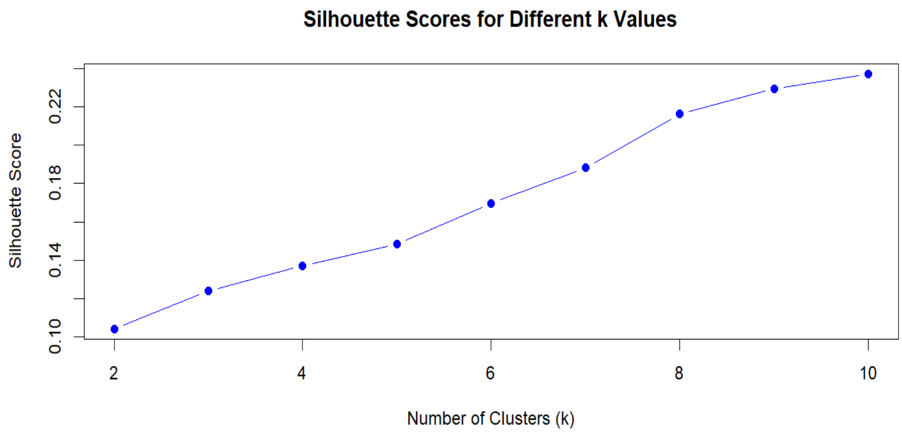
The fourth cluster included a large set of variables encompassing psychological and social wellbeing outcomes (HADS, SSS, MHC-SF), physical fitness (SPPB), Frailty, IC and DT IC global scores, ΔLF%, cognitive functions (MMSE, Phonemic Verbal Fluency) and dual task costs (DTC TUG in fast pace and Stroop test on the Dividat Senso exergame platform).

Frailty score showed its strongest associations with measures of physical capacity: grip strength ($\rho = -0.654$, $p < 0.001$, FDR $p \approx 0.001$), Short Physical Performance Battery (SPPB; $\rho = -0.642$, $p < 0.001$, FDR $p \approx 0.0015$) and the locomotor domain ($\rho = -0.621$, $p < 0.001$, FDR $p \approx 0.005$). Frailty was also strongly and negatively associated with global intrinsic-capacity metrics (IC_Dtglobal: $\rho = -0.621$, $p = 0.0001$, FDR $p \approx 0.005$; IC_global: $\rho = -0.626$, $p = 0.0001$, FDR $p \approx 0.0045$), indicating that higher Frailty covaries with lower overall functional reserve.

Higher Frailty was significantly associated with worse HADS scoring (HADS Depression: $\rho = 0.502$, $p = 0.0021$, FDR $p \approx 0.038$; HADS total: $\rho = 0.550$, $p = 0.0006$, FDR $p \approx 0.016$).

Contrary to what expected Frailty positively correlated with performance on screening measures of cognition (MMSE: $\rho = 0.542$, $p = 0.0008$, FDR $p \approx 0.017$) and the cognitive domain (Cognition_IC: $\rho = 0.592$, $p = 0.0005$, FDR $p \approx 0.0122$).

Heart-rate-variability (HRV) indices displayed very large internal correlations reflecting the expected mathematical and physiological relationships among these metrics. Importantly, HRV metrics also related to functional capacity outcomes: for instance, the peak of expiratory flow (PEF) correlated with standing HF absolute power (HFa_stand: $\rho \approx 0.577$, $p = 0.0025$, FDR $p \approx 0.043$).



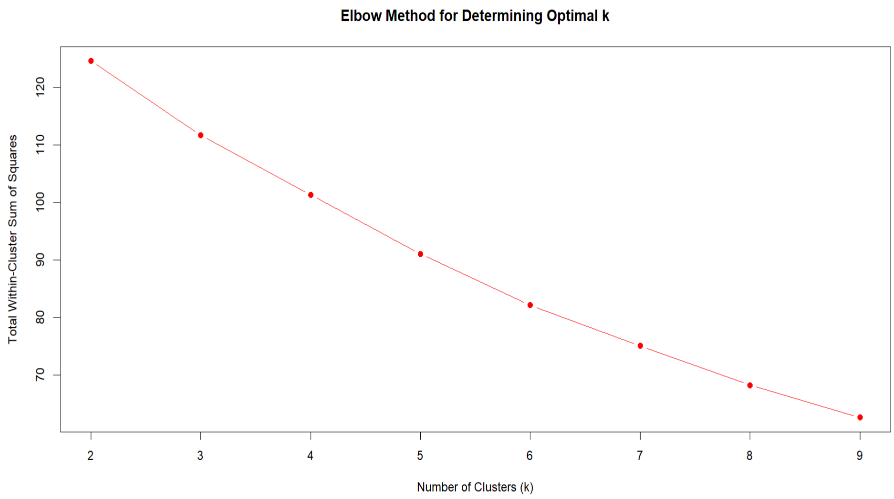


FIGURE 44. *Comparison of cluster validity metrics for the dataset PRAISE T1, raw data. While the silhouette analysis (above) shows increasing cohesion with higher values of k, the elbow method (below) suggested a solution for k=4, corresponding to a silhouette score of 0.14.*

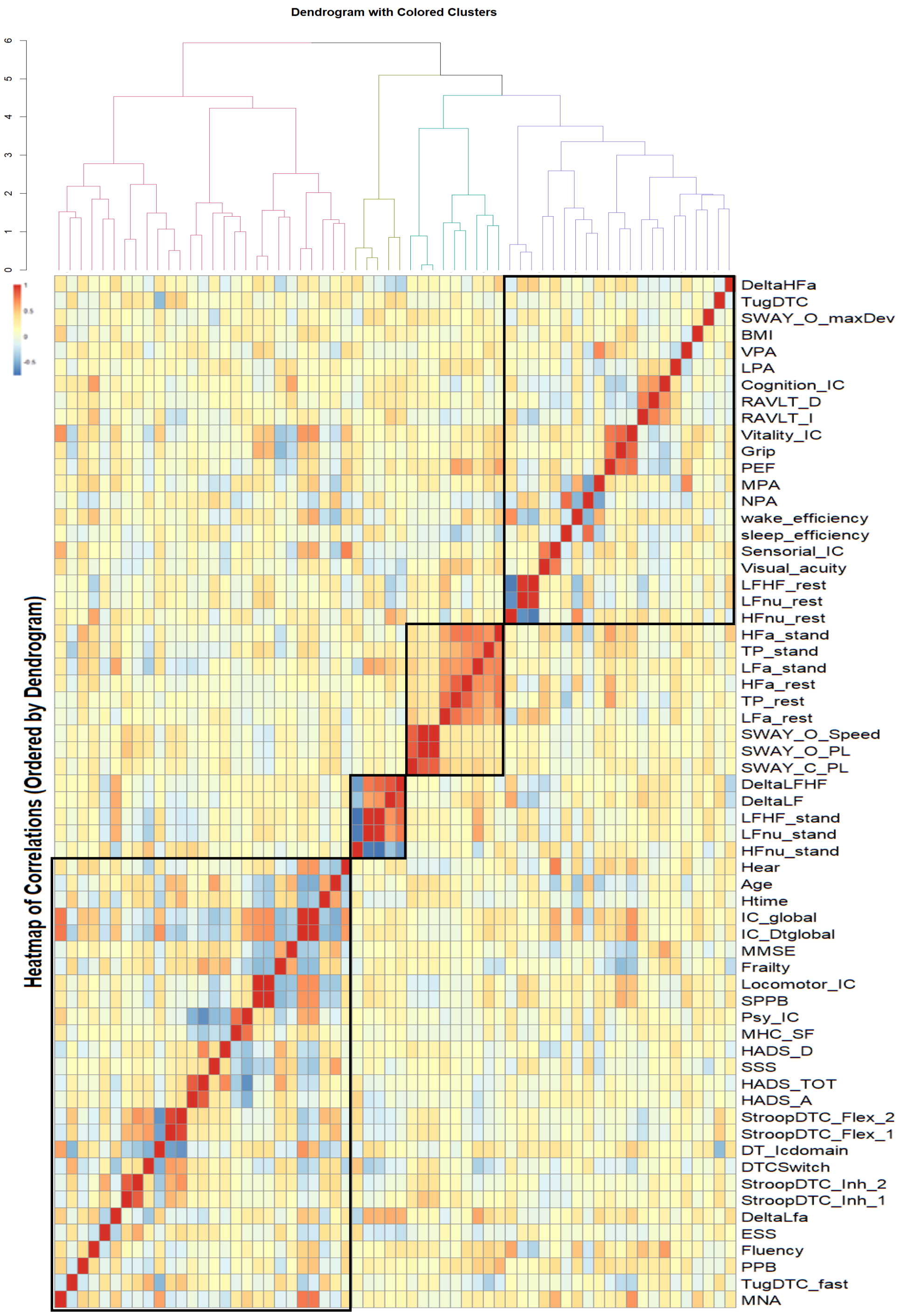


FIGURE 45. *Dendrogram with clusters (top) and corresponding heatmap of pairwise correlations (bottom) for the raw dataset of PRAISE T1. The heatmap highlights the correlation structure among variables, with blocks outlined to indicate clusters derived from hierarchical clustering. Warmer colours represent stronger positive correlations, while cooler colours indicate negative associations*

3.2.2 NETWORK COMMUNITIES AND MODULARITY

The correlation networks were constructed using absolute pairwise Pearson correlations and both a threshold of $|r| \geq 0.40$ (Fig. 46) and of $|r| \geq 0.35$ (Fig. 47) were applied to raw data.

The thresholded ($|r| \geq 0.40$) network contained 62 nodes and 241 unique edges (sum of degrees = 482), with mean degree ≈ 7.77 and density ≈ 0.127. Louvain community detection partitioned the nodes into 7 communities with sizes:

- Community 1: 16 nodes
- Community 2: 5 nodes
- Community 3: 8 nodes
- Community 4: 13 nodes
- Community 5: 8 nodes
- Community 6: 9 nodes
- Community 7: 3 nodes

The largest and most central community (Community 1) contained the Intrinsic Capacity composites (IC_global, IC_Dtglobal), Frailty and multiple functional measures; IC_Dtglobal (degree = 23, strength = 13.05, betweenness = 0.173) and IC_global (degree = 22, strength = 12.32) occupied the structural core.

Several nodes are markedly more central than others across multiple centrality measures:

- IC_Dtglobal: degree = 23, strength = 13.05, betweenness = 0.173; eigenvector = 1.00 (Community 1). Highest-degree node and the principal connector.
- IC_global: degree = 22, strength = 12.32, betweenness = 0.146, eigenvector = 0.937 (Community 1). Structural core alongside IC_Dtglobal.
- Age: degree = 17, strength = 8.86, eigenvector = 0.705 (Community 1). Strongly embedded with IC measures.
- Frailty: degree = 15, strength = 7.95, eigenvector = 0.599 (Community 1). Highly connected to IC and functional variables.
- DTCSwitch: degree = 15, strength = 7.62, betweenness = 0.085 (Community 5). Principal dual-task hub.
- Vitality_IC: degree = 14, strength = 7.57 (Community 1). High centrality within intrinsic-capacity module.
- LFa_stand / HFa_stand: degrees = 11 each; strengths ≈ 6.19 / 6.18 (Community 6).

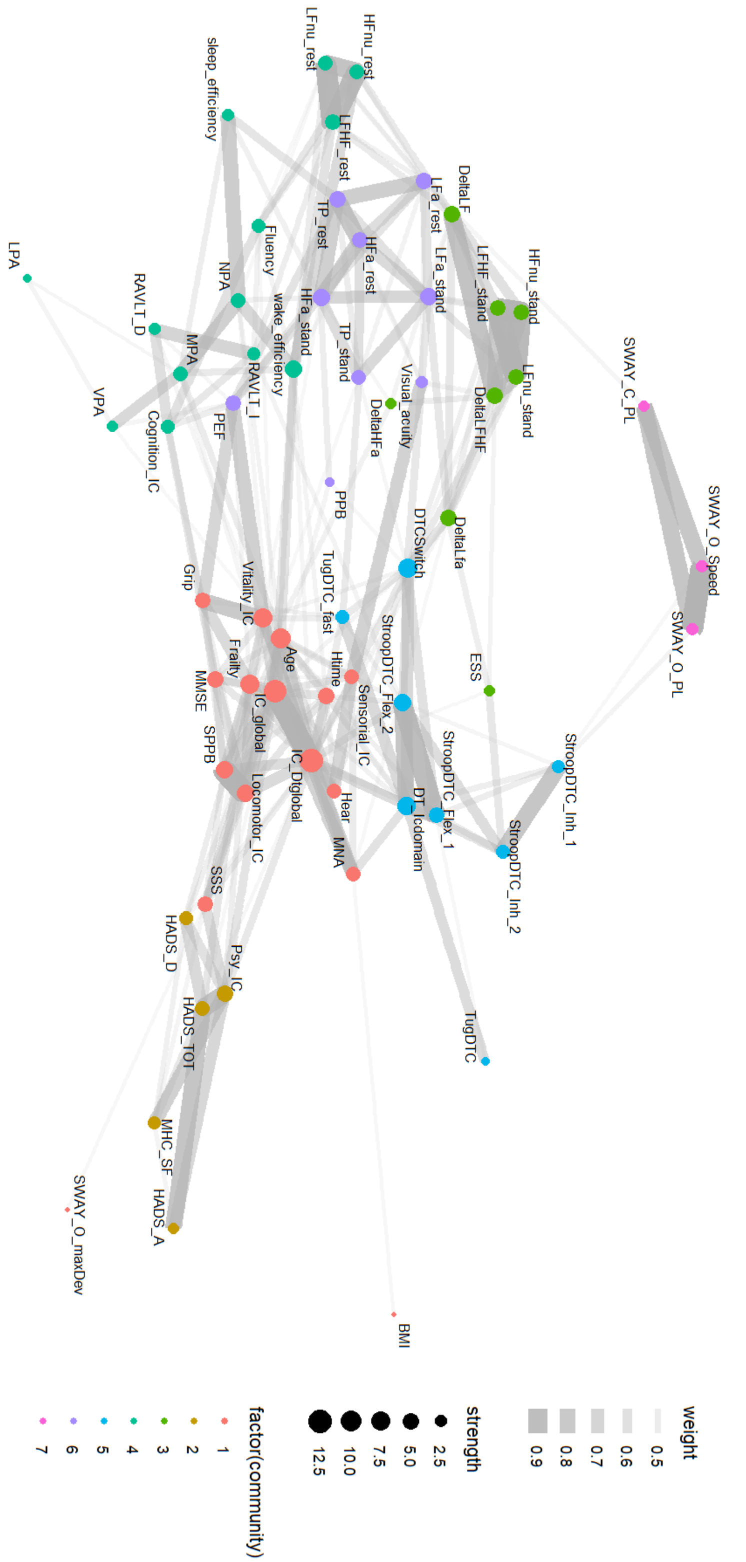


FIGURE 46. *Correlation network at threshold |r| ≥ 0.4 at T1. Each node represents a variable, with node size proportional to node strength (sum of absolute edge weights). Node colour indicates community membership as identified by the Louvain algorithm. Edges represent pairwise absolute correlations exceeding the threshold, with thickness proportional to the correlation strength. The network comprises 62 nodes and 241 edges, organized into 7 communities.*

Communities, as visible in Table 13, were composed as follows:

- **Community 1:** Age, Frailty, BMI, Grip, MMSE, SSS, MNA, SPPB, Htime, Hear, SWAY_O_maxDev, Sensorial_IC, Vitality_IC, Locomotor_IC, IC_DT, IC. This is the principal network core that aggregates Intrinsic Capacity constructs, main functional tests (SPPB, Grip, Hear), age and Frailty. High-degree and high-eigenvector values for IC metrics indicate these composites are integrative summaries that correlate broadly with many domain-specific variables, a predictable and important result given their construction.
- **Community 2:** MHC_SF, HADS_A, HADS_D, HADS_TOT, Psychological_IC. A compact module of mental-health and subjective well-being variables that is connected to the IC core.
- **Community 3**: ESS, DeltaLfa, DeltaHFa, DeltaLF, LFnu_stand, HFnu_stand, LFHF_stand, DeltaLFHF. A module capturing autonomic reactivity (ΔHRV) and normalized standing HRV measures. The ΔHRV indices are the most connected, suggesting that autonomic reactivity forms a coherent physiological subnetwork. The sleepiness scale (ESS) is connected to stroop measures (Community 5) through a positive correlation (Spearman's $\rho = 0.54$, $p = 0.0008$, FDR-adjusted $p = 0.0186$).
- **Community 4**: RAVLT_I, RAVLT_D, Fluency, NPA, LPA, MPA, VPA, sleep_efficiency, wake_efficiency, LFnu_rest, HFnu_rest, LFHF_rest, Cognition_IC. Wake efficiency and activity measures show high connectivity within this module along with Phonemic Verbal Fluency and resting HRVnu indices.
- **Community 5**: DTCSwitch, StroopDTC_Inh_1, StroopDTC_Inh_2, StroopDTC_Flex_1, StroopDTC_Flex_2, TugDTC, TugDTC_fast, DT_Icdomain. A tightly connected dual-task community with DTCSwitch acting as principal hub bridging dual-task performance and HRV parameters.
- **Community 6:** Visual_acuity, PEF, PPB, LFa_rest, HFa_rest, TP_stand, LFa_stand, HFa_stand, TP_rest. This community groups HRV absolute spectral-power indices (rest and stand) with functional reserves (PEF, visual acuity).
- **Community 7:** SWAY_O_PL, SWAY_C_PL, SWAY_O_Speed. A small module of postural sway measures that is weakly connected to the rest of the network at the chosen threshold.

It is important to note that the HRV measures at T1 include participants who were under medications known to influence autonomic regulation. Due to the small overall sample size (N = 35), we did not exclude these individuals, in order to retain statistical power and network stability. As a result, the HRV-related findings at T1 should be interpreted with caution, as they are likely less robust and more prone to medication-related confounding compared to PRAISE HRV T0, where such effects were not present.

TABLE 13. *Node-level centrality metrics for all variables in the thresholded raw correlation network (|r| ≥ 0.4) – dataset PRAISE T1. Degree = number of edges; Strength = sum of absolute edge weights; Betweenness = proportion of shortest paths passing through the node; Closeness = inverse of average path length to all other nodes; Eigenvector = importance based on connections to other central nodes; Community = Louvain cluster assignment.*

Variable	Degree	Strength	Betweenness	Closeness	Eigenvector	Community
Age	**17**	**8.857**	**0.051**	**0.269**	**0.705**	**1**
Frailty	**15**	**7.946**	**0.069**	**0.262**	**0.599**	**1**
BMI	1	0.401	0.000	0.157	0.025	1
Grip	8	4.519	0.008	0.229	0.329	1
MMSE	10	5.202	0.013	0.232	0.499	1
SSS	9	4.535	0.035	0.223	0.417	1
MNA	7	3.987	0.033	0.257	0.384	1
SPPB	**10**	**5.838**	**0.000**	**0.240**	**0.599**	**1**
Htime	10	5.071	0.000	0.244	0.491	1
Hear	7	3.890	0.002	0.236	0.411	1
SWAY_O_maxDev	1	0.407	0.000	0.145	0.027	1
Sensorial_IC	7	3.879	0.023	0.230	0.338	1
Vitality_IC	**14**	**7.574**	**0.041**	**0.260**	**0.619**	**1**
Locomotor_IC	10	6.038	0.001	0.242	0.620	1
IC_Dtglobal	**23**	**13.052**	**0.173**	**0.308**	**1.000**	**1**
IC_global	**22**	**12.318**	**0.146**	**0.301**	**0.937**	**1**
MHC_SF	5	2.627	0.000	0.176	0.122	2
HADS_A	3	1.950	0.000	0.175	0.085	2
HADS_D	6	3.135	0.000	0.209	0.263	2
HADS_TOT	7	4.265	0.010	0.208	0.280	2
Psy_IC	8	5.112	0.051	0.226	0.352	2
ESS	4	1.872	0.007	0.210	0.104	3
DeltaLfa	**11**	**5.389**	**0.030**	**0.238**	**0.244**	**3**
DeltaHFa	4	1.795	0.007	0.204	0.071	3
DeltaLF	**10**	**5.544**	**0.026**	**0.206**	**0.112**	**3**
LFnu_stand	7	4.802	0.006	0.212	0.137	3
HFnu_stand	7	4.632	0.000	0.200	0.128	3
LFHF_stand	7	4.862	0.000	0.208	0.135	3
DeltaLFHF	8	5.072	0.018	0.199	0.104	3
RAVLT_I	5	2.632	0.017	0.195	0.061	4
RAVLT_D	4	2.161	0.003	0.189	0.074	4
Fluency	7	3.348	0.007	0.213	0.121	4
NPA	7	3.928	0.023	0.226	0.199	4
LPA	2	0.849	0.000	0.145	0.018	4
MPA	7	3.775	0.038	0.214	0.189	4
VPA	4	1.924	0.004	0.188	0.081	4
sleep_efficiency	4	2.283	0.004	0.198	0.061	4

wake_efficiency	**11**	**5.788**	**0.063**	**0.251**	**0.330**	**4**
LFnu_rest	7	3.982	0.001	0.204	0.088	4
HFnu_rest	6	3.952	0.019	0.218	0.087	4
LFHF_rest	7	4.457	0.017	0.219	0.089	4
Cognition_IC	6	3.283	0.009	0.199	0.111	4
DTCSwitch	**15**	**7.622**	**0.085**	**0.262**	**0.457**	**5**
StroopDTC_Inh_1	6	3.062	0.042	0.185	0.109	5
StroopDTC_Inh_2	5	3.091	0.008	0.198	0.135	5
StroopDTC_Flex_1	8	4.644	0.009	0.241	0.319	5
StroopDTC_Flex_2	**10**	**5.708**	**0.030**	**0.250**	**0.377**	**5**
TugDTC	2	1.044	0.000	0.186	0.072	5
TugDTC_fast	7	3.590	0.009	0.236	0.286	5
DT_Icdomain	**12**	**7.232**	**0.101**	**0.260**	**0.494**	**5**
Visual_acuity	5	2.443	0.017	0.211	0.068	6
PEF	9	4.876	0.045	0.238	0.207	6
PPB	3	1.315	0.000	0.210	0.107	6
TP_rest	8	4.986	0.028	0.226	0.104	6
LFa_rest	**10**	**5.136**	**0.065**	**0.216**	**0.090**	**6**
HFa_rest	8	4.797	0.007	0.227	0.119	6
TP_stand	8	4.208	0.004	0.228	0.155	6
LFa_stand	**11**	**6.189**	**0.050**	**0.234**	**0.167**	**6**
HFa_stand	**11**	**6.181**	**0.060**	**0.242**	**0.161**	**6**
SWAY_O_PL	3	2.260	0.008	0.150	0.010	7
SWAY_C_PL	3	2.071	0.028	0.155	0.009	7
SWAY_O_Speed	3	2.217	0.000	0.147	0.010	7

Lowering the absolute-correlation threshold at T1 from |r| ≥ 0.40 to |r| ≥ 0.35 increased network connectivity substantially: unique edges rose from 241 to 330 (Δ = +89, +37%), mean node degree from ~7.77 to ~10.65, and density from 0.127 to 0.175. The largest increases in direct connections were observed for variables across cognitive (Fluency, RAVLT_I), autonomic (DeltaLfa, LFa_stand, TP_stand), actigraphic activity (NPA, MPA) and dual-task (TugDTC_fast). The IC composites (IC_Dtglobal, IC_global) also acquired additional neighbours. Importantly, Louvain community assignments were stable across thresholds, indicating that the modular architecture is robust while the strength of inter- and intra-module coupling increases at the lower threshold. These sensitivity results show that many HRV-cognitive and HRV-functional associations lie in the 0.35–0.40 correlation band and are revealed only when the threshold is relaxed (Fig. 47).

Since age appeared as a major hub in the original T1 network (high degree and eigenvector centrality) we recalculated all pairwise correlations after adjusting each variable for age and rebuilt the thresholded network at cutoff (|r| ≥ 0.40) in order to determine how much of the observed topology reflected direct dependence on age rather than age-independent associations among variables.

Age adjustment produced a noticeably sparser graph (Fig. 48) (edges 241 → 201, mean degree ~7.77 → ~6.59, density 0.127 → 0.110).

Several clinically important nodes lost many connections after adjustment, the most affected being:

- IC_global: 22 → 11 (Δ = −11)
- MMSE: 10 → 2 (Δ = −8)
- SSS (social support): 9 → 2 (Δ = −7)
- DTCSwitch: 15 → 9 (Δ = −6)
- Frailty: 15 → 9 (Δ = −6)
- Vitality_IC: 14 → 8 (Δ = −6)

Conversely, some variables gained neighbours post-adjustment, especially:

- LFnu_stand: 7 → 15 (Δ = +8)
- ESS (Epworth): 4 → 8 (Δ = +4)
- HFnu_stand: 7 → 11 (Δ = +4)
- LFa_stand: 11 → 15 (Δ = +4)
- DT_domain: 12 → 15 (Δ = +3)
- LFHF_stand: 7 → 10 (Δ = +3)

Because the sample size is modest (N = 35), these should be interpreted as sensitivity results that clarify which associations are robust to age effects and which may be more age-driven.

Network modularity analysis is visible in Table 14, while changes in Community assignment are depicted if Figure 49 (page 123). Two main shifts occurred when adjusting for age:

1. The psychological measures became integrated with the Intrinsic-Capacity / Frailty core
2. Dual-task performance measures grouped with ΔHRV indices.

These patterns indicate that, once the linear influence of age is removed, affective/psychological status is more tightly coupled to global functional resources and Frailty, whereas dual-task performance is more tightly coupled to autonomic reactivity.

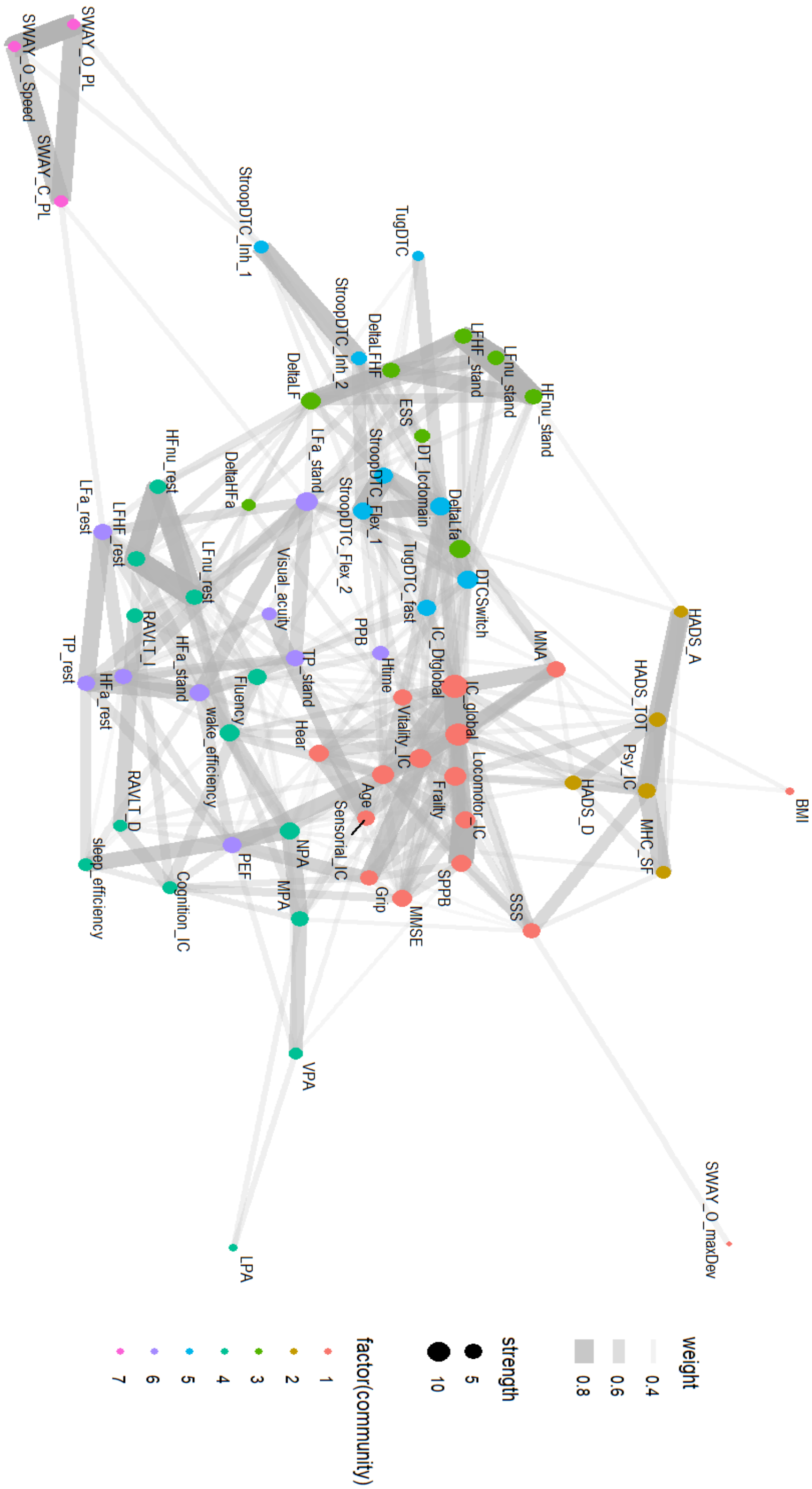


FIGURE 47. *Correlation network at threshold |r| ≥ 0.35 at T1. Each node represents a variable, with node size proportional to node strength (sum of absolute edge weights). Node colour indicates community membership as identified by the Louvain algorithm. Edges represent pairwise absolute correlations exceeding the threshold, with thickness proportional to the correlation strength. The network comprises 62 nodes and 330 edges, organized into 7 communities.*

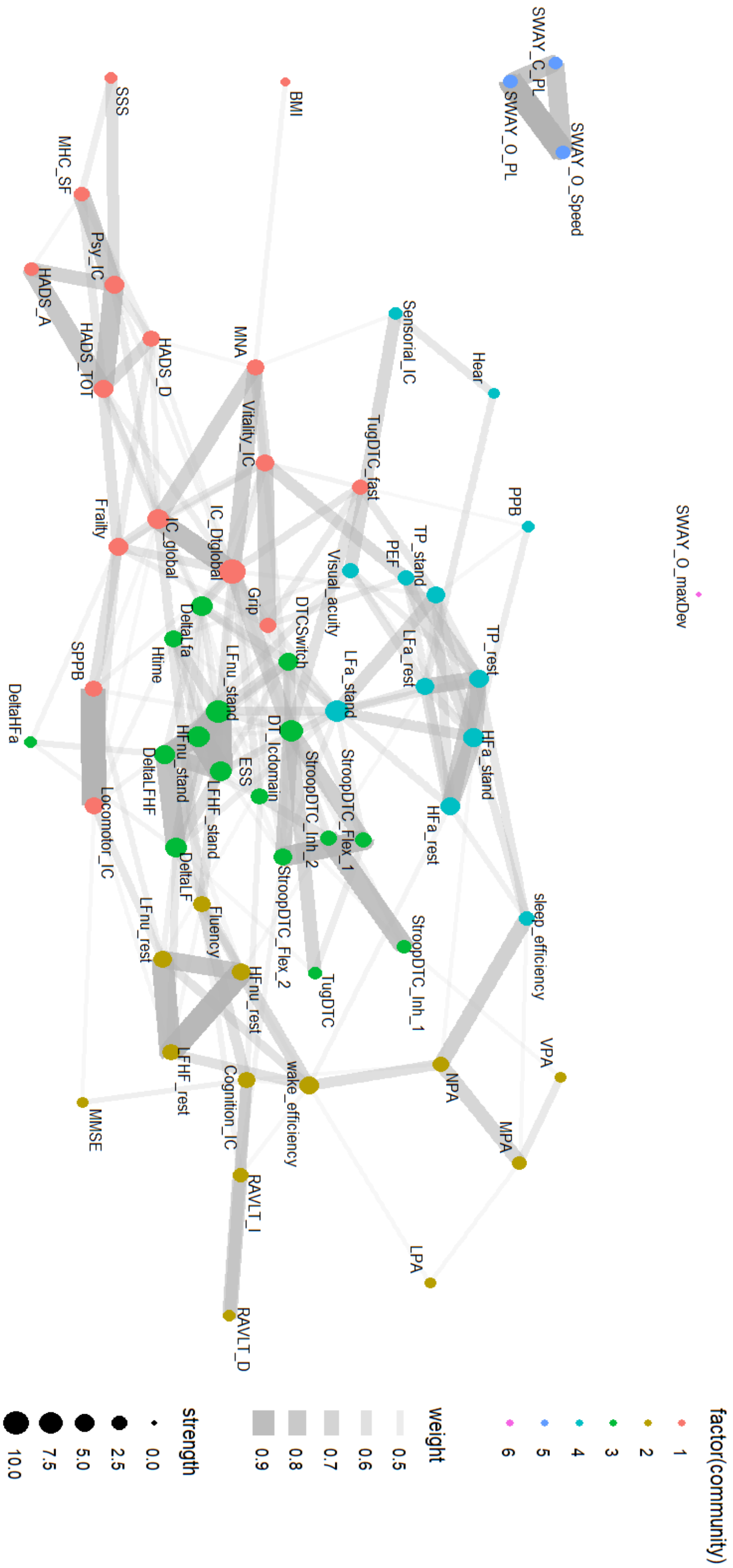


FIGURE 48. *Correlation network of age-adjusted data at threshold |r| ≥ 0.40 at T1. Each node represents a variable, with node size proportional to node strength (sum of absolute edge weights). Node colour indicates community membership as identified by the Louvain algorithm. Edges represent pairwise absolute correlations exceeding the threshold, with thickness proportional to the correlation strength. The network comprises 61 nodes and 201 edges, organized into 6 communities.*

TABLE 14. *Node-level centrality metrics for all variables in the thresholded* ***age-adjusted*** *correlation network (|r| ≥ 0.4) – dataset PRAISE T1. Degree = number of edges; Strength = sum of absolute edge weights; Betweenness = proportion of shortest paths passing through the node; Closeness = inverse of average path length to all other nodes; Eigenvector = importance based on connections to other central nodes; Community = Louvain cluster assignment.*

Variable	Degree	Strength	Betweenness	Closeness	Eigenvector	Community
Frailty	**9**	**4.736**	**0.029**	**0.227**	**0.281**	**1**
BMI	1	0.431	0.000	0.153	0.023	1
Grip	5	2.716	0.011	0.215	0.102	1
SSS	2	1.098	0.000	0.151	0.030	1
MHC_SF	5	2.696	0.000	0.163	0.083	1
MNA	7	3.783	0.052	0.234	0.288	1
SPPB	6	3.303	0.003	0.216	0.275	1
HADS_A	3	1.943	0.000	0.169	0.074	1
HADS_D	7	3.463	0.002	0.198	0.211	1
HADS_TOT	8	4.889	0.046	0.210	0.281	1
TugDTC_fast	6	3.041	0.023	0.230	0.232	1
Vitality_IC	8	4.394	0.027	0.231	0.282	1
Psy_IC	7	4.442	0.050	0.199	0.197	1
Locomotor_IC	8	4.131	0.031	0.216	0.268	1
IC_Dtglobal	**20**	**10.536**	**0.177**	**0.293**	**0.837**	**1**
IC_global	**11**	**6.004**	**0.058**	**0.259**	**0.413**	**1**
MMSE	2	0.878	0.002	0.161	0.025	2
RAVLT_I	5	2.593	0.014	0.188	0.074	2
RAVLT_D	2	1.334	0.000	0.161	0.016	2
Fluency	7	3.553	0.071	0.237	0.188	2
NPA	5	2.841	0.042	0.185	0.048	2
LPA	2	0.811	0.000	0.143	0.010	2
MPA	4	2.017	0.016	0.153	0.014	2
VPA	2	0.923	0.007	0.145	0.012	2
wake_efficiency	**9**	**4.476**	**0.068**	**0.212**	**0.121**	**2**
LFnu_rest	7	4.153	0.032	0.222	0.238	2
HFnu_rest	7	4.337	0.032	0.226	0.230	2
LFHF_rest	6	3.789	0.000	0.213	0.188	2
Cognition_IC	7	3.579	0.040	0.201	0.054	2
ESS	**8**	**3.671**	**0.005**	**0.213**	**0.442**	**3**
Htime	8	3.893	0.007	0.221	0.505	3
DTCSwitch	**9**	**4.856**	**0.001**	**0.238**	**0.667**	**3**
StroopDTC_Inh_1	4	2.132	0.023	0.185	0.143	3
StroopDTC_Inh_2	5	2.760	0.004	0.204	0.278	3
StroopDTC_Flex_1	5	3.108	0.000	0.218	0.333	3
StroopDTC_Flex_2	**8**	**4.299**	**0.020**	**0.234**	**0.502**	**3**
TugDTC	3	1.581	0.000	0.200	0.173	3
DeltaLfa	**13**	**6.220**	**0.023**	**0.247**	**0.729**	**3**
DeltaHFa	3	1.365	0.002	0.184	0.131	3

DeltaLF	**11**	**6.048**	**0.030**	**0.231**	**0.625**	**3**
LFnu_stand	**15**	**8.507**	**0.051**	**0.256**	**1.000**	**3**
HFnu_stand	**11**	**6.609**	**0.006**	**0.232**	**0.864**	**3**
LFHF_stand	**10**	**6.160**	**0.000**	**0.231**	**0.831**	**3**
DeltaLFHF	9	5.582	0.029	0.230	0.634	3
DT_Icdomain	**15**	**8.149**	**0.109**	**0.269**	**0.755**	**3**
Hear	2	1.070	0.000	0.160	0.026	4
Visual_acuity	6	3.086	0.026	0.198	0.171	4
PEF	5	2.927	0.018	0.208	0.121	4
sleep_efficiency	5	2.694	0.007	0.183	0.076	4
PPB	3	1.303	0.000	0.173	0.061	4
TP_rest	8	5.043	0.021	0.220	0.239	4
LFa_rest	8	4.402	0.030	0.215	0.222	4
HFa_rest	8	4.593	0.012	0.217	0.222	4
TP_stand	8	4.087	0.006	0.228	0.276	4
LFa_stand	**15**	**7.786**	**0.101**	**0.264**	**0.783**	**4**
HFa_stand	**10**	**5.712**	**0.054**	**0.226**	**0.248**	**4**
Sensorial_IC	3	1.603	0.012	0.178	0.045	4
SWAY_O_PL	2	1.816	0.000	0.901	0.000	5
SWAY_C_PL	2	1.646	0.000	0.823	0.000	5
SWAY_O_Speed	2	1.803	0.000	0.894	0.000	5
SWAY_O_maxDev	0	0.000	0.000	NA	0.000	6

MAIN FINDINGS AT PRAISE T1:

- FRAILTY: it is a more central node at T1, negatively connected to psychological wellbeing scales, to the locomotor and vitality domains, to parasympathetic driven indices of HRV and to the global composites of Intrinsic capacity.
- Contrary to what expected MMSE at T1 positively correlates with Frailty and negatively with the IC scores, the SPPB, and the vitality, sensorial and locomotor domains.
- Dual-task measures are more central and strongly connected to other communities than cognitive outcomes.
- Low Frequency indices, in relation to T0, gain centrality and are more strongly connected inside the network.

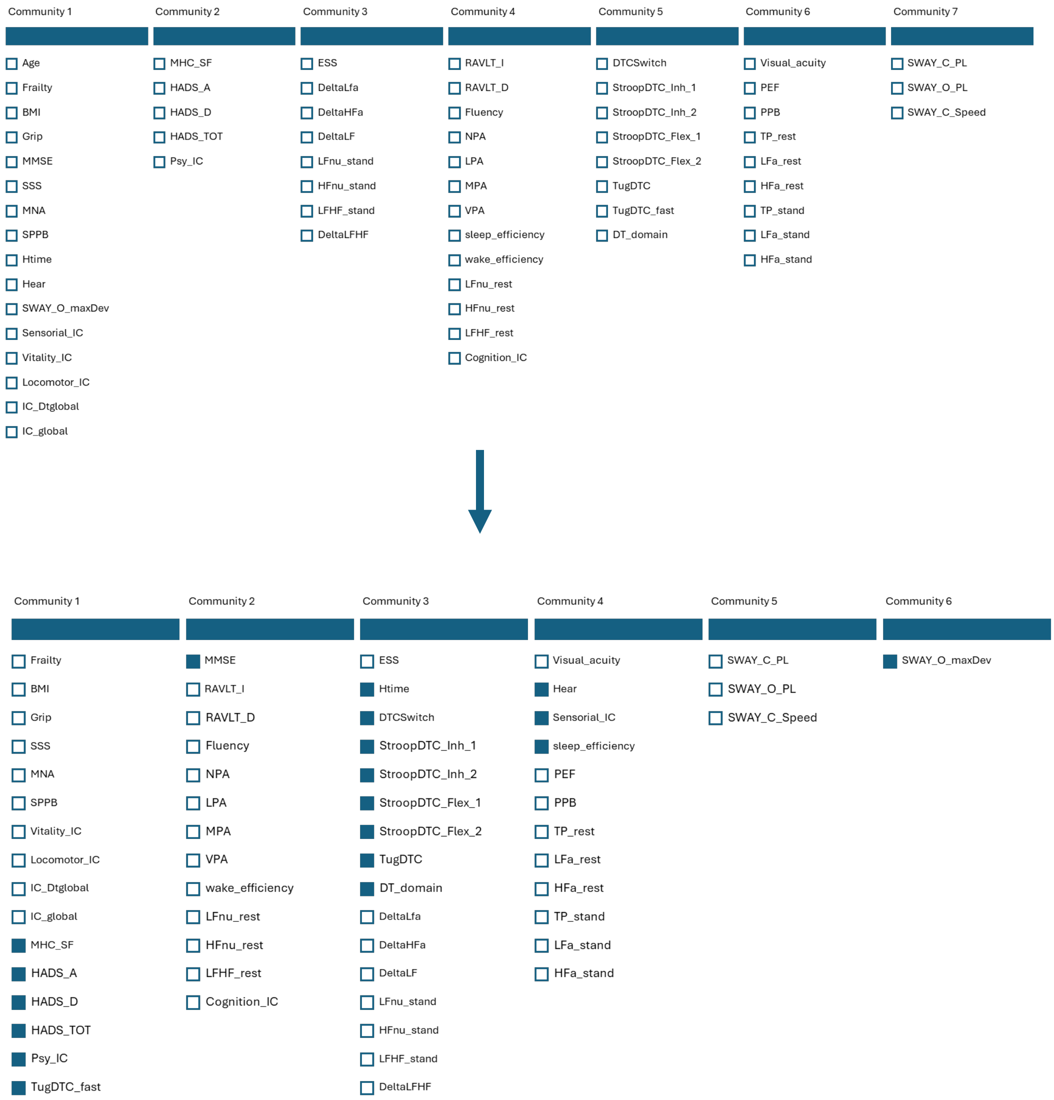


FIGURE 49. *Communities derived from Network analysis of raw (above) and age-adjusted (below) data at T1. Variables highlighted with blue squares indicate those that changed cluster membership compared with the raw data clustering, illustrating the main differences introduced by age adjustment.*

3.2.3 INTERVENTION EFFECTS

3.2.3.1 EFFECTS BETWEEN GROUPS

Mixed effect analysis is reported in Table 15, showing that significant group-by-time interactions emerged for:

- **Frailty**: The intervention group showed a greater reduction in Frailty compared to controls (Estimate = –0.047, SE = 0.020, *t* = –2.39, *p* = 0.023) (Fig. 50).
- **Grip strength**: The intervention group had a significant loss in handgrip strength compared to the control group (Estimate = –2.68, SE = 1.00, *t* = –2.69, *p* = 0.011).

- **Stroop inhibition test dual-task cost**: Significant group × time effects were found for dual-task inhibition measures (StroopDTC_Inh_1: Estimate = –0.19, *p* = 0.043; StroopDTC_Inh_2: Estimate = –0.20, *p* = 0.017), suggesting better cognitive control under dual-task conditions in the intervention group.
- **Pulmonary function (PEF)**: A significant positive effect was observed (Estimate = 36.58, SE = 15.03, *t* = 2.43, *p* = 0.021).
- **Cognition domain score**: The intervention group showed higher gains (Estimate = 0.45, SE = 0.18, *t* = 2.45, *p* = 0.020).

Several other outcomes approached statistical significance. Improvements were suggested for hearing ability (*p* = 0.063), sway speed (*p* = 0.077), and low-frequency heart rate variability during standing (*p* = 0.078). The locomotor domain scores, on the other hand, showed a trend toward significance (*p* = 0.063), with the control group improving in relation to the intervention group. No significant differences were found for BMI, MMSE, psychological scales, actigraphic activity registration, or HRV indices.

Overall, the results suggest that the intervention was associated with improvements in Frailty, aspects of dual-task and cognitive performance and pulmonary function.

TABLE 15. *Results of linear mixed-effects models testing group × time interactions for clinical, cognitive, psychological, physical performance, and physiological outcomes. Estimates represent the differential change between the intervention (S) and control (C) groups from baseline to follow-up. Standard errors (SE), degrees of freedom (DF), t values, and p values are shown, along with the number of participants contributing data in each group (N). Significant effects (p < 0.05) are observed for frailty, grip strength, Stroop dual-task cost (inhibition measures), peak expiratory flow (PEF), and the cognition domain score.*

VARIABLE	ESTIMATE	STD ERROR	DF	T VALUE	P VALUE	N C	N S
FRAILTY	**-0.047**	**0.020**	**31.616**	**-2.392**	**0.023**	15	20
BMI	-0.023	0.360	32.071	-0.064	0.950	15	20
GRIP	**-2.683**	**0.997**	**32.083**	**-2.692**	**0.011**	15	20
MMSE	-0.433	0.379	32.606	-1.141	0.262	15	20
SSS	-0.666	0.660	32.296	-1.010	0.320	15	20
MHC_SF	-2.434	3.408	30.681	-0.714	0.480	15	20
ESS	-1.087	1.132	31.419	-0.961	0.344	15	20
MNA	1.159	0.811	32.729	1.430	0.162	15	20
RAVLT_I	-0.114	2.050	32.434	-0.056	0.956	15	20
RAVLT_D	0.012	0.680	32.417	0.018	0.986	15	20
SPPB	0.840	0.653	30.980	1.286	0.208	15	20
HTIME	-4.498	5.462	30.776	-0.824	0.416	15	20
FLUENCY	-1.722	2.025	29.408	-0.850	0.402	15	20
HADS_A	-1.200	0.853	32.573	-1.407	0.169	15	20
HADS_D	0.228	1.214	32.835	0.187	0.852	15	20
HADS_TOT	-0.979	1.683	32.685	-0.582	0.565	15	20
DTCSWITCH	-0.116	0.126	31.756	-0.919	0.365	15	20

STROOPDTC_INH_1	**-0.188**	**0.089**	**32.334**	**-2.108**	**0.043**	15	20
STROOPDTC_INH_2	**-0.199**	**0.079**	**31.402**	**-2.508**	**0.017**	15	20
STROOPDTC_FLEX_1	-0.260	0.223	32.311	-1.165	0.253	15	20
STROOPDTC_FLEX_2	-0.263	0.196	32.362	-1.341	0.189	15	20
TUGDTC	6.717	5.841	28.045	1.150	0.260	14	19
TUGDTC_FAST	-11.537	8.421	29.233	-1.370	0.181	14	19
HEAR	0.183	0.095	31.155	1.930	0.063	15	20
VACUITY	-0.087	0.073	31.978	-1.191	0.243	15	20
PEF	**36.579**	**15.027**	**28.427**	**2.434**	**0.021**	15	20
SENSORIAL_D	-0.016	0.210	30.000	-0.076	0.940	15	17
IC	0.037	0.130	30.000	0.282	0.780	15	17
IC_DT	0.105	0.117	30.000	0.895	0.378	15	17
PSYCHOLOGICAL_D	0.153	0.154	30.000	0.991	0.329	15	17
LOCOMOTOR_D	-0.430	0.223	30.000	-1.927	0.063	15	17
COGNITION_D	**0.445**	**0.181**	**30.000**	**2.453**	**0.020**	15	17
VITALITY_D	0.044	0.271	30.000	0.161	0.873	15	17
DUALTASK_D	0.385	0.364	30.000	1.058	0.298	15	17
NPA	-0.439	1.329	30.824	-0.331	0.743	15	20
LPA	1.624	1.390	31.099	1.169	0.251	15	20
MPA	-1.036	1.384	30.679	-0.749	0.460	15	20
VPA	-0.138	0.099	30.192	-1.388	0.175	15	20
SLEEP_EFFICIENCY	-1.266	2.059	31.007	-0.615	0.543	15	20
WAKE_EFFICIENCY	-1.219	1.725	30.959	-0.706	0.485	15	20
PPB	0.179	0.313	31.536	0.572	0.571	15	20
SWAY_O_PL	-52.815	34.504	33.000	-1.531	0.135	15	20
SWAY_C_PL	-12.696	69.031	32.125	-0.184	0.855	15	20
SWAY_O_MAXDEV	-7.698	7.723	66.000	-0.997	0.323	15	20
SWAY_O_SPEED	-2.115	1.159	33.000	-1.825	0.077	15	20
TP_REST	725.942	495.209	28.987	1.466	0.153	15	19
LFA_REST	77.236	89.962	29.386	0.859	0.398	15	19
HFA_REST	100.511	156.868	29.663	0.641	0.527	15	19
LFNU_REST	-0.272	9.170	25.250	-0.030	0.977	15	19
HFNU_REST	1.734	8.927	27.175	0.194	0.847	15	19
LFHF_REST	-0.626	0.589	53.000	-1.062	0.293	15	19
DELTALF	9.369	13.081	24.978	0.716	0.480	15	19
TP_STAND	97.008	338.693	29.122	0.286	0.777	15	19
LFA_STAND	107.393	58.753	27.979	1.828	0.078	15	19
HFA_STAND	20.323	58.492	23.688	0.347	0.731	15	19
LFNU_STAND	10.612	10.829	26.032	0.980	0.336	15	19
HFNU_STAND	-6.441	9.457	24.778	-0.681	0.502	15	19
LFHF_STAND	0.062	1.325	23.357	0.047	0.963	15	19
DELTALFHF	0.766	1.239	21.225	0.618	0.543	15	19
DELTAHFA	22.425	33.690	24.495	0.666	0.512	15	19
DELTALFA	12.837	82.496	53.000	0.156	0.877	15	19

Results were largely consistent when missing values were imputed using median substitution. Significant effects were again observed for Frailty (Estimate = –0.046, *p* = 0.016), handgrip strength (Estimate = –2.58, *p* = 0.013), Stroop dual-task inhibition measures (StroopDTC_Inh_1: *p* = 0.032; StroopDTC_Inh_2: *p* = 0.015), and the cognition domain score (Estimate = 0.41, *p* = 0.020).

However, some differences were noted. In the sensitivity analysis, the peak of expiratory flow (PEF) no longer reached statistical significance (*p* = 0.144), while LFa during standing became significant (Estimate = 95.44, *p* = 0.042), and hearing ability showed a stronger trend toward significance (*p* = 0.051).

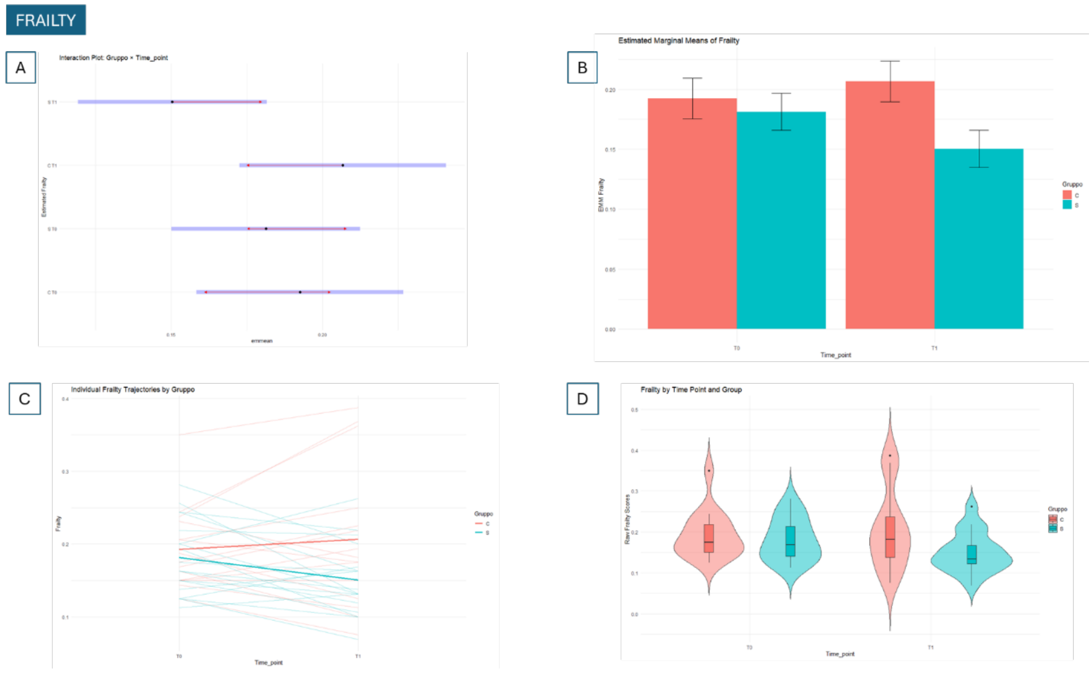


FIGURE 50. *Interaction plot group x time point of frailty (A). Estimated marginal means of frailty across group (C → Control group in orange; S → study group in light blue) and time points (T0 and T1) (B). Individual Frailty trajectories by group (C). Distribution of raw frailty index scores by group and time points (D). The intervention group showed a greater reduction in Frailty Index compared to controls.*

3.2.3.2 Effects Within Group

In addition to the between-group interaction results reported above, within-group contrasts analysis (using both omission and median substitution for missing values) clarified the nature of change within each arm. In the intervention group (S), significant within-group improvements or changes from baseline to follow-up were observed on multiple outcomes. Key findings, reported for the “omit” analysis (estimate = mean change T1 − T0, SE, df, *t*, *p*) for the S group included:

- **Frailty:** mean change = –0.0328, SE = 0.0134, df = 31.56, *t* = –2.45, *p* = 0.0199 (reduction in Frailty).

- **Grip strength:** mean change = –2.2780, SE = 0.6619, df = 32.09, t = –3.44, p = 0.0016 (diminished muscle strength).
- **Short Physical Performance Battery (SPPB):** mean change = +1.4402, SE = 0.4436, df = 32.17, t = 3.25, p = 0.0027 (improved physical function).
- **Epworth Sleepiness Scale (ESS):** mean change = –1.6873, SE = 0.7609, df = 31.90, t = –2.22, p = 0.0338 (reduced daytime sleepiness).
- **HADS Anxiety Scale:** mean change = –1.3999, SE = 0.5651, df = 32.59, t = –2.48, p = 0.0186 (reduced anxiety symptoms).
- **Dual-task cost of Switching task:** mean change = –0.1935, SE = 0.0857, df = 32.40, t = –2.26, p = 0.0308 (improved dual-task switching).
- **Cognitive inhibition dual-task cost (StroopDTC_Inh_2):** mean change = –0.1166, SE = 0.0535, df = 33.03, t = –2.18, p = 0.0365 (reduced inhibition cost under dual task).
- **Light Physical activity (LPA):** mean change = +2.0843, SE = 0.9477, df = 31.25, t = 2.20, p = 0.0354 (increase in light activity).
- **Moderate Physical activity (MPA):** mean change = –3.4362, SE = 0.9455, df = 30.68, t = –3.63, p = 0.0010 (decrease in moderate activity).

Several of these within-group changes in the intervention arm are coherent with the significant group x time interaction effects reported in the primary analysis (notably Frailty and Stroop inhibition dual costs), indicating that the intervention arm experienced substantive within improvements that contributed to the observed between-group differences.

The control group (C) also showed a small number of significant within-group changes that warrant consideration. Notably: StroopDTC_Inh_1 increased in controls (mean change = +0.1391, SE = 0.0657, df = 30.39, p = 0.042), suggesting a worsening of cognitive inhibition; hearing capacity showed significant within-group shifts in controls (Hearing: mean change = –0.1538, SE = 0.0713, p = 0.039), suggesting greater impairments; on the other hand visual acuity had a trend in the opposite direction (Vacuity: mean change = +0.1347, SE = 0.0545, p = 0.019).

In Table 16 mean and standard deviation are reported for all variables, for both groups across timepoints, for clarity.

Overall, the within-group contrasts from both the "omit" and "median" analysis support the interpretation that the intervention produced meaningful gains/improvements in Frailty, physical performance measured through SPPB, some aspects of cognitive dual-tasking, daytime sleepiness, and anxiety.

TABLE 16. *Descriptive statistics (means and standard deviations) of clinical, cognitive, psychological, physical, and physiological variables at baseline (T0) and follow-up (T1) for control (C) and intervention/study (S) groups.*

Values in bold indicate mean and SD pairs that were significantly different in within-group analyses across timepoints.

VARIABLE	GROUP	MEAN T0	SD T0	MEAN T1	SD T1
FRAILTY	C	0.193	0.057	0.207	0.099
FRAILTY	**S**	**0.184**	**0.049**	**0.149**	**0.050**
BMI	C	25.475	4.429	25.198	4.495
BMI	S	25.644	2.404	25.276	2.375
GRIP	C	21.245	7.660	21.651	8.198
GRIP	**S**	**26.157**	**9.810**	**24.088**	**7.734**
MMSE	C	27.700	1.294	27.987	0.770
MMSE	S	27.305	0.963	27.174	1.197
SSS	C	6.533	2.503	6.600	2.558
SSS	S	5.950	2.724	5.421	1.835
MHC_SF	C	38.267	11.677	36.867	11.789
MHC_SF	S	38.700	11.131	34.222	10.282
ESS	C	7.533	4.673	6.933	4.906
ESS	**S**	**6.000**	**4.205**	**4.389**	**2.380**
MNA	C	26.867	2.150	26.267	3.396
MNA	S	26.825	1.370	27.368	1.862
RAVLT_I	C	51.247	7.896	53.580	9.112
RAVLT_I	S	55.660	7.712	57.789	6.089
RAVLT_D	C	11.804	2.685	12.607	3.190
RAVLT_D	S	12.445	2.207	13.232	2.484
SPPB	C	8.533	1.642	9.133	2.295
SPPB	**S**	**9.450**	**1.820**	**10.765**	**1.300**
HTIME	C	97.533	17.828	101.200	18.276
HTIME	S	83.850	21.847	82.412	22.858
FLUENCY	C	37.133	11.488	38.000	8.384
FLUENCY	S	40.900	10.857	38.000	7.992
HADS_A	C	7.200	2.426	7.000	3.071
HADS_A	**S**	**6.950**	**2.685**	**5.579**	**2.589**
HADS_D	C	6.000	3.338	5.000	3.854
HADS_D	S	4.600	2.280	3.842	1.214
HADS_TOT	C	13.200	3.913	12.000	6.425
HADS_TOT	S	11.550	3.873	9.421	3.006
DTCSWITCH	C	0.543	0.473	0.466	0.281
DTCSWITCH	**S**	**0.429**	**0.334**	**0.251**	**0.149**
STROOPDTC_INH_1	**C**	**0.133**	**0.169**	**0.272**	**0.291**
STROOPDTC_INH_1	S	0.247	0.228	0.202	0.115
STROOPDTC_INH_2	C	0.125	0.163	0.207	0.211
STROOPDTC_INH_2	**S**	**0.179**	**0.202**	**0.065**	**0.104**
STROOPDTC_FLEX_1	C	1.261	0.796	1.398	0.726
STROOPDTC_FLEX_1	S	1.070	0.444	0.955	0.358
STROOPDTC_FLEX_2	C	1.232	0.704	1.262	0.556
STROOPDTC_FLEX_2	S	0.954	0.391	0.733	0.320
TUGDTC	C	5.601	14.656	0.378	16.974

TUGDTC	S	-3.050	11.040	-1.287	15.277
TUGDTC_FAST	C	13.350	15.539	25.599	25.645
TUGDTC_FAST	S	8.971	14.317	9.511	15.320
HEAR	**C**	**0.525**	**0.393**	**0.366**	**0.362**
HEAR	S	0.681	0.331	0.700	0.372
VACUITY	**C**	**0.669**	**0.227**	**0.803**	**0.188**
VACUITY	S	0.707	0.233	0.746	0.207
PEF	C	305.587	129.909	297.157	138.307
PEF	S	307.311	86.277	321.771	88.364
SENSORIAL_D	C	-0.093	0.744	-0.066	0.770
SENSORIAL_D	S	0.082	0.592	0.093	0.689
IC	C	-0.131	0.509	-0.119	0.553
IC	S	0.115	0.424	0.164	0.277
IC_DT	C	-0.128	0.500	-0.155	0.532
IC_DT	S	0.109	0.378	0.187	0.270
PSYCHOLOGICAL_D	C	-0.104	0.810	-0.178	0.938
PSYCHOLOGICAL_D	S	0.092	0.723	0.170	0.576
LOCOMOTOR_D	C	-0.125	0.846	0.177	0.658
LOCOMOTOR_D	S	0.110	0.650	-0.018	0.739
COGNITION_D	C	-0.116	0.703	-0.336	0.676
COGNITION_D	S	0.079	0.642	0.303	0.522
VITALITY_D	C	-0.134	0.747	-0.138	1.002
VITALITY_D	S	0.118	0.759	0.158	0.564
DUALTASK_D	C	-0.197	0.945	-0.339	1.182
DUALTASK_D	S	0.174	1.043	0.416	0.656
NPA	C	33.940	3.909	35.833	5.395
NPA	S	34.647	6.314	36.022	7.606
LPA	C	36.427	5.338	36.887	5.638
LPA	**S**	**34.368**	**5.661**	**36.394**	**5.377**
MPA	**C**	**28.993**	**6.051**	**26.593**	**7.223**
MPA	**S**	**30.179**	**8.916**	**26.939**	**7.520**
VPA	C	0.653	0.623	0.687	0.726
VPA	S	0.795	0.654	0.644	0.691
SLEEP_EFFICIENCY	C	73.120	8.115	73.507	8.511
SLEEP_EFFICIENCY	S	75.500	10.508	74.733	9.358
WAKE_EFFICIENCY	C	90.973	6.013	90.227	4.799
WAKE_EFFICIENCY	S	90.226	6.180	87.928	8.433
PPB	C	1.840	0.889	1.720	0.963
PPB	S	1.953	0.717	1.978	1.041
SWAY_O_PL	C	370.992	106.039	397.387	147.944
SWAY_O_PL	S	393.140	161.036	366.720	136.851
SWAY_C_PL	C	570.036	199.326	609.120	303.169
SWAY_C_PL	S	618.657	364.054	619.820	472.294
SWAY_O_MAXDEV	C	15.537	4.056	22.213	32.283
SWAY_O_MAXDEV	S	18.237	8.965	17.215	5.239
SWAY_O_SPEED	C	12.252	3.499	13.493	5.007

SWAY_O_SPEED	S	13.098	5.365	12.225	4.555
TP_REST	C	1340.793	1340.455	1082.824	963.825
TP_REST	S	889.942	734.595	1297.056	1479.106
LFA_REST	C	159.543	181.655	194.050	154.712
LFA_REST	S	125.016	112.126	230.068	308.078
HFA_REST	C	216.751	269.562	240.741	290.558
HFA_REST	S	159.571	184.854	290.346	637.270
LFNU_REST	C	38.188	19.559	44.824	23.259
LFNU_REST	S	39.828	17.980	44.009	16.300
HFNU_REST	C	53.269	18.318	45.917	22.767
HFNU_REST	S	49.502	15.979	44.929	12.675
LFHF_REST	C	0.961	0.850	1.725	1.915
LFHF_REST	S	1.018	0.786	1.156	0.746
DELTALF	C	7.765	20.046	-4.916	29.824
DELTALF	S	17.628	34.899	14.289	11.833
TP_STAND	C	810.872	808.398	821.092	901.121
TP_STAND	S	760.881	763.409	891.200	454.692
LFA_STAND	C	116.665	128.284	89.090	101.762
LFA_STAND	S	140.832	129.441	223.726	179.454
HFA_STAND	C	111.629	156.379	66.138	55.894
HFA_STAND	S	131.282	194.083	134.916	136.904
LFNU_STAND	C	45.953	21.665	39.907	25.382
LFNU_STAND	S	57.456	22.859	60.505	16.462
HFNU_STAND	C	39.639	19.664	44.521	21.709
HFNU_STAND	S	32.882	16.750	31.834	13.827
LFHF_STAND	C	2.145	2.945	1.786	2.477
LFHF_STAND	S	2.969	2.945	2.507	1.741
DELTALFHF	C	1.183	2.824	0.062	2.084
DELTALFHF	S	1.951	3.283	1.351	1.799
DELTAHFA	C	-45.433	58.604	-54.911	24.196
DELTAHFA	S	-22.340	76.500	-8.424	77.334
DELTALFA	C	1.605	112.801	-47.752	61.374
DELTALFA	S	111.339	223.942	74.818	134.436

MAIN FINDINGS OF THE INTERVENTION:

- Intervention vs Control: reduced Frailty and Grip strength, improved performance in dual-task Stroop Inhibition, cognitive domain and pulmonary function (PEF). Increase of LF standing absolute power in the "median" analysis.
- Intervention group: reduced Frailty, daytime sleepiness, anxiety, moderate physical activity (MPA) and Grip strength. Improved dual-task performance on Switching task and Stroop Inhibition, physical performance (SPPB) and increased light physical performance (LPA).
- Control group: worsening of hearing abilities and dual-task Stroop Inhibition performance. Reduced moderate physical activity (MPA) and improved visual acuity.

CHAPTER 4

PRAISE: DISCUSSION OF THE RESULTS

This chapter will focus on the discussion of the results at T0 and T1, from the associations between the variables chosen for the assessments to the intervention effects.

As a general comment while the effects of the intervention are undoubtedly of great relevance in this experimental interventional study, the most critical findings emerge from the analysis of the interrelationships among the multiple variables used to functionally characterize the participants. This is the first multidimensional study to integrate such a wide range of variables, therefore, beyond evaluating the outcomes of the intervention itself, it is essential to first understand how these variables are interconnected. This analysis provides a functional 'snapshot' of how the system integrates its various resources, shedding light on the underlying connections and mechanisms. It is within this framework that the results of the intervention can be meaningfully interpreted. As such, the discussion of baseline (T0) data represents the most crucial part of this study, even more so than the post-intervention findings.

The first section will be exploring the assessment results, the networks and clusters, by focusing on two main topics: Frailty and Heart Rate Variability.

4.1 ASSESSMENT RESULTS

4.1.1 FRAILTY

FRAILTY AT T0. Surprisingly, at baseline Frailty did not occupy a central, network-hub position. This may be due to the fact that the subjects were selected based on Frailty level, therefore resulting in a relatively narrow distribution of Frailty scores. Restricted variability reduces correlation strength with other measures and, in turn, lowers centrality estimates in network models (Epskamp et al., 2018). Thus, the lack of centrality does not indicate that Frailty is not relevant in multi-domain ageing, rather it reflects the baseline condition of this sample.

Even if it did not show a large set of associations with other communities or clusters, the analysis showed that Frailty had a distinct pattern of correlations. A higher Frailty Index significantly correlated with weaker grip strength (Spearman's ρ = -0.52, FDR-adjusted p < .0001), lower Intrinsic Capacity (IC) (ρ = -0.52, FDR-adjusted p < .0005) and also lower dual-task Intrinsic Capacity (IC_DT) (ρ = –0.49, FDR-adjusted p = .001). Within the IC subdomains, Frailty was negatively related to locomotor domain scores (ρ = –0.40, FDR-adjusted p = .02), psychological domain (ρ = –0.37, p = .0040), and vitality domain (ρ = –0.48, FDR-adjusted p = .04).

Specifically, Frailty correlated negatively with nutritional status (MNA) (ρ = –0.37, FDR-adjusted p = .04), six-minute walking test (6MWT) (ρ = –0.50, FDR-adjusted p = .01), and Short Physical Performance Battery (SPPB) scores (ρ = –0.44, FDR-adjusted p = .006). Conversely, Frailty correlated positively with anxiety and depression symptoms (HADS_TOT, HADS_A, HADS_D) (HADS_TOT: ρ = 0.39, FDR-adjusted p = .02). Moreover, in the dataset praise HRV T0, Frailty correlated positively also with normalized high frequencies in standing (ρ = 0.38, p = .03) and the dual task cost of the Stroop test (ρ = 0.46, p = .01), even if these associations did not survive FDR corrections (Fig. 51). These data suggest that Frailty displayed a distinct profile of associations, marked by significant correlations with physical and psychological performance measures. While some additional associations emerged, not all remained significant after correction, underscoring the specificity of the main findings.

Specifically, the inverse IC-Frailty relationship and the positive Frailty–Stroop cost association suggests the convergence of reduced adaptive capacity, affective burden and poorer inhibitory control in pre-frail individuals; this configuration plausibly reduces resilience to external demands and increases the risk of functional loss.

Frailty and HRV. In the clustering and networks community analyses Frailty grouped together with autonomic indices (dataset PRAISE HRV T0) specifically ΔLF% (the percentage change in low-frequency absolute power) and resting supine normalized-unit HRV measures (LFnu/HFnu); these association may reflect common underlying physiological resources that only emerge when there are not medical or pharmaceutical confounders and may be more evident in larger and heterogenous cohorts. Moreover, interpreting HRV findings requires caution: normalized units represent the *relative* spectral allocation (LFnu, HFnu, LF/HF) rather than absolute autonomic tone; therefore, shifts in LFnu reflect reductions in HF power (parasympathetic withdrawal) as much as increases in sympathetic modulation (Billman, 2013). On the other hand ΔLF% plausibly captures autonomic responsiveness to the posture challenge, and orthostatic reactivity is often more sensitive to reduced physiological reserve than resting and absolute HRV indices (Laborde et al., 2017).

The adjacency of Frailty to autonomic reactivity indices may suggests that a component of physiological dysregulation co-occurs with cognitive and affective vulnerabilities, in line with the Neurovisceral Integration Model. From an intervention perspective, these results support targeting executive function under dual-task training together with measures aimed at improving autonomic adaptability. However, because normalized measures are mathematically interdependent (see 4.1.2 for an extended explanation) and susceptible to preprocessing choices, the presence of a Frailty-HRV cluster in this sample should be probed further in larger, heterogenous cohorts with careful control for medications and respiration.

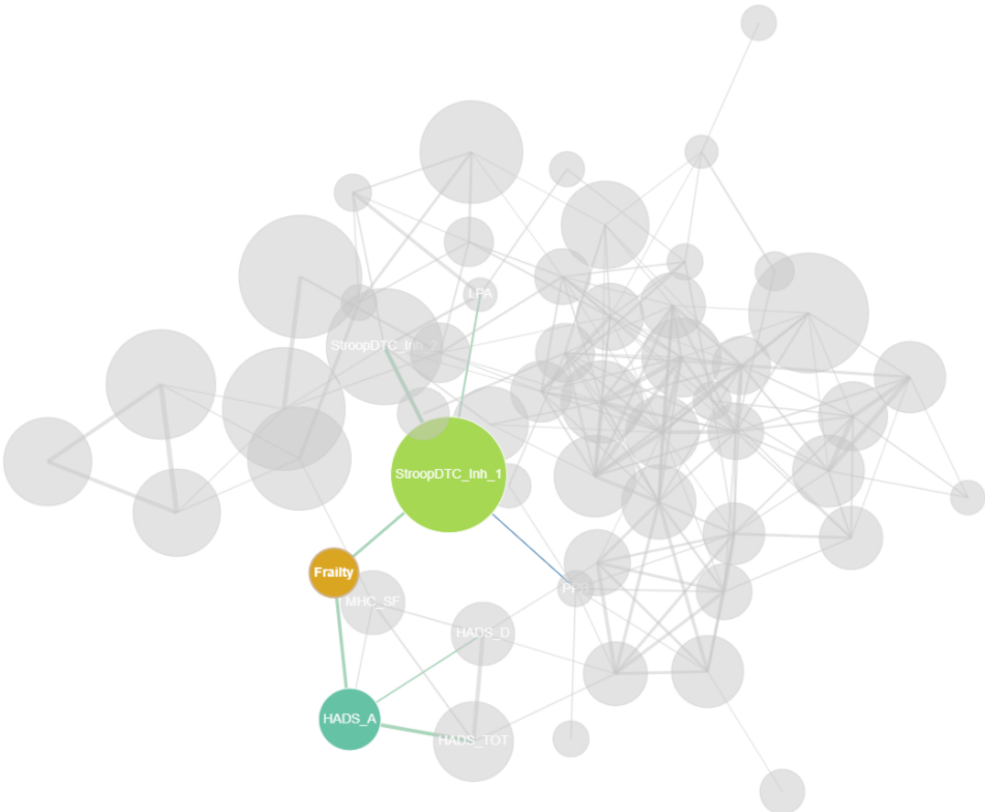


FIGURE 51. *Visual Network of PRAISE HRV T0 at threshold |r| ≥ 0.40. The selected variable, Frailty, is linked through positive associations (green edges) to anxiety symptoms (HADS_A) and a greater dual-task cost of cognitive inhibition (StroopDTC_Inh-1). The visual interactive network is visible at [The Adaptive Potential of a Multi-Domain System](https://lucia-pp.github.io/PRAISE/) (https://lucia-pp.github.io/PRAISE/).*

Frailty at T1. At T1 (N=35) Frailty had a much greater distribution across the sample, therefore in network and correlational analysis it increased its relevance and assumed a more central and connected role (Fig.52). Confirming the T0 scenario, at T1 Frailty was negatively associated to several IC scores and domains (IC, dual-task IC, locomotor, psychological and vitality domain), reflecting the inverse relationship between perceived and assessed deficits (Frailty Index), and functional resources (IC). It was also negatively associated to physical performance measures (SPPB and PPB- pseudo periodic behaviour), and a greater index was also found to correlate with a worst social support (SSS) and depressive symptoms (HADS_D, HADS_TOT). Notably, at T1 the strength of Frailty connection with HRV indices increased, in particular in relation to standing HFa and TP - both reflecting parasympathetic activity - and ΔHF% i.e. parasympathetic withdrawal. It was also negatively associated to pulmonary function (PEF: ρ = -0.43, p = .013) and handgrip strength (Grip: ρ = -0.65, FDR-adjusted p = .001). Contrary to expected results MMSE positively correlated with FI (ρ = 0.54, FDR-adjusted p = .017); this apparent contradictory result may be due to the "near top ceiling performance" in the screening test, which may be too simple to discriminate between pre-frail subjects. Indeed, MMSE scores at T1 also negatively correlated with IC variables (IC, dual-task IC, sensorial, locomotor and vitality domains), grip strength and SPPB, all results contrary to current literature on the association between cognitive and physical capacities.

The T0–T1 comparison shows that Frailty becomes a more central and connected node over time, displaying stronger and more numerous correlations with functional, psychological, social, and autonomic domains. These findings reinforce the view of Frailty as a complex and multidimensional marker, whose impact is more noticeable with the progression of the clinical-functional profile. Despite Frailty becoming more central and interconnected at T1, the improvement observed in a subset of participants highlights the dynamic and potentially reversible nature of pre-Frailty. These findings suggest that multi-domain functional trajectories can shift in response to internal or external resources, reinforcing the importance of early, targeted interventions aimed at strengthening physiological reserve and psychosocial resilience.

FRAILTY IN A PRE-FRAIL POPULATION. It must be noted that these data reflect the interconnections of behavioural and physiological functions in a specific population of pre-frail older adults. Stratified larger studies, confronting frail, pre-frail and robust individuals could therefore intel different patterns according to available functional and neurovegetative resources. Nonetheless, the thorough assessment of this pilot study confirmed previous research while highlighting novel critical systemic outcomes. **Frailty** connection to **mobility capacities** (SPPB, 6MWT) and nutritional state (MNA) was expected and it aligns with previous research (Apóstolo et al., 2018a; Kim & Rockwood, 2024; Ng et al., 2015; Racey et al., 2021). Our research highlighted the close connection of pre-Frailty and **psychological distress**, aligning with a multi-domain biopsychosocial vision of the construct (C. I. Cohen et al., 2023), and supporting research showing how psychological wellbeing can impact the incidence of Frailty (Brennan et al., 2025; Gale et al., 2014).

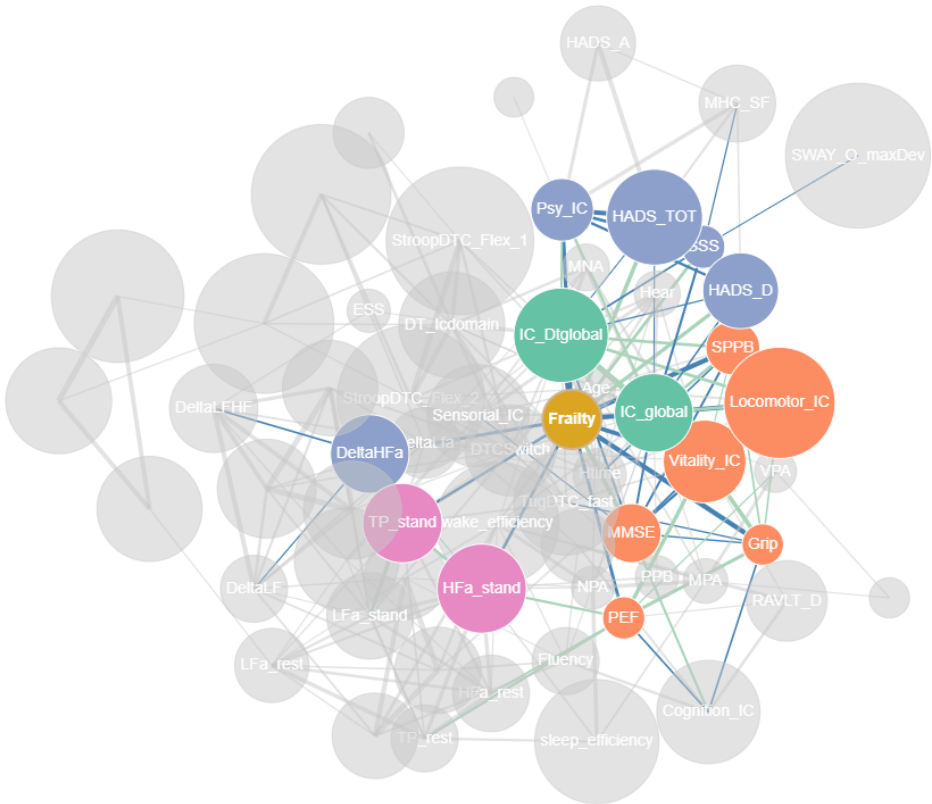


FIGURE 52. *Visual Network at T1 with threshold |r| ≥ 0.40. The selected variable, Frailty, is linked through positive associations (green edges) to SSS (worst social support), MMSE, HADS_D and HADS_TOT. It is negatively linked (blue edges) to IC scores and domains, grip strength, SPPB, PEF and parasympathetic indices (ΔHF%, HFa_stand, TP_stand). The visual interactive network is visible in the study repository: The Adaptive Potential of a Multi-Domain System.*

The **MMSE**, although being one of the items used to derive the Frailty Index, did not show a strong connection with FI in our pre-frail sample at T0, and actually showed a positive correlation at T1, suggesting that greater Frailty is associated with better global cognition. This apparent contradiction may be due to the almost near ceiling performance in the screening test (variance distribution of the scores was mostly due to the age and years of education correction, but the actual mean performance was high for almost every subject), that may be not sensitive enough to characterize subtle changes in cognitive performance – presumably occurring in pre-frail individuals (Macuco et al., 2012). **Dual-task** testing, on the other hand, by challenging the system, yielded stronger associations with functional reserves (IC) and also relatively (through the DT Stroop) with Frailty. Another parameter connected to pre-Frailty was HRV (especially at T1), showing that a greater FI correlates with **lower parasympathetic drive**, both while standing and as a percentage change of HF when the system needs to adjust and adapt to an external request (active standing), an outcome underexplored in literature. Coupling physiological and functional dual-task challenges allowed for a deeper understanding of the affected multi-domain system in a pre-frail population by probing its functionality. In particular, the study highlighted how psychological well-being, neurovegetative flexibility and dual-task capacities may be parameters to attention more closely for the prevention of Frailty.

4.1.2 HRV

The presented findings at PRAISE HRV T0 highlight the distinction of different autonomic and cognitive profiles in a population of pre-frail older adults. Network analysis showed a robust highly connected hub of cognitive, dual-task and HRV indices. The discussion of the data and results cannot be separated from a critical consideration of the specific HRV measures used, as the choice of indices can substantially influence the interpretation.

Two populations within our sample. Starting from a broad multidimensional dataset, encompassing fitness level, psychological and social wellbeing, cognitive functioning, dual task capabilities, autonomic regulation, and general physiological status, a mixed cluster of HRV and cognitive variable was identified. Within this set two subgroups were distinguished through secondary clustering analysis. Subjects in Cluster 1 were characterized by better neuropsychological and dual-task performance, alongside less pronounced autonomic response to orthostatic stress. In contrast, Cluster 2 showed poorer cognitive outcomes and dual-task efficiency, coupled with greater gain in normalized low frequency (ΔLFnu) activation during postural change. Specifically, Cluster 1 performed significantly better in immediate verbal recall (RAVLT I), phonemic verbal fluency (PVF), and also showed a lower cognitive cost during the dual task Timed Up and Go (TugDTC and TugDTC_fast). On the other hand, Cluster 2 was characterized by a significant greater ΔLFnu and ΔLF/HF suggesting an increase in sympathetic modulation upon standing according to previous research (Lucini et al., 2017; Montano et al., 1994; Nicolini et al., 2020, 2022; Shaffer & Ginsberg, 2017). However, LFa did not significantly differ between groups in either position. Rather, Cluster 2 exhibited a more substantial drop in HFa activity in response to the orthostatic challenge, pointing to a parasympathetic withdrawal.

Parasympathetic withdrawal. These findings align with the interpretation of reciprocal nature of normalized HRV indices (Heathers, 2014; Reyes del Paso et al., 2013); in light of the fact that LFnu and HFnu are calculated relative to total power minus the VLF component, any reduction in one band (in this case HFa) will inherently elevate the other (here LFnu), even in the absence of changes in absolute LF power. The significant rise in ΔLFnu and ΔLF/HF, in this context could be better explained by a sharper decline in HFa, rather than a true increase in absolute LF power, suggesting that it is the amount of parasympathetic withdrawal, rather than the apparent absolute increase (actually not occurring) of sympathetic tone (indexed as ΔLFnu), the main distinguishing factor between the two clusters and, above all, the real marker of the adaptive power of the neurovegetative system to homeostatic challenges.

Parasympathetic withdrawal and cognition. The association between the dynamic autonomic balance and cognitive functions was further supported by correlation analyses. A steeper parasympathetic withdrawal, represented by a more negative ΔHF%, correlated with worse performance on the phonemic verbal fluency test (PVF), delayed verbal memory recall (RAVLT D), and increased cognitive cost during a working memory dual-task TUG. A greater gain in low frequency activity, ΔLFnu, was associated with poorer cognitive performance during the PVF, the immediate and delayed recall of the RALVT, and with a greater cognitive cost during the dual task TUG. A greater ΔHFnu was only associated with a worst performance during the cognitive TUG. Importantly, LFa did not significantly correlate with any cognitive outcome in either position, while HFa during active standing correlated with the cognitive TUG performed at a normal pace and the immediate verbal memory recall (RAVLT I), also showing a trend towards significance for the delayed RAVLT (RAVLT D) and the phonemic verbal fluency.

ΔLFnu vs ΔHF%. Some of the few studies to our knowledge directly investigating the complexity of the autonomic dynamic balance as measured in response to a sympathetic challenge and cognitive functioning, are the ones by Nicolini and colleagues (Nicolini et al., 2020, 2022). In these studies, researchers found that a greater ΔLFnu predicted a faster decline in episodic memory in MCI patients; the authors argued that a higher gain in LFnu could be associated to an hyperactivation of those cerebral areas generating sympathetic outflow and underpinning cognitive functions such as episodic memory. Our study targeted healthy ageing adults and added ΔHRV% (Grant et al., 2012; Rani et al., 2022) as a possible measure to estimate shifts in autonomic balance. It is the first study to our knowledge to investigate the interplay between percentage shifts in autonomic balance and cognitive functions. ΔLFnu could possibly reflect either an actual raise in LFa, a drop in HFa, or both. ΔHF% on the other hand reflects the shift in HFa from supine to standing, not as a mere difference, that wouldn't be comparable between subjects given the great interindividual physiological differences in absolute HRV measures, but in that it quantifies the relative change in HFa power activity from the baseline. This measure, expressed in percentage for practicality, allows to directly compare the dynamic adaptive responses across subjects in each frequency band.

A flexible system. The analysis of all the presented indices of HRV supports the interpretation of an exaggerated autonomic shift under orthostatic challenge in Cluster 2, consistent with a parasympathetic withdrawal rather than a sympathetic gain. These results are in line with the neurovisceral integration model (NVI) (Thayer et al., 2009) and the role of parasympathetic system in cognitive functioning. In literature, indices referring to the parasympathetic branch of the autonomic system are found to be positively associated with different cognitive functions, such as cognitive flexibility, working memory and attention. Higher parasympathetic tone, reflected by greater HF, is considered a marker of better top-down regulatory capacity (Eggenberger et al., 2020; Forte et al., 2019; Mahinrad et al., 2016; Thayer, Sollers, et al., 2009). According to the NVI theory, higher HRV may represent a physiological marker of a more flexible and balanced system better equipped to manage cognitive demands. Smith and colleagues (Smith et al., 2017) extended this view by arguing that HRV is a reflection of the brain's ability to hierarchically integrate and regulate cognitive functions and bodily states via Bayesian inferences and predictive coding mechanisms. In this framework, flexible adaptations to environmental demands are enabled by prefrontal networks. The brain continuously generates predictions about internal and external states, allowing for the allocation of both cognitive and physiological resources in advance of actual needs. When predictions align with input requests, a less effortful processing is needed, and resources are preserved. A higher HRV could therefore be an indicator of the system's ability to better minimize prediction errors, leading to a more balanced and flexible system capable to adjust to autonomic and cognitive requests in real time.

This is well depicted in our study, designed to investigate the network response to an induced perturbation in the autonomic balance, and how this adaptive response, as measure of the flexibility of the system, relates to cognitive and dual task demands. Studying the dynamicity and flexibility of this hierarchical network, by imposing an orthostatic challenge, led to novel and underrepresented insights on how the system regulates the resources needed to meet different yet connected demands.

The association between the greater cognitive performance and the autonomic stability observed in Cluster 1 may reflect more efficient predictive updating and error minimization, consistent with higher NVI functioning. In contrast, the exaggerated autonomic reactivity observed as a parasympathetic withdrawal in Cluster 2 may index a less adaptive system, characterized by reduced model precision in predicting system needs and/or in allocating resources, possibly suggesting an impaired integration across levels of the NVI hierarchy.

HRV, COGNITION AND MOTOR ABILITIES. Interestingly, the absence of between-group differences in motor and balance performances (6MWT, SWAY) further supports the specificity of autonomic-cognitive associations, independently of overall fitness level, a result not expected. While indeed in young adults physical fitness is usually associated with greater total HRV (Dorey et al., 2019; Grant et al., 2012; Lucini et al., 2017; Souza et al., 2021), the three-way association between HRV, cognition and physical fitness appears fragile and not consistent when referring to older adults (De Oliveira Matos et al., 2020; Eggenberger et al., 2020). The lack of motor-based differences between the two subgroups may also suggest that autonomic efficiency may be more relevant in association to complex task request than basic locomotor demands.

Interestingly, no associations were found between ΔHRV indices and performance on the Stroop task performed on the Dividat Senso, or the H Cancellation test. These tasks are usually implemented to assess executive functioning, such as inhibitory control and selective attention. The absence of associations with HRV parameters may indicate that not all the subdomains of executive functions are equally sensitive to autonomic networks regulation. In the specific, the execution timing of the Letter H Cancellation task, executed with near-ceiling performance, relies more on visual scanning and processing speed, rather than on complex cognitive demands. Regarding the Stroop test, the relationship between HRV parameters and cognitive inhibition appears to be inconsistent in previous research (De Oliveira Matos et al., 2020; Vazan et al., 2017), and it also may be possible that the exergame assessment modality may have introduced additional motor related variance not accounted for.

Although the Switching task performed on the Dividat Senso platform was found to correlate with normalized units' indices during the active standing, it did not correlate with any absolute power measure, nor ΔHRV indices.

FUTURE STEPS. Taken together, these findings suggest that autonomic adaptability, and particularly the parasympathetic withdrawal during postural challenge, is meaningfully related to cognitive, dual-task and executive functioning in older adults. More studies are needed to better understand the specificity of the association. This link points toward a shared physiological substrate supporting both autonomic and complex cognitive requests. To investigate this predictive coding system, future research on neuropsychological variables should focus on the dynamic adaptability of the autonomic regulatory system by challenging it through similar paradigms. More research is needed to uncover the predictive role of the different ΔHRV indices, focusing also on ΔHRV% parameters as markers of autonomic flexibility. Moreover, dual task capabilities and motor-cognitive interplay should be investigated more thoroughly in relation to heart rate variability. Longitudinal designs with larger cohorts are needed to determine whether these cluster profiles are predictive of cognitive decline in ageing populations.

LF INDICES OF HRV AT T1. Contrary to our expectations at T1 HRV measures were not so tightly interconnected to cognitive outcomes. One of the central nodes of the network was the dual task cost of the Switching task, which was connected, among others, to HRV indices (Fig.53). Specifically, it was negatively related to standing measure such as the total power and low frequencies absolute power, suggesting that greater HRV while standing is associated with better cognitive flexibility. Moreover, DTC Switch showed a negative interaction also with ΔLF% (even though the correlation did not survive FDR correction: $p = .053$), pointing to the hypothesis that a greater percentual gain in low frequencies in response to a system activation request is related to a better performance in switching tasks. The association between low frequencies and dual task costs is underrepresented in current studies, focusing mostly on HF indices, but these results show that cognitive flexibility may share common physiological basis also with LF parameters. Dual-task paradigm may indeed probe different yet complementary resources.

ΔLF% especially needs to be further investigated trough multi-domain interventions. In our sample at T1 this index was positively correlated with the dual- task global IC composite score (ρ = 0.43, p = .04) and the Mini Nutritional Assessment (ρ = 0.40, p = .047), while it showed significant negative correlations with daytime sleepiness (ESS: ρ = - 0.46, p = .01), dual-task cost of the Switching cost as mentioned above, and the processing speed of the Letter H Cancellation test (ρ = - 0.41, p = .03) (Fig. 54). Given the contradicting results relative to ΔLFnu measures in previous research (see 1.2.2.2) (Mellingsæter et al., 2015; Nicolini et al., 2020; Nicolini et al., 2022) and our results at T0 focusing on the mixed nature of normalized units, future research should focus on both ΔHF% and ΔLF% indices to detangle measures of sympathovagal balance and aim to better understand the nature and significance of each frequency.

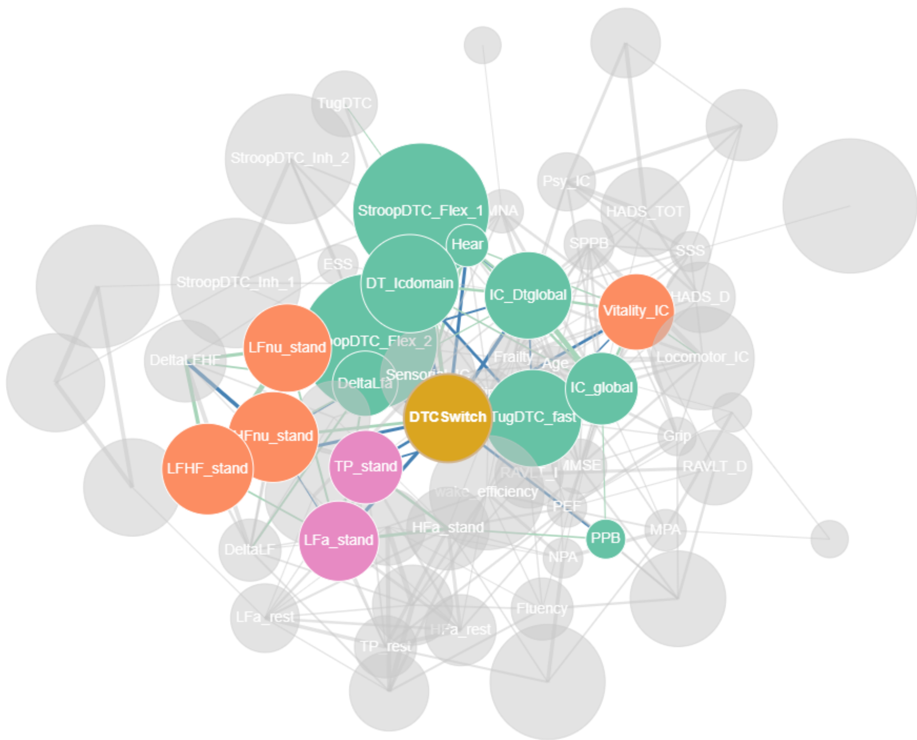


FIGURE 53. *Visual Network at T1 with threshold |r| ≥ 0.40. The selected variable, DTC_Switch, is linked through negative associations (blue edges) to TP_stand, LFa_stand, DeltaLFa, PPB and Hear, constituting a central and a bridge to other communities.*

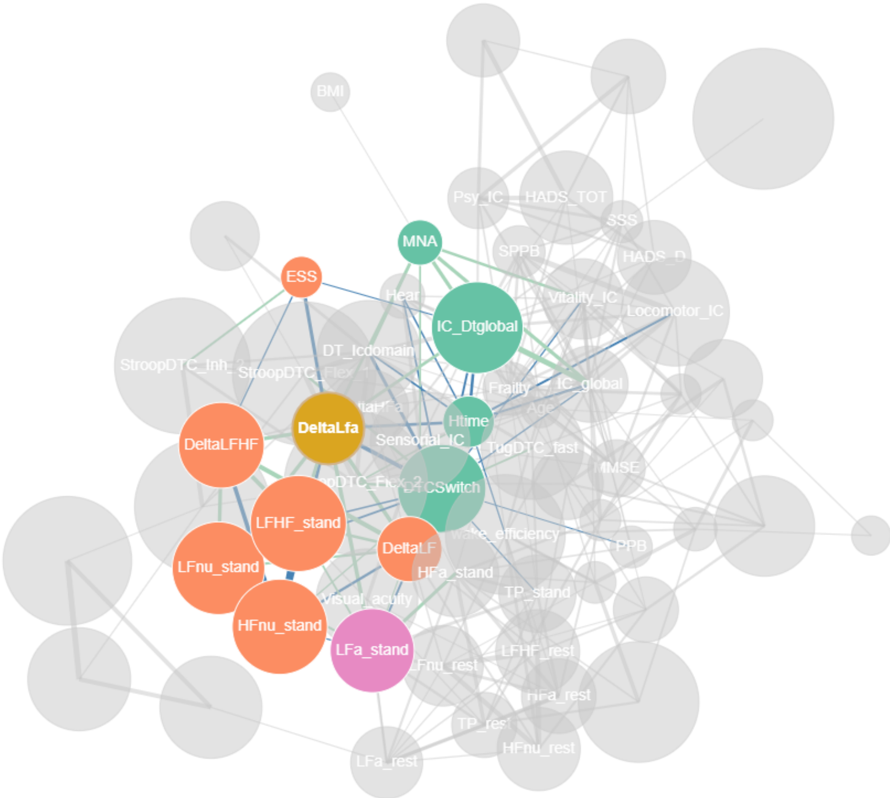


FIGURE 54. *Visual Network at T1 with threshold |r| ≥ 0.40. The selected variable, DeltaLFa (**ΔLF%**), is linked through negative associations (blue edges) to ESS, Htime and DTC_Switch, while it correlates positively (green edges) to MNA and dual-task global IC composite score (in figure IC_Dtglobal).*

LIMITATIONS OF THE STUDY. Limitation of the results deserve a comment. The small sample size of the PRAISE HRV T0 dataset (N=30) and PRAISE T1 (n=35), although sufficient for exploratory clustering analyses, may limit the statistical power and generalizability of the results. Replication in larger cohorts is needed to confirm the observed profiles and the methodological usage of ΔHRV% indices. Future longitudinal studies in larger cohorts are essential to determine the reliability of HRV dynamics expressed through percentual changes in the prediction of cognitive and dual-task decline over time. Moreover, results at T1 are based on a population not corrected for pharmacological intake and should therefore interpreted as exploratory and further investigated.

4.2 INTERVENTION RESULTS

When looking at the interventional results, PRAISE addressed its main outcome in that the intervention impacts on Frailty. The mixed-effects models show a pattern of coherent, clinically meaningful intervention effects: the intervention arm experienced a greater reduction in Frailty and larger gains in the cognition domain, along with improved dual-task inhibitory control (StroopDTC_Inh_1 and 2) and a positive effect on peak expiratory flow (PEF). These primary effects were robust to median imputation, with minor differences concerning PEF and LFa in standing. Within-arm contrasts confirm substantive improvements in the intervention group for SPPB, reduced daytime sleepiness (ESS), lower HADS-Anxiety, increased light physical activity and improved dual-task switching, while the control group showed some relative worsening in Stroop inhibition and hearing. Overall, the intervention appears efficient in exploiting multi-domain gains in functional reserve, cognition and some physiological indices. The improvement in SPPB alongside reduced Frailty is clinically meaningful and concordant with meta-analytic evidence that multicomponent exercise improves mobility and reduces Frailty risk: these findings fit with larger multi-domain and multicomponent programs that improve cognition and function in at-risk older adults (Castro et al., 2023; Ngandu et al., 2015; Robinson et al., 2022).

Frailty reduction and Dual task intervention. The joint reduction in Frailty and the improvement in dual-task control suggests that the intervention may have acted on interdependent components of functional reserve. Dual-task training explicitly targets the integration of executive control with motor planning, capacities underpinning safe, adaptive behaviour in everyday life (e.g., walking while talking), therefore improvements on Stroop and Switching dual-task costs are plausible mediators (or co-drivers) of reduced Frailty because better inhibitory control and cognitive flexibility reduce the cognitive load of everyday actions and the risk of falls (T. J. Buracchio et al., 2011; Hofheinz & Mibs, 2016; Mirelman et al., 2012; San Martín Valenzuela et al., 2020). The present pattern (Frailty reduction alongside cognitive/dual-task gains) is therefore consistent with the hypothesis that dual-task stimulation can strengthen top-down control and thereby support system-level reserve.

The role of reduced anxiety in Frailty regression. Given the baseline results, another important factor to be considered is the reduction in self-reported anxiety levels (HADS A). Given the tight connection between psychological measures and Frailty at T0, changes in this domain can plausibly have contributed to reduce Frailty. Behaviourally, reductions in anxiety increase activity, engagement and adherence to training, reducing avoidance and social withdrawal, thereby restoring real-world opportunity for strength, balance and endurance gains that underpin lower Frailty scores. Physiologically, decreased anxiety is also likely to reflect improved autonomic regulation: the Neurovisceral Integration Model links prefrontal regulatory capacity, vagally-mediated HRV and emotion regulation, so that improvements in top-down control and vagal tone accompany reductions in anxiety and better adaptive responding to stressors (Thayer & Lane, 2000a).

Taken together, these outcomes imply two main possible explicative chains for the PRAISE data:

(a) intervention → reduced anxiety → greater activity/engagement → improved executive control → reduced Frailty

(b) intervention → improved executive control → reduced anxiety → reduced Frailty.

Both of these possible paths could be connected to autonomic changes, according to the majority or current research, although our study did not capture robust results in that sense.

INTERVENTION-RELATED HRV MODULATION. Intervention effects on HRV parameters were modest and partly sensitive to analysis: LFa during standing reached significance in the "median substitution" analysis (Estimate = 95.44, p = 0.042). Interpreting these frequency-domain changes requires caution, especially in a small sample without correcting for medicine intake. Results reflecting parasympathetic (HF) shifts may have been covered by these factors. Results at T1 highlighted on the other hand the possible relationship of LF activity and functional resources.

A possible way to interpret the heart rate variability findings in our data is to distinguish between **adaptability resources** versus **reactivity to demand**. A higher vagally-mediated HRV, as we previously saw, could represent a physiological marker of a more flexible and balanced system better equipped to adapt and manage functional resources (Smith et al., 2017). On the other hand, complex dual-task paradigms, imposing important cognitive loads, may be more likely to also recruit LF-band spectral changes that could index the system's reactivity under load.

This idea is consistent with the neurovisceral integration model, which posits that HF-HRV links basal emotional and attentional regulation via prefrontal control (higher HF corresponds to stronger top-down regulatory control and ability to stay calm) (Thayer & Lane, 2000). A recent study (Muthukrishnan et al., 2017.) found that rises in cognitive load were associated to increases in LF absolute power, while HFa was not affected, but research on absolute values of LF or percentual shifts in LFa/HFa following a request, is still lacking.

The negative association of Frailty and HRV measures found at T1 (ΔHF%, TP and HFa in standing) perfectly fits a model of reduced parasympathetic-mediated autonomic flexibility in Frailty and pre-Frailty (Samuel et al., 2025; Sergi et al., 2015): FI correlated with lower HF power, reduced overall spectral power and greater HF% loss during the orthostatic challenge conditions.

Respiratory function. Moreover, results showed also a positive correlation between PEF and HFa_stand (ρ = 0.57, FDR-adjusted p = .047) and TP at rest (ρ = 0.57, FDR-adjusted p = .047), an expected result given that HF is also called the "respiratory band" (Berntson et al., 1997), but that should be further explored. An initial positive PEF effect is consistent with literature relating the respiratory function to Frailty and overall vitality: reduced PEF predicts disability and Frailty in cohort studies (Vaz Fragoso et al., 2008; Wang et al., 2024). The PEF effect lost significance in a sensitivity analysis ("median") however, suggesting the effect may be less robust or sensitive to analytic choices. Still, improvement in PEF is plausible and may underlie or be an influential factor of an autonomic-Frailty association.

Grip strength. A robust and unexpected finding was decreased handgrip strength in the intervention group (Estimate = −2.68, p = 0.011; within-group mean change -2.28 kg, p = 0.0016). There could be two main explanations for this apparent paradox:

1. Training specificity: our dual-task intervention emphasized balance, stepping and cognitive engagement, not including sufficient strength resistance exercises to maintain or increase maximal grip strength; on the other hand, the control group may have maintained grip-strength following the exercises given in the good practice booklet. Although handgrip strength declined in the intervention arm, participants nevertheless showed clear gains on the Short Physical Performance Battery (SPPB), which primarily indexes lower-limb function (balance, gait speed and repeated chair stands).
2. Measurement and timing effects: grip strength is sensitive to testing conditions, participant effort and diurnal factors; follow-up tests occurred at different times or after sessions, and temporary reductions could appear.

Improved cognitive inhibition, daytime sleepiness and autonomic reactivity. The intervention improved the performances on a specific dual-task paradigm in particular, the Stroop Inhibition task. At T0 Frailty positively correlated with the cognitive cost of the DT Stroop, that contrary to what expected was not associated and did not cluster with the cognitive/dual-task/HRV community. At T1 the Stroop task was connected to HRV parameters through the ESS variable, measuring daytime sleepiness. ESS positively correlated with Stroop dual-task cost (greater daytime sleepiness ↔ worst dual-task cognitive inhibition) and was negatively associated to ΔLF% (greater daytime sleepiness ↔ lower percentage gain of LFa following a request) (Fig. 55). This pattern is theoretically and empirically plausible. Daytime sleepiness is a reliable predictor of poorer attentional and executive performance in older adults and longitudinally predicts cognitive decline (Hayden et al., 2023). Sleepiness also associates with altered autonomic profiles and reduced HRV, suggesting that lower arousal/alertness may blunt autonomic responsivity to demand (Taranto Montemurro et al., 2014).

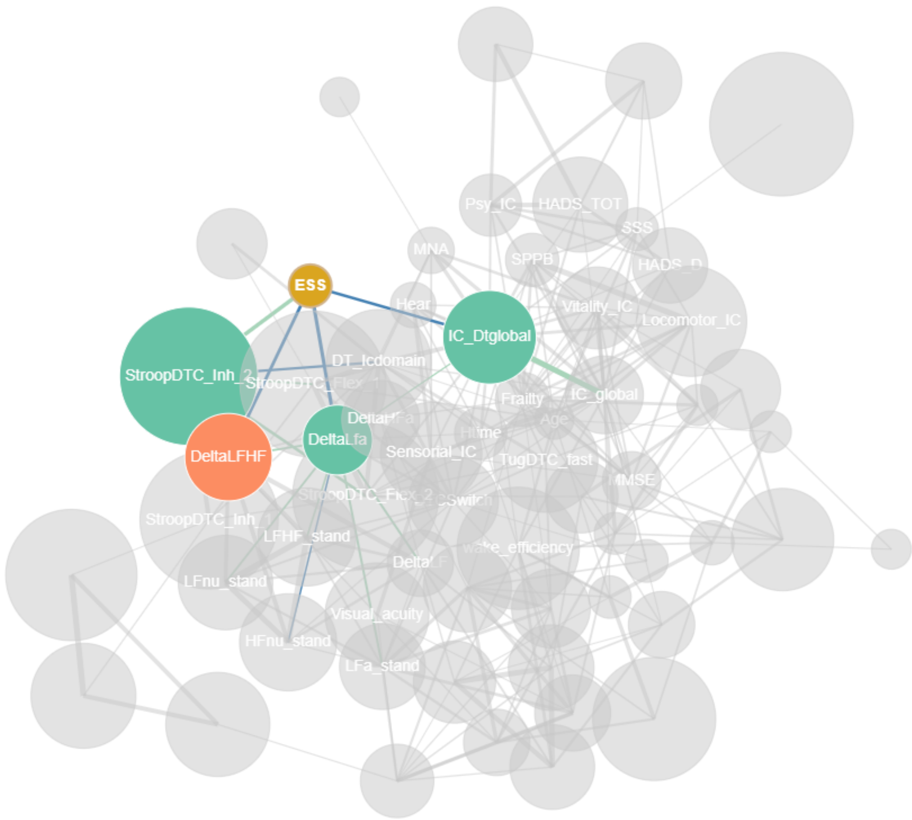


FIGURE 55. *Visual Network at T1 with threshold |r| ≥ 0.40. The selected variable, ESS, is positively associated to Stroop_DTC_Inh_2 (green edge) and negatively to DeltaLFa (ΔLF%), acting as a possible link between cognitive control and autonomic reactivity.*

Intervention Effects. In conclusion, the PRAISE trial produced a coherent pattern of multi-domain changes: mixed-effects models and within-group contrasts show that the dual-task *intervention reduced Frailty* (primary outcome of the study), *improved the cognition domain*, specific measures of dual-task *inhibitory control* (StroopDTC_Inh_1/2), and yielded gains in *functional mobility* (SPPB), *pulmonary function* (PEF) and increased the *absolute power of low frequencies* (LFa_stand). These primary effects were robust to alternative missing-data handling, although the PEF signal and LFa standing proved sensitive to analytic choices.

The intervention also *reduced daytime sleepiness* (ESS) and *anxiety* (HADS-A), outcomes that are relevant also given the baseline Frailty ↔ psychological domain association and the plausible behavioural and neurovisceral (improved top-down control and vagal regulation) routes by which reduced anxiety could influence Frailty status (Thayer & Lane, 2000).

The paradoxical decline in handgrip strength most likely reflects training specificity and/or fatigue effects rather than a net loss of functional reserve; future protocols should focus on this association to test its validity, considering also SPPB and lower limb function, improved in the training group.

HRV findings suggest a nuanced picture: T1 associations between higher Frailty and reduced parasympathetic markers (ΔHF%, standing TP, standing HFa) fit models of blunted autonomic flexibility in frail and in this case pre-frail subjects (De Oliveira Matos et al., 2020; Samuel et al., 2025), while links between sleepiness, reduced LF% reactivity and worse Switching/Stroop cognitive costs point to reactivity-related pathways that merit careful interpretation given known limitations of LF metrics (Billman, 2013; Goldstein et al., 2011; Reyes del Paso et al., 2013).

Taken together, the results support two plausible, non-exclusive explanatory chains:

(a) intervention → reduced anxiety → greater engagement → greater autonomic flexibility/reactivity → cognitive gains → reduced Frailty

(b) intervention → improved executive control → greater autonomic flexibility/reactivity → reduced anxiety → reduced Frailty

both of which could interact with autonomic adaptation in different complementary ways.

FUTURE DIRECTIONS. To move from association to mechanism, a larger and more robust trial is needed, ideally a multicentric design to increase heterogeneity, external validity, and statistical power. Such study should stratify participants by Frailty level (robust-pre-frail, frail) in order to determine whether the capacity to benefit from dual-task interventions differs across the Frailty spectrum (and to identify thresholds beyond which adaptability becomes difficult to restore) and to characterize population-specific patterns of system interdependence. It should also include standardized HRV protocols (including orthostatic reactivity measures) and control for pharmacological influences on cardiac activity. Moreover, future studies should incorporate continuous ECG recording during the administration of cognitive and/or dual-task paradigms and psychophysiological assessment in order to capture a broader range and real-time autonomic responses associated with executive performance.

Rather than the low-frequency, year-long schedule used in the pilot (≈5 sessions/month for 12 months), a definitive trial should concentrate the training stimulus into a shorter, more intensive core phase (for example, ≈6 months) with an increased session frequency (approximately 2–3 sessions per week, ≈8–12 sessions/month), followed by a structured longer-term follow-up. Shorter, higher-dose training phases have been shown to produce clinically relevant gains in mobility, cognition and physiological indices within 3–6 months in multicomponent and dual-task studies, and exercise dose-response literature indicates that ≥2 sessions/week is a practical minimum to elicit strength and functional adaptations in older adults (Apóstolo et al., 2018a; Borde et al., 2015; Eggenberger et al., 2020; Sánchez-Sánchez et al., 2022).

In this context, it will be essential to probe adaptability across multiple reserves i.e. cognitive (dual-task cost, cognitive flexibility), autonomic (neurovisceral flexibility and reactivity), functional (SPPB, pulmonary function, sleepiness), and psychological (mood, anxiety, perceived social support). Such a multi-domain panel would allow investigators not only to confirm intervention efficacy but to map how changes in one domain propagate across the system, for example whether improved executive control mediates reductions in Frailty via enhanced autonomic flexibility, or whether gains in psychological reserve (reduced anxiety, improved sleepiness) mediate increased engagement in everyday-life and thus functional improvement.

By scaling up to a multicentric, stratified trial with a rigorous, targeted protocol, it will be possible to determine whether dual-task training restores system-level reserve through strengthening top-down control, improving psychological wellbeing, enhancing autonomic adaptability and reactivity, or some combination of these interlinked pathways. In this way, the field can progress from demonstrating promising associations in pilot cohorts to establishing mechanistic, generalizable evidence that multi-domain dual-task interventions represent a viable strategy to preserve independence and resilience in ageing populations.

CONCLUSIONS

This thesis set out to examine Frailty and Intrinsic Capacity not as isolated outcomes, but as features of a complex, interacting system, and to test whether a targeted dual-task exergame intervention could improve multi-domain reserves in older adults. Across correlation, clustering, network and longitudinal analyses, a consistent picture emerged: Frailty and IC are not isolated, unitary constructs but nodes embedded within a dynamic, multi-domain architecture whose topology depends on physiological and functional states. The principal contribution of this work is therefore (1) empirical, showing that a dual-task exergame intervention can drag improvements in other domains, producing coherent, clinically meaningful changes, and (2) conceptual: it demonstrates that preserving independence in later life requires strengthening and challenging adaptive responses across cognitive, physiological, psychological and functional subsystems.

The PRAISE protocol reduced Frailty (the trial primary outcome), improved cognitive performance and specific dual-task inhibitory control (StroopDTC_Inh_1/2), enhanced lower-limb function (SPPB), and elicited gains in pulmonary function (PEF) and standing low frequency HRV power (LFa_stand). These effects were broadly robust to alternative missing-data strategies and sensitivity checks, although some physiological indicators (PEF, absolute standing LF power) were relatively sensitive to analytic choice and the HRV results should be interpreted with caution given known measurement and interpretation issues.

At baseline, network and clustering results reveal why a systems perspective is essential. Since the trial recruited pre-frail participants by design, Frailty showed restricted variability at T0 and did not appear as a global network hub, a sampling-driven non-centrality. This methodological point underscores that centrality must be interpreted in light of sample composition (Epskamp et al., 2018). Nonetheless, even without global centrality, Frailty manifested a coherent set of associations at baseline: it correlated negatively with the Intrinsic Capacity composites and with performance measures (Grip, SPPB, 6MWT, MNA, vitality domain) and positively with psychological burden, and dual-task Stroop cost. This constellation of associations signals co-occurrence of physical deficit, psychological stress, reduced functional capacity and compromised inhibitory control in pre-frail older adults.

These results speak directly to the goals of healthy ageing and to the World Health Organization's concept of Intrinsic Capacity. Our finding that IC composites sit at the heart of the network and are negatively associated to Frailty levels, underscores that healthy ageing is a systems problem: preserving independence requires maintaining the capacity to mobilize cognitive, psychological, autonomic and motor resources in an integrated way rather than treating domains independently. Interventions set out to target multiple domains (as dual-tasking having a direct impact on cognitive and locomotor subsystems) may be more likely to influence variables of other domains (as the psychological or the vitality domains in our study).

Heart-rate variability findings add nuance rather than simple answers. At follow-up (T1) higher Frailty correlated to lower parasympathetic markers (reduced ΔHF%, reduced standing high frequency power and total power), consistent with models of blunted parasympathetic drive and reduced executive functioning in older adults (Chaves et al., 2008; De Oliveira Matos et al., 2020; Eggenberger et al., 2020; Mahinrad et al., 2016; Samuel et al., 2025; Thayer, Sollers, et al., 2009; Varadhan et al., 2009). At the same time, links between sleepiness, reduced LF% reactivity and worse switching/Stroop costs indicate reactivity-related pathways deserving careful interpretation because of long-standing debate around the meaning of LF and LF/HF metrics (Berntson et al., 1997; Goldstein et al., 2011; Montano et al., 1994; Reyes del Paso et al., 2013).

Clustering and subject-level analyses on a restricted sample (PRAISE HRV T0) further refined this portrait: a distinct cluster combined cognitive and dual-task measures with ΔHRV reactivity parameters, which in our datasets proved to be among the most central nodes, bridges to other communities. A greater gain in ΔLFnu was associated to a worst cognitive and dual-task performance. The absence of between-group differences in motor and balance performances further supports the specificity of autonomic-cognitive associations, independently of overall fitness level.

By inspecting the data, we demonstrated that this HRV index reflected a parasympathetic withdrawal rather than an actual raise in LFa. Parasympathetic withdrawal may be better expressed as a percentual relative shift in HFa (ΔHF%). This measure is rarely used in current literature (Grant et al., 2012; Rani et al., 2022) and no study to our knowledge has implemented this parameter to measure how parasympathetic withdrawal can influence cognitive performance or vice versa. It is a measure of “neurovegetative cost”, that such as dual-cost measures highlights how, in this case autonomic and not directly cognitive, resources are being handled by the system, how much the task influences and puts a load on the adaptability and flexibility of the organism.

In the HRV-cleaned subsample, Frailty clustered with ΔLF% and normalized HRV measures (LFnu/HFnu supine), suggesting that relative shifts in autonomic allocation represented by low frequency signals may accompany Frailty. Moreover, the training longitudinal effects showed a trend indicating augmented LF absolute power while standing, a result not expected but that may be influenced by medicine intake. Previously obtained results connecting ΔHRV and cognitive functioning may not be contradictive or mutually exclusive per se (Nicolini et. al, 2020; 2022), but a reflection of either a parasympathetic withdrawal (ΔHF%) or a good orthostatic reactivity (ΔLF%).

Overall, orthostatic HRV indices and standing absolute power measures appear more sensitive and reliable to reflect the reserve that Frailty erodes, than resting supine HRV in isolation. The Task Force standards and subsequent methodological critiques caution against overinterpreting isolated spectral indices; orthostatic protocols and combined measures of absolute power and normalized metrics provide a more informative picture of autonomic adaptability (1996). More research is essential to investigate the difference between ΔHRV parameters and their validity.

The randomized intervention results provide practical evidence that challenging the system through exergaming yields coordinated benefits. The overall pattern (i.e. reduced Frailty together with improved cognition, dual-task inhibitory control, pulmonary function and mobility, alongside reduced anxiety and daytime sleepiness) aligns with prior multi-domain interventions (Murukesu et al., 2020; Ngandu et al., 2015; Yang et al., 2023), but it also shows novel insights, expanding the results to other functional domains and to the neurovegetative system through an extended detailed evaluation.

Some apparently paradoxical results illustrate the trade-offs inherent in training specificity. The intervention group showed a decline in handgrip strength despite improvements in SPPB and overall Frailty. This dissociation likely reflects programme content: dual-task training improves more likely lower-limb function without necessarily providing the progressive, high-force stimulus needed to maintain maximal upper-limb strength. Practically, this implies that future interventions aiming to preserve or enhance global strength must embed explicit resistance dosing alongside cognitive-motor challenges. Moreover, the MMSE may not be sensitive enough to capture early cognitive deficits in a pre-Frail population, and more challenging cognitive tests should be integrated into IC and Frailty research.

Interpreting the possible mechanism at the base of such a complex, adaptable and interconnected network requires integrating multiple behavioural and physiological parameters while probing the dynamicity of the system. The baseline Frailty ↔ anxiety association and the intervention's anxiolytic effect suggest a behavioural pathway: reducing anxiety can increase engagement, activity and adherence, thereby creating opportunities for strength, balance and endurance gains that lower Frailty. Parallelly, the Neurovisceral Integration framework provides a physiological bridge: improved prefrontal top-down control (reflected in better dual-task performance) is linked to vagally-mediated autonomic regulation, so cognitive gains can coincide with improvements in autonomic flexibility and stress responsiveness (Thayer & Lane, 2000). In this study, T1 findings that higher Frailty is associated with lower standing HF, lower total power and reduced ΔHF% fit a model of _blunted parasympathetic flexibility in Frailty (pre-Frailty)_ which _plausibly reduces physiological reserve._

The data support two complementary chains by which dual-task training may reduce Frailty. First, a ***PSYCHO–BEHAVIOURAL*** route:

Intervention → reduced anxiety and daytime sleepiness → (enhanced autonomic flexibility) → enhanced physical and cognitive stimulation → improved reserves and reduced Frailty

Second, a ***COGNITIVE–DUAL TASK*** route:

Intervention → improved executive/dual-task control → (greater autonomic flexibility/reactivity) → improved stress adaptation and reduced daytime sleepiness→ reduced Frailty

Both pathways are plausible, not mutually exclusive, and may act in concert; our network results are compatible with both and suggest they interact through autonomic adaptation, top-down control and behavioural changes (Fig. 56).

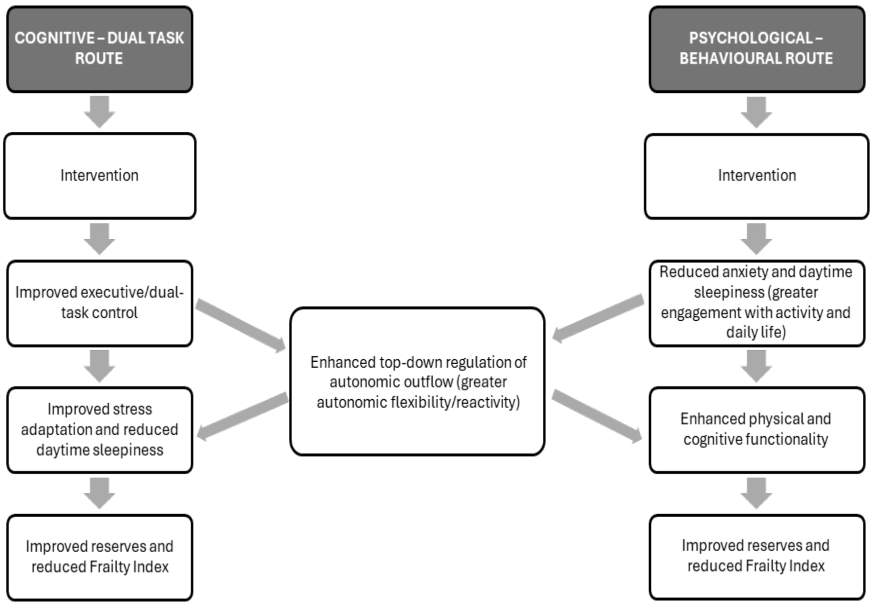


FIGURE 56. *Schematic representation of the two plausible complementary pathways: a Cognitive-Dual Task Route and a Psychological-Behavioural Route through which PRAISE intervention may have improved cognitive and dual-task capabilities and reduced Frailty. Improvements in executive control, anxiety, and daily sleepiness may contribute to enhance top-down regulation of autonomic outflow, ultimately leading to improved IC reserves and a reduced Frailty Index.*

Taken together, the empirical and theoretical threads converge on a single practical insight: maintaining independence in older age is fundamentally about **preserving adaptability**, the ability to deploy cognitive, physiological, psychological and motor resources rapidly and appropriately when challenged. The PRAISE data show that a coordinated, exergame intervention can shift multiple nodes of the system in a mutually reinforcing way: cognitive control improves, anxiety and daytime sleepiness decline, mobility and some physiological indices trend favourably, and Frailty decreases. To transform these associative findings into causal understanding, future trials should scale up sample sizes in a multi-centric study, include HRV task reactivity measures, stratify for Frailty status, control for medications and sleep disorders, and testing how autonomic, psychological and cognitive changes mediate Frailty reduction and how they are interconnected.

On a more qualitative based approach, we received good feedback from the subjects in the intervention group, the engagement was high and several individuals reported a higher perceived functional well-being in relation to previous years. Below you can find some of the phrases they wrote to us regarding the study:

“I have more willingness to take action, more responsiveness.”
(“Ho più voglia di fare, più reattività”)

“I noticed a gain in short time memory and balance”
(“Ho notato un miglioramento nella memoria a breve termine e nell’equilibrio”)

“I have fewer aches, more energy, more optimism, and more motivation to get things done”
(“Ho meno dolori, più energia, più ottimismo e voglia di fare le cose”)

“I’m sad to be finishing the course”
(“Mi spiace terminare il corso”)

“I feel more determined in trying to achieve the goals I set for myself, and I have broadened my cultural interests. It seems to me that I now appreciate more the kind of life I have built for myself”
(“Sono più decisa nel cercare di raggiungere gli obiettivi che mi propongo e ho allargato i miei interessi culturali. Mi sembra di apprezzare di più il tipo di vita che mi sono costruita”).

In conclusion, this thesis argues for a systems-level approach to ageing: Frailty and Intrinsic Capacity are reflective constructs of interacting subsystems. Interventions that intentionally challenge and thereby strengthen this interconnected network, hold promise to restore *flexibility* and preserve function in later life. The PRAISE findings provide preliminary but coherent evidence that such multi-domain, adaptability-focused strategies are both feasible and effective levers for healthy ageing.

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This work would not have been possible without the support, participation, encouragement, sharing of ideas, moments and work of many people. I don't know how to thank you all, but I would like to dedicate my gratitude and this work to you.

First of all, to my supervisor, Prof. Gabriella Cerri. Thank you for believing in me, for your optimism that lifted me up in the most desperate moments, for always having an idea to share, and for the passion and enthusiasm you bring. It is needless to say that this work could have not been possible without you. Thank you.

To all the members of the MoCA Lab: Luca, Guglielmo, Antonella, Viga, Marta, and Vinni, you helped me with timely, precise and much needed advice and by sharing the daily ups and downs of the research life. Thank you.

To those who played an essential role in the research outcomes: Prof. Daniela Lucini and her research team, including Mara Malacarne, for the ECG data analyses, and Dr. Marco Rabuffetti for the actigraphy data analyses. Thank you not only for the signal analyses themselves, but also for teaching me the techniques behind them.

To my fellow PhD students, the 37^{th} *cycle, the people who shared fears and laughter with me, Marina, Sara, Alessandro, Matteo,Yazan and Rodrigo: you, more than anyone, truly understood the joy, paranoia, and frustration behind this work, because you've been walking the same winding and uncertain path. Thank you.*

To Luli, my lifelong friend, desk mate, and constant point: I simply know we'll always be there for each other, and I couldn't be happier for that.

To Mmmarco, who over these four years has endured my low moments and managed to make me laugh like few others can: I hope I can do the same for you.

To Chiarrra, Mati and Panni, because sitting on a step, drinking and venting, was truly essential for my mental health. Really.

To Cecilia and all my theatre mates: I dedicate this work to you as well, as you were a fundamental part of my life in Milano. Thank you.

To my family. What can I say, you've made everything possible and continue to do so. It's impossible to express what that means in just a few lines. Mom and Dad, thank you for giving me a million opportunities, for teaching me to fight for what I believe in, for pushing me to take a leap (Mom), but with a good head on my shoulders (Dad). To Franci, my big brother, always there for me, you are as short tempered as I am, but a reference point I can aim for and always return to, thank you. Coki, I think no one understands me the way you do. You've been essential for me and always will be: you are my laughter.

Finally, I dedicate this thesis to all those who took part in the PRAISE project, "i miei soggetti": thank you for your dedication, for sharing part of your life with me, for the fun stories and the sad ones. Thank you for making all this possible.

Lucia

SUPPLEMENTAL MATERIALS

APPENDIX A: PRAISE PROTOCOL

ID______ NOME E COGNOME ____________

DATA__________

RANDOMIZZAZIONE C S **T0**

ETA'______ GENERE M F

ANNI DI SCUOLA FREQUENTATI 0-4 5-7 8-12 13-17

PESO________ ALTEZZA _______ BMI_________

STATO CIVILE Nubile Celibe Convivente Sposato/a Vedovo/a Separato/a Divorziato/a

CON CHI VIVE____________ DATA DI NASCITA ___/___/____

SPORT_________ MINUTI DI ATTIVITA' GIORNALIERA ______________

PROFESSIONE_____________________

ANAMNESI

POTUS	SI	NO
FUMO	SI	NO
ABUSO SOSTANZE	SI	NO
FAMILIARITA' MALATTIE NEUROLOGICHE	SI	NO

____

FAMILIARITA' MALATTIE PSICOLOGICHE	SI	NO

____

- ☐ Ipertensione
- ☐ Diabete
- ☐ Ipercolesterolemia
- ☐ Osteoporosi

COMORBITA'____

FARMACI____

____

____

Durante l'ultimo mese....

Mai=0 Una o due volte=1 Circa una volta a settimana=2 Circa due o tre volte a settimana= 3 Quasi ogni giorno= 4 Ogni giorno= 5

Ti sei sentito felice	0	1	2	3	4	5
Ti sei sentito interessato alla vita	0	1	2	3	4	5
Ti sei sentito soddisfatto	0	1	2	3	4	5
Hai sentito di poter fare qualcosa di importante per la società	0	1	2	3	4	5
Ti sei sentito parte di una comunità (un gruppo o il tuo quartiere)	0	1	2	3	4	5
Hai sentito che la nostra società sta diventando un posto migliore per gente come te	0	1	2	3	4	5
Hai sentito che le persone sono fondamentalmente buone	0	1	2	3	4	5
Hai sentito che il modo in cui funziona la nostra società ha un senso per te	0	1	2	3	4	5
Hai sentito che ti piacciono la maggior parte degli aspetti della tua personalità	0	1	2	3	4	5
Ti sei sentito bene nel gestire le responsabilità della tua vita quotidiana	0	1	2	3	4	5
Hai sentito di avere delle relazioni sincere e cordiali con gli altri	0	1	2	3	4	5
Hai sentito di aver avuto delle esperienze che ti hanno aiutato a crescere e a diventare una persona migliore	0	1	2	3	4	5
Ti sei sentito capace di pensare o esprimere le tue idee e opinioni	0	1	2	3	4	5
Hai sentito che la tua vita ha un senso	0	1	2	3	4	5

Leggere in posizione seduta

☐ Nessuna probabilità di appisolarsi

	☐ Lieve probabilità di appisolarsi ☐ Moderata probabilità di appisolarsi ☐ Elevata probabilità di appisolarsi
Guardare la televisione	☐ Nessuna probabilità di appisolarsi ☐ Lieve probabilità di appisolarsi ☐ Moderata probabilità di appisolarsi ☐ Elevata probabilità di appisolarsi
Restare seduto e inattivo in un luogo pubblico	☐ Nessuna probabilità di appisolarsi ☐ Lieve probabilità di appisolarsi ☐ Moderata probabilità di appisolarsi ☐ Elevata probabilità di appisolarsi
Restare seduto un'ora in auto nel posto del passeggero	☐ Nessuna probabilità di appisolarsi ☐ Lieve probabilità di appisolarsi ☐ Moderata probabilità di appisolarsi ☐ Elevata probabilità di appisolarsi

Restare sdraiato il pomeriggio per riposarsi	□ Nessuna probabilità di appisolarsi □ Lieve probabilità di appisolarsi □ Moderata probabilità di appisolarsi □ Elevata probabilità di appisolarsi
Parlare con un'altra persona stando seduti	□ Nessuna probabilità di appisolarsi □ Lieve probabilità di appisolarsi □ Moderata probabilità di appisolarsi □ Elevata probabilità di appisolarsi
Restare seduti tranquilli dopo pranzo (senza aver consumato alcolici)	□ Nessuna probabilità di appisolarsi □ Lieve probabilità di appisolarsi □ Moderata probabilità di appisolarsi □ Elevata probabilità di appisolarsi
Restare seduto in automobile, fermo per pochi minuti a causa del traffico	□ Nessuna probabilità di appisolarsi □ Lieve probabilità di appisolarsi □ Moderata probabilità di appisolarsi

☐ Elevata probabilità di appisolarsi

Nell'ultimo mese, di solito, a che ora è andato/a a letto la sera?	ORARIO IN CUI SI DISPONE A LETTO ____________________
Nell'ultimo mese, di solito, quanto tempo (in minuti) ha impiegato ad addormentarsi ogni notte?	DURATA DELL'ADDORMENTAMENTO IN MINUTI ____________________
Nell'ultimo mese, di solito, a che ora si è alzato/a al mattino?	ORARIO IN CUI SI ALZA DAL LETTO ____________________
Nell'ultimo mese, quante ore ha dormito effettivamente per notte? (Potrebbero essere diverse dal numero di ore passate a letto)	ORE DI SONNO PER NOTTE ____________________

Nell'ultimo mese, quanto spesso ha avuto problemi di sonno dovuti a....

Non riuscire ad addormentarsi entro 30 minuti

☐ Non durante l'ultimo mese

☐ Meno di una volta a settimana

☐ Una o due volte a settimana

☐ Tre o più volte a settimana

Svegliarsi nel mezzo della notte o al mattino presto senza riaddormentarsi subito	□ Non durante l'ultimo mese □ Meno di una volta a settimana □ Una o due volte a settimana □ Tre o più volte a settimana
Alzarsi nel mezzo della notte per andare in bagno	□ Non durante l'ultimo mese □ Meno di una volta a settimana □ Una o due volte a settimana □ Tre o più volte a settimana
Non riuscire a respirare bene	□ Non durante l'ultimo mese □ Meno di una volta a settimana □ Una o due volte a settimana □ Tre o più volte a settimana
Tossire o russare forte	□ Non durante l'ultimo mese □ Meno di una volta a settimana □ Una o due volte a settimana □ Tre o più volte a settimana
Sentire troppo freddo	□ Non durante l'ultimo mese □ Meno di una volta a settimana □ Una o due volte a settimana □ Tre o più volte a settimana

Sentire troppo caldo	□ Non durante l'ultimo mese □ Meno di una volta a settimana □ Una o due volte a settimana □ Tre o più volte a settimana
Fare brutti sogni	□ Non durante l'ultimo mese □ Meno di una volta a settimana □ Una o due volte a settimana □ Tre o più volte a settimana
Avere dolori	□ Non durante l'ultimo mese □ Meno di una volta a settimana □ Una o due volte a settimana □ Tre o più volte a settimana
C'è qualche altro problema che può aver disturbato il suo sonno?	□ SI □ NO
(Specificare)	______________________
E quanto spesso ha avuto problemi a dormire per questo motivo?	□ Non durante l'ultimo mese □ Meno di una volta a settimana □ Una o due volte a settimana □ Tre o più volte a settimana
Nell'ultimo mese, come valuta complessivamente la qualità del suo sonno?	□ Molto buona □ Abbastanza buona □ Abbastanza cattiva

	☐ Molto cattiva
Nell'ultimo mese, quanto spesso ha preso farmaci (prescritti dal medico o meno) per aiutarsi a dormire?	☐ Non durante l'ultimo mese ☐ Meno di una volta a settimana ☐ Una o due volte a settimana ☐ Tre o più volte a settimana
Nell'ultimo mese, quanto spesso ha avuto difficoltà a rimanere sveglio/a alla guida o nel corso di attività sociali?	☐ Non durante l'ultimo mese ☐ Meno di una volta a settimana ☐ Una o due volte a settimana ☐ Tre o più volte a settimana
Nell'ultimo mese, ha avuto problemi ad avere energie sufficienti per concludere le sue normali attività?	☐ Per niente ☐ Poco ☐ Abbastanza ☐ Molto

CHECKLIST FRAGILITA'

1. Aiuto nel lavarsi	SI = 1	No = 0			
2. Aiuto nel vestirsi	SI = 1	No = 0			
3. Aiuto nel sedersi o alzarsi dalla sedia	SI = 1	No = 0			
4. Aiuto nel camminare in casa	SI = 1	No = 0			
5. Aiuto nel mangiare	SI = 1	No = 0			
6. Aiuto nella cura della casa	SI = 1	No = 0			
7. Aiuto nell'utilizzare il bagno	SI = 1	No = 0			
8. Aiuto nel salire o scendere le scale	SI = 1	No = 0			
9. Aiuto nell'alzare 4.5 kg	SI = 1	No = 0			
10. Aiuto nel fare la spesa	SI = 1	No = 0			
11. Aiuto nei lavori di casa	SI = 1	No = 0			
12. Aiuto nel preparare i pasti	SI = 1	No = 0			

13. Aiuto nell'assumere i farmaci	SI = 1	No = 0			
14. Aiuto nella gestione del denaro	SI = 1	No = 0			
15. Perdita di più di 4.5 kg di peso nell'ultimo anno	SI = 1	No = 0			
16. Giudizio sulla propria salute	Scarsa = 1	Discreta=0.75	Buona = 0.5	Molto buona = 0.25	Eccellente=0
17. Come è cambiata la sua salute nell'ultimo anno?	Peggiorata= 1	Migliorata/ stessa = 0			
18. Persistenza a letto almeno 1/2 giornata per motivi di salute, nell'ultimo mese?	SI = 1	No = 0			
19. Riduzione della solita attività nell'ultimo mese?	SI = 1	No = 0			
20. Uscire	<3 Giorni = 1	≥3 Giorni = 0			
21. Affaticarsi per qualsiasi cosa	Spesso = 1	Qualche volta = 0.5	Raramente = 0		
22. Sentirsi depresso	Spesso = 1	Qualche volta = 0.5	Raramente = 0		

23. Sentirsi infelice	Spesso = 1	Qualche volta = 0.5	Raramente = 0		
24. Social support score (vedi pagina 11)	>13 = 1	6–13 = 0.5	1–5 = 0		
25. Avere difficoltà a mettersi in moto	Spesso = 1	Qualche volta = 0.5	Raramente = 0		
26. Ipertensione	SI = 1	Sospetta = 0.5	No = 0		
27.Angina pectoris	SI = 1	Sospetta = 0.5	No = 0		
28. Insufficienza cardiaca cronica	SI = 1	Sospetta = 0.5	No = 0		
29. Ictus	SI = 1	Sospetta = 0.5	No = 0		
30. Cancro	SI = 1	Sospetta = 0.5,	No = 0		
31. Diabete	SI = 1	Sospetta = 0.5	No = 0		
32. Artrosi	SI = 1	Sospetta = 0.5	No = 0		
33.Broncopneumopatia cronica	SI = 1	Sospetta = 0.5	No = 0		
34. MMSE (pag.7)	<10 = 1	11–17 = 0.75	18–20 = 0.5	20–24 = 0.25	>24 = 0
35. BMI	<18.5, ≥30 = 1	25–<30 = 0.5	18.5–24.9 = 0		

36. Picco flusso espiratorio = _______L/min 1 = ______ 2 = ______ 3 = ______	≤340 (uomo), ≤310 (donna) = 1	>340 (uomo), >310 (donna) = 0			
37. Forza muscolare sollevamento - spalla = Kg 1 = ______ 2 = _______ 3 = ______	≤12 (uomo), ≤9 (donna) = 1	>12 (uomo), >9 (donna) = 0			
38. Forza muscolare presa =	Uomo = 1		Uomo = 0		
	BMI ≤24,	Kg ≤29	BMI ≤24	Kg >29	
Kg	BMI 24.1–28	Kg ≤30	BMI 24.1–28	Kg >30	
1 = ______	BMI >28	Kg ≤32	BMI >28	Kg >32	
	Donna = 1		Donna = 0		

2 = _______	BMI ≤23	Kg ≤17	BMI ≤23	Kg >17	
3 = ______	BMI 23.1–26	Kg ≤ 17.3	BMI 23.1–26	Kg >17	
	BMI 26.1–29	Kg ≤18	BMI 26.1–29	Kg >18	
	BMI >29	Kg ≤21	BMI >29	Kg >21	
39. Mini nutritional Assessment (vedi pagina 17)	<17 = 1	17–23.5 = 0.5	24 = 0		
40. Tempo impiegato per percorrere 4 metri con passo rapido (sec)	>10 = 1	≤10 = 0			

TOT: ____ / 40

MMSE

Orientamento *(massimo 10 punti)*		errato (0)	corretto (1)
In che anno siamo?	____________	☐	☐
In che stagione dell'anno siamo?	____________	☐	☐
Quanti ne abbiamo oggi (data)?	____________	☐	☐
Che giorno della settimana è oggi?	____________	☐	☐
In che mese siamo?	____________	☐	☐
In che nazione siamo?	____________	☐	☐
In che cantone siamo?	____________	☐	☐
In che città siamo?	____________	☐	☐
In che luogo siamo (ospedale o casa)?	____________	☐	☐
A che piano siamo?	____________	☐	☐

Registrazione *(massimo 3 punti)*

Annunciare al soggetto che si farà un test di memoria. Dire al soggetto: "**Adesso le dirò il nome di tre oggetti. Lei dovrà ripeterli dopo che io li avrò detti tutti e tre.**" Dire: "**CASA, PANE, GATTO**", nominandoli uno al secondo. Chiedere poi al paziente di ripetere il nome dei tre oggetti. Assegnare 1 punto per ogni risposta esatta al primo tentativo.

Casa ☐ no ☐ sì *Pane* ☐ no ☐ sì *Gatto* ☐ no ☐ sì ☐

Nel caso in cui il paziente non sia in grado di rievocarli tutti e tre al primo tentativo, ripeterli, fino ad un massimo di 6 volte, finché il soggetto non li abbia appresi tutti e tre. Registrare qui di seguito il numero dei tentativi:

Attenzione e calcolo *(massimo 5 punti)*

A) Serie di "sette". Chiedere al soggetto di sottrarre la cifra "**7**" da 100 (che non viene calcolato nel punteggio) per 5 volte.
Trascrivere nell'apposito spazio qui sotto le prime 5 risposte date dal soggetto senza mai correggerlo e calcolare solo successivamente il numero delle volte in cui è stato correttamente sottratto "7" *(93, 86, 79, 72, 65)*

☐☐☐ ☐☐☐ ☐☐☐ ☐☐☐ ☐☐☐ N° risposte corrette ☐

B) "**Ora le dirò una parola e le chiederò di scandirla lettera per lettera in avanti e all'indietro. La parola è "CARNE". Può scandirla lettera per lettera in avanti?" ....**
"**Ora la scandisca lettera per lettera all'indietro.**" (E – N – R – A – C)
Il punteggio è dato dal numero di risposte esatte nella "prova all'indietro".

☐ ☐ ☐ ☐ ☐ N° risposte corrette ☐

Dopo aver fatto entrambe le prove assegnare il migliore fra i due punteggi ottenuti. ☐

Rievocazione *(massimo 3 punti)*
"Quali erano i tre nomi degli oggetti che le ho chiesto di ricordare?"
Assegnare 1 punto per ogni oggetto correttamente ricordato

Casa ☐ no ☐ sì *Pane* ☐ no ☐ sì *Gatto* ☐ no ☐ sì ☐

Linguaggio

★ Mostrare al soggetto un **orologio da polso** e chiedere **"Che cos'è?"**
Fare lo stesso con una **matita**. Un punto per ogni risposta esatta *(massimo 2 punti)*

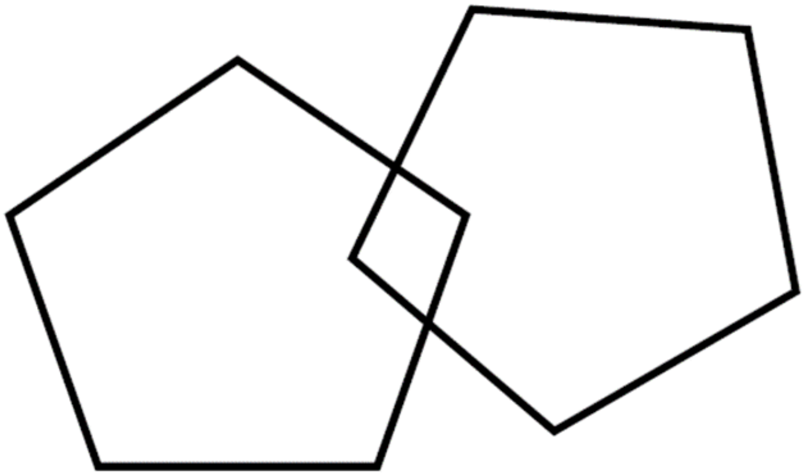
Orologio ☐ no ☐ sì *Matita* ☐ no ☐ sì ☐

P.G. ____

P.C.____

Intervallo di età	65-69	70-74	75-79	80-84	85-89
Anni di scolarizzazione					
0-4 anni	+0,4	+0,7	+1,0	+1,5	+2,2
5-7 anni	-1,1	-0,7	-0,3	+0,4	+1,4
8-12 anni	-2,0	-1,6	-1,0	-0,3	+0,8
13-17 anni	-2,8	-2,3	-1,7	-0,9	+0,3

FRASE:



SCALA SUPPORTO SOCIALE

Stato Civile	Vedovo/Celibe	**1**	Coniugato	**0**
Figli viventi	No	**1**	Si	**0**
Fratelli/ sorelle viventi	No	**1**	Si	**0**
Frequenza rapporti familiari	Mai, raramente	**1**	Spesso/ di frequente	**0**
Con chi abita	Solo	**1**	In compagnia	**0**
Aiuto finanziario da parte dei familiari	No	**1**	Si	**0**
Rapporti stretti con parenti non familiari	No	**1**	Si	**0**
Aiuto concreto da parte dei familiari	No	**1**	Si	**0**
Con quante persone del vicinato si vede almeno una volta a settimana	Nessuno	**1**	Almeno una	**0**
Ha amici intimi	No	**1**	Si	**0**
Frequenza rapporti	Mai, raramente	**1**	Spesso/ di frequente	**0**
Frequenza posti pubblici	Mai, raramente	**1**	Spesso/ di frequente	**0**
Frequenza cinema/ teatri	Mai, raramente	**1**	Spesso/ di frequente	**0**
Frequenza associazioni di volontariato/ ricreative	Mai, raramente	**1**	Spesso/ di frequente	**0**
Legge i giornali	Mai, raramente	**1**	Spesso/ di frequente	**0**
Ascolta radio e/o vede TV	Mai, raramente	**1**	Spesso/ di frequente	**0**

Si prende cura dei bambini	Mai, raramente	**1**	Spesso/ di frequente	**0**
TOT	**____ / 17**			

1-5/17 à **0** (Buon supporto sociale)

6-13/17 à **0.5** (Discreto supporto sociale)

14-17/17 à **1** (Scarso supporto sociale)

MINI NUTRITIONAL ASSESSMENT (MNA)

SCREENING

Punteggio

A. Presenta perdita appetito? Ha mangiato meno negli ultimi 3 mesi? (perdita appetito, problemi digestivi, difficoltà di masticazione o deglutizione)	**0** = Grave riduzione dell'assunzione di cibo	**1** = Moderata riduzione dell'assunzione di cibo	**2** = Nessuna riduzione dell'assunzione di cibo		
B. Perdita di peso recente (< 3 mesi)	**0** = Perdita di peso > 3 kg	**1** = Non sa	**2** = Perdita di peso tra 1 e 3 kg	**3** = Nessuna perdita di peso	
C. Motricità	**0** = Dal letto alla poltrona	**1** = Autonomo a domicilio	**2** = Esce di casa		
D. Malattie acute o stress psicologici < 3 mesi	**0** = Sì	**1** = No			
E. Problemi neuropsicologici	**0** = Demenza o depressione grave	**1** = Demenza moderata	**2** = Nessun problema psicologico		
F. 1) Indice di massa corporea	**0** = IMC < 19	**1** = IMC tra 19 compreso e 21	**2** = IMC tra 21 compreso e 23	**3** = IMC > 23 compreso	

2) Circonferenza Polpaccio – se F1 non è disponibile	**0** = CP <31	**1** = CP >31 compreso		
TOT		**/14**		

VALUTAZIONE GLOBALE

G. Vive autonomamente al domicilio	**0** = No	**1** = Si			
H. Prende più di tre medicinali al giorno	**0** = Si	**1** = No			
I. Presenza di decubiti. Ulcere cutanee	**0** = Si	**1** = No			
J. Numero pasti completi al giorno	**0** = 1 pasto	**1** = 2 pasti		**2** = 3 pasti	
K. Consuma:	Almeno una volta al giorno prodotti lattiero-caseari	No	Sì	Se 0 o 1 Sì à **0.0** Se 2 sì à **0.5** Se 3 sì à**1**	
	Una o due volte a settimana uova o legumi	No	Sì		
	Ogni giorno della carne, del pesce o del pollame	No	Sì		
L. Consuma almeno due volta al giorno frutta o verdura	**0** = No	**1** = Si			
M. Numero bicchieri bevuti al giorno (acqua, the, succhi, caffè, latte...)	**0.0** = Meno di 3 bicchieri	**0.5** = Da 3 a 5 bicchieri	**1.0** = Più di 5 bicchieri		

N. Come si nutre	**0** = Necessita di assistenza	**1** = Autonomamente con difficoltà	**2** = Autonomamente senza difficoltà		
O. Il paziente si considera ben nutrito?	**0** = Malnutrizione grave	**1** = Malnutrizione moderata o non sa	**2** = Nessun problema nutrizionale		
P. Il paziente considera il suo stato di salute migliore o peggiore rispetto ad altre persone della sua età?	**0.0** = Meno buono	**0.5** = Non sa	**1.0** = Uguale	**2.0** = Migliore	
Q. Circonferenza brachiale (CB in cm)	**0.0** = CB < 21	**0.5** = CB tra 21 e 22 compresi	**1.0** = CB > 22		
R. Circonferenza polpaccio (CP in cm)	**0** = CP < 31	**1** = CP >31 compreso			
TOT					**/16**

VALUTAZIONE TOTALE ______/30

Valutazione dello stato nutrizionale

24-30 da 24 a 30 punti	☐	stato nutrizionale normale
17-23.5 da 17 a 23,5 punti	☐	rischio di malnutrizione
meno 17 punti	☐	cattivo stato nutrizionale

MNA (pagina 2/2)

ISTRUZIONI PER IL TEST DEL SUSSURRO

L'esaminatore si posiziona a una distanza di un braccio (~ 0,6 m) dietro il paziente (per impedire la lettura labiale).

Il canale uditivo opposto viene occluso dal paziente o dall'esaminatore e il trago viene strofinato con un movimento circolare (obiettivo; bloccare l'udito da quell'orecchio).

L'esaminatore espira e sussurra un numero a 2 cifre. Sussurrare alla fine dell'espirazione significa garantire una voce il più possibile calma e standardizzata.

Se il paziente risponde correttamente, l'udito è considerato normale e non sono necessari ulteriori screening su quell'orecchio.

Se il paziente risponde in modo errato, ripetere utilizzando una diversa combinazione di numeri e lettere.

Il soggetto fallisce la prova se dopo 2 tentativi con numeri diversi non riesce a ripetere.

DX 1 __________

2 __________

SX 1 __________

2 __________

15 Parole di Rey

	1	2	3	4	5	Differita
TENDA						
TAMBURO						
CAFFE’						
CINTURA						
SOLE						
GIARDINO						
BAFFI						
FINESTRA						
FIUME						
PAESANO						
COLORE						
TACCHINO						
SCUOLA						
CASA						
CAPPELLO						
TOT	/15	/15	/15	/15	/15	/15
Intrusioni						

Rievocazione immediata					
Scolarità/Età	**65**	**70**	**75**	**80**	**P.E.**
5	**6.1**	**8.0**	**10.0**	**12.2**	**0= 0-28.52**
					1= 28.53- 32.24
8	**4.0**	**5.9**	**7.9**	**10.1**	**2= 32.25- 36.34**

13	**1.3**	**3.1**	**5.2**	**7.4**	**3=36.35- 41.69**
17	**-0.5**	**1.3**	**3.3**	**5.6**	**4= 41.70 ed oltre**

P.G ____/75

P.C. ______

P.E. ______

Rievocazione differita					
Scolarità/Età	**65**	**70**	**75**	**80**	**P.E.**
5	**1.8**	**2.4**	**3.1**	**3.8**	**0= 0-4.68**
					1= 4.69- 5.78
8	**1.3**	**1.9**	**2.6**	**3.3**	**2= 5.79- 7.16**
13	**0.6**	**1.2**	**1.9**	**2.6**	**3=7.17- 8.72**
17	**0.1**	**0.8**	**1.4**	**2.2**	**4= 8.73 ed oltre**

P.G ____/15

P.C. ______

P.E. ______

SHORT PHISICAL PERFORMANCE BATTERY

1. valutazione dell'equilibrio in 3 prove :

- il mantenimento della posizione a piedi uniti per 10"
- il mantenimento della posizione di semi-tandem per 10" (alluce di lato al calcagno)
- il mantenimento della posizione tandem sempre per 10" (alluce dietro al tallone)

il punteggio varia da un minimo di 0 se il paziente non riesce a mantenere la posizione a piedi uniti per almeno 10" a un massimo di 4 se riesce a compiere tutte e tre le prove

2. valutazione del cammino (gait) su 4 metri lineari

il punteggio della sezione varia sulla base del tempo occorrente per la prova da 0 se incapace, a 4 se riesce ad assolvere il compito in meno di 4,1"

3. valutazione della capacità di eseguire, per 5 volte consecutive, il sit to stand da una sedia senza utilizzare gli arti superiori che per la prova devono essere incrociati davanti al petto

il punteggio varia da 0 se incapace a 4 se la prova è svolta in meno di 11,2".

Il punteggio totale della scala ha quindi un range da 0 a 12

Punteggio	**0**	**1**	**2**	**3**	**4**
Equilibrio Prova	Piedi paralleli	Semitandem 0 – 9"	Tandem 0-2"	Tandem 3" – 9"	Tandem 10"
Cammino m 4 Tempo	Incapace	>7,5"	7,4" - 5,4"	5,3" - 4,1"	<4,1"
SIT to STAND Tempo	Incapace	<16,6"	16,6" - 13,7"	13,6" - 11,2"	<11,2"

PUNTEGGIO TOTALE: ____/12

TEST VISIVO

20/200	20/100	20/70	20/50	20/40	20/30	20/25	20/20

TEST DI CANCELLAZIONE DI LETTERE

Foglio A3

Scoring:

N MISSED: ____/104 (cut-off 5/104)

N MISSED DX: ___

N MISSED SX: ____

N MISSED DX – N MISSED SX: ______ (cut-off 3)

INTRUSIONI, TEMPO IMPIEGATO

____

____

____

FLUENZA FONEMICA

Il paziente deve rievocare tutte le parole che riesce che iniziano con determinate lettere seguendo delle specifiche limitazioni (non può direi nomi di città o di persona)

	F	P	L
1			
2			
3			
4			
5			
6			
7			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			

24			
25			
26			
27			
28			
29			
30			

P.G. ______

P.C. ______

P.E. ______

Tabella di correzione		
SCOL/ ETA’	65	75
3	12	13
5	8	9
8	4	5
13	-1	0
17	-5	-4

Punteggi equivalenti	
0	Da 0 a 16
1	Da 17 a 22
2	Da 23 a 26
3	Da 27 a 31
4	Da 32 e oltre

SCALA CLINICA DELL'ANSIA E DELLA DEPRESSIONE - HADS

Zigmond A.S., Snaith R.P., The Hospital Anxiety and Depression Scale, Acta Psychiatrica Scand., 67(6): 361-370, 1983

Che i sentimenti contribuiscono in maniera significativa al decorso della maggior parte delle malattie è cosa risaputa negli ambienti medici. Scopo di questo questionario è facilitare la comunicazione al medico/psicologo dello stato d'animo del paziente.

1. *"Si sente agitato e teso …"*	**A**
a. Quasi sempre	(3)
b. Spesso	(2)
c. Ogni tanto, a volte	(1)
d. Mai	(0)

2. *"Le cose che le piacevano una volta le piacciono ancora …"*	**D**
a. Come prima	(0)
b. Meno di prima	(1)
c. Molto poco	(2)
d. Quasi per nulla	(3)

3. *"Le capita di avvertire come un senso di paura, come se stesse accadendo qualcosa di terribile …"*	**A**
a. Sì, molto forte	(3)
b. A volte, ma in modo non troppo oppressivo	(2)
c. Di rado	(1)
d. Mai	(0)

4. *"Riesce a ridere e ad accorgersi del lato comico delle cose …"*	**D**
a. Come ha sempre fatto	(0)
b. Un po' meno di prima	(1)
c. Indubbiamente molto meno di prima	(2)
d. No, affatto	(3)

5. *"Le capita che le passino per la mente dei pensieri preoccupanti …"*	**A**
a. Molto spesso	(3)
b. Spesso	(2)
c. A volte, non troppo spesso	(1)
d. Solo ogni tanto	(0)

6. *"Le capita di sentirsi allegro …"*	**D**
a. Mai	(3)
b. Qualche volta	(2)
c. Abbastanza spesso	(1)
d. Quasi sempre	(0)

7. *"Quando si siede si sente rilassato …"*	**A**
a. Sì, certo	(0)
b. di solito	(1)
c. Non capita spesso	(2)
d. No, affatto	(3)

1

8. ***"Quando fa qualcosa, si sente fiacco …"***	**D**
a. Quasi sempre	(3)
b. Molto spesso	(2)
c. Qualche volta	(1)
d. No, affatto	(0)

9. ***"Le capita di provare un sentimento di apprensione, come se avesse lo stomaco in subbuglio …"***	**A**
a. Niente affatto	(0)
b. Qualche volta	(1)
c. Abbastanza spesso	(2)
d. Molto spesso	(3)

10. ***"Del suo aspetto fisico, se ne cura ancora …"***	**D**
a. Sì, quanto prima	(0)
b. Forse se ne cura di meno	(1)
c. Non abbastanza	(2)
d. Indubbiamente poco	(3)

11. ***"Le capita di sentirsi irrequieto, come se dovesse stare sempre in movimento …"***	**A**
a. Sì, molto spesso	(3)
b. Sì, abbastanza	(2)
c. No, non particolarmente	(1)
d. Assolutamente no	(0)

12. ***"Le capita di non vedere l'ora di fare cose nuove …"***	**D**
a. Sì, come prima	(0)
b. Sì, ma meno di prima	(1)
c. Molto meno di prima	(2)
d. Per niente	(3)

13. ***"Le capita di provare improvvisamente come un sentimento di panico …"***	**A**
a. Molto spesso	(3)
b. Abbastanza spesso	(2)
c. Non molto spesso	(1)
d. No, Mai	(0)

14. ***"Leggere un bel libro, o guardare una bella trasmissione TV, le da piacere …"***	**D**
a. Sì, capita spesso	(0)
b. Sì, abbastanza spesso	(1)
c. Qualche volta	(2)
d. Molto raramente	(3)

COMPILAZIONE A CURA DELL'ESAMINATORE

PUNTEGGIO OTTENUTO

Cut-Off 8-10	**ANSIA:**	**/ 21**	**DEPRESSIONE:**	**/ 21**

2

TOT: ___/ 42

6MWT

Distanza percorsa in 6 minuti: ________ metri

Ausili utilizzati: ____

TUG

Timed up and go

Scoring: 1) ____secondi 2)_____ secondi

DUAL TUG

Scoring: 1) ____secondi 2)_____ secondi

Numeri: 90, 83, 76, 69, 62, 55, 48, 41, 34, 27, 20, 13, 6

DIFFERENZA TUG - DUAL TUG: ______________

Applicazione Actigrafo : DATA: _________ ORA: __________

Restituzione Actigrafo : DATA: _________ ORA: __________

APPENDIX B: BOOKLET OF GOOD PRACTICE

PRAISE

Opuscolo buone pratiche

Moca Lab

Gentilissimo e Gentilissima,

grazie per aver accettato di partecipare al nostro progetto.

In questo opuscolo troverà alcune indicazioni pratiche per aiutarla a mantenersi in buona salute e migliorare alcuni aspetti della sua vita e suggerimenti da mettere in pratica fino a quando non ci rivedremo per il controllo (fra circa 1 anno)!
L'opuscolo si divide in cinque parti riguardanti:

1. **Il Movimento**
2. **L'Alimentazione**
3. **Il Benessere Psicologico**
4. **I Sensi (udito e vista)**
5. **La Mente**

I consigli che troverà all'interno dell'opuscolo sono stati adattati alle sue capacità e abilità funzionali attuali, valutate durante il nostro primo incontro.

BUON LAVORO!

Invecchiamento sano e attivo significa "invecchiare in buona salute per poter svolgere autonomamente le attività della vita quotidiana come lavarsi, vestirsi, camminare, etc. per una vita indipendente e partecipare appieno alla vita della collettività".
In poche parole, vuol dire essere più autonomi nel quotidiano e più impegnati nella società (http://europa.eu/ey2012).

Secondo le raccomandazioni dell'Organizzazione Mondiale della Sanità (OMS), gli adulti e gli anziani dovrebbero **limitare la quantità di tempo trascorso in attività sedentarie** e sostituire il tempo sedentario con attività fisica di qualsiasi intensità perché questo fornisce benefici per la salute
https://apps.who.int/iris/bitstream/handle/10665/336657/9789240015111-eng.pdf 4

Per **invecchiare in buona salute**, l'OMS raccomanda a tutti coloro che hanno raggiunto o superato i 65 anni di età, (purché abbiano consultato prima un medico) di svolgere regolarmente attività fisica.

È stato infatti dimostrato che il **regolare svolgimento di attività fisica è importante per la salute**: le persone attive rispetto a quelle sedentarie, hanno una minore frequenza di malattie coronariche, ipertensione, ictus, diabete, cancro al colon e al seno, un miglior funzionamento cardiorespiratorio e muscolare, migliori indici di massa corporea, migliore composizione e salute delle ossa e anche più alti livelli di salute, minor rischio di caduta e funzioni cognitive migliori.

È importante essere più attivi possibile.

Le persone inattive dovrebbero iniziare con piccole quantità di attività fisica ed incrementare gradualmente nel tempo la durata, la frequenza e l'intensità: sono proprio coloro che passano da una condizione di inattività ad una attività moderata ad avere i maggiori benefici.

http://www.who.int/dietphysicalactivity/pa/en/index.html; dietandhealth@who.int

SVOLGA REGOLARMENTE ATTIVITA' FISICA

Per essere in buona salute, l'OMS raccomanda agli anziani di svolgere da **150-300 minuti alla settimana in attività fisica di tipo aerobico ad intensità moderata, oppure da 75-150 minuti attività ad intensità vigorosa** o una combinazione delle due.

Attività moderata: richiede uno sforzo "medio", fa aumentare di poco l'attività respiratoria, come andare in bicicletta o fare la cyclette a media velocità, trasportare pesi leggeri, palleggiare a tennis, fare semplici esercizi ginnici, giocare a golf, giocare a pallavolo, nuotare adagio, camminare a passo veloce, fare pulizie pesanti della casa, etc.

Attività vigorosa: richiede un grande sforzo fisico, fa aumentare molto l'attività respiratoria, come fare jogging, correre, nuotare a stile libero, andare in bicicletta a velocità elevata, giocare a calcio, fare sport agonistici in genere, etc

Queste attività possono comprendere ciò che si fa nel tempo libero, spostamenti a piedi o in bicicletta, faccende domestiche, attività ludiche o sportive oltre ad un programma di esercizi.
In particolare, gli esercizi mirati al miglioramento dell'equilibrio, alla coordinazione ed alla prevenzione delle cadute dovrebbero essere svolti almeno 3 volte alla settimana, mentre gli esercizi di rinforzo muscolare almeno 2 volte.
L'attività motoria dovrebbe essere eseguita in sessioni della durata di almeno 10 minuti consecutivi.

Un programma completo di attività fisica deve comprendere:

Attività aerobica: richiede uno sforzo moderato per un periodo di tempo prolungato come la marcia, la corsa di resistenza, il nuoto, la bicicletta e attività simili eseguite senza scatti. L'esercizio aerobico aiuta a mantenere il fisico in salute: l'attività costante tonifica i muscoli in generale e quelli della respirazione, migliora la funzionalità cardiaca portando a una migliore circolazione sanguigna e a una riduzione della pressione.

Esercizi di forza: questi esercizi sono importanti per il potenziamento della muscolatura e quindi delle prestazioni di forza in generale. Possono prevedere anche l'utilizzo di resistenze (pesi e elastici).

Esercizi di mobilità articolare: migliorano la mobilità delle articolazioni globalmente, si eseguono con movimenti lenti e controllati e posizioni mantenute (stretching e mobilizzazioni), che portano ad un miglioramento delle lunghezze muscolari e delle mobilità articolari.

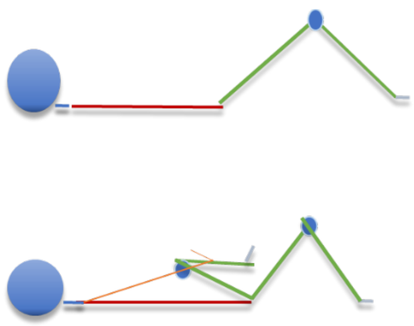
IMPORTANTE!!

- Indossare abbigliamento adatto: scarpe comode, pantaloni elasticizzati non troppo stretti e con l'elastico in vita (es. tuta da ginnastica);
- vestirsi a strati per evitare di sudare eccessivamente preferendo abbigliamento di materiale tecnico;
- evitare borse a tracolla, preferendo zaini oppure marsupi;
- mantenere una corretta postura: busto eretto e spalle rilassate;
- al momento del passo: la pianta del piede deve appoggiare bene sul terreno, rullando dal tallone fino alla punta

Alcuni suggerimenti per mantenersi attivo:

ESERCIZI PER LA COLONNA:

La colonna vertebrale è costituita dalle vertebre sovrapposte; ha lo scopo di sostenere il corpo umano, protegge il midollo spinale da traumi che possono arrecare danni e ci permette di muovere la testa nello spazio, di piegare il busto in avanti, di estenderlo in senso opposto e di ruotarlo. Il mal di schiena è un problema molto diffuso e quasi tutti hanno avuto l'esperienza di dolore nel corso della vita che può variare da lieve a molto forte, può essere di breve o di lunga durata e spesso può rendere difficile praticare molte attività della vita quotidiana. Anche l'invecchiamento può essere causa di dolore lombare perché provoca alterazioni degenerative della colonna vertebrale. Tuttavia, questo non impedisce alla maggior parte delle persone di essere attive e, in generale, di condurre una vita senza dolore.
Un programma mirato di esercizi in molti casi può essere molto utile.

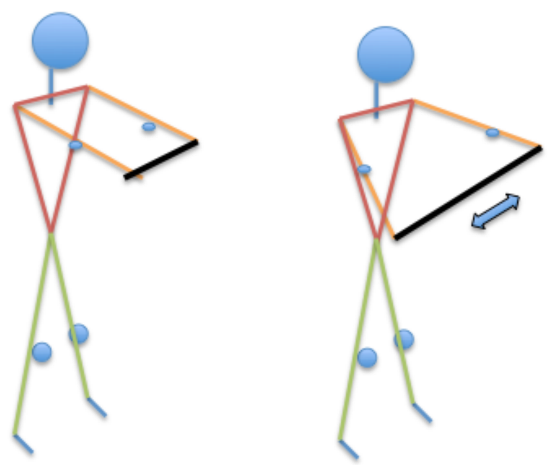


ESERCIZIO: Sdraiarsi in posizione supina (pancia in alto) con anche e ginocchia flesse e piedi che appoggiano sul tappetino, braccia lungo i fianchi. Portare il ginocchio destro al petto e trattenerlo con entrambe le braccia associando la respirazione (inspirare l'aria dal naso prima di partire ed espirare durante il movimento). Mantenere il ginocchio al petto qualche secondo anche dopo che è finita la fase di espirazione. Poi tornare in posizione di partenza. Ripetere 5 volte per ciascuna parte, alternando ginocchio destro e sinistro.
Ripetere per 10 volte con entrambe le gambe.

ESERCIZI PER LA FORZA:

La forza muscolare è quella capacità motoria che permette di vincere una resistenza o di opporvisi tramite lo sviluppo di tensione da parte della muscolatura. Al contrario, in ambito geriatrico si parla di sarcopenia, cioè la progressiva riduzione della massa e della forza muscolare che accompagna l'invecchiamento in maniera più o meno accelerata che è una componente della

fragilità. La fragilità è uno stato di eccessiva vulnerabilità a fattori stressanti ambientali con una sostanziale diminuzione delle riserve funzionali di numerosi organi e apparati, spesso associata ad aumentato rischio di cadute/fratture, perdita/riduzione della mobilità, ospedalizzazione e morte. Numerosi studi hanno dimostrato che programmi di esercizio fisico strutturato hanno effetti positivi sia sulla sarcopenia che sulla disabilità.
I metodi per lo sviluppo della forza sono molteplici come l'impiego di una resistenza esterna che provochi tensioni adeguate nel muscolo (esempio: elastici).
Da cosa dipende la forza? Da molte variabili, alcune congenite e non modificabili con l'esercizio, altre invece suscettibili di miglioramento con l'allenamento. Ciascun soggetto nasce infatti con una sua personale dotazione di fibre muscolari (quantità e tipologia delle fibre), una caratteristica non modificabile con l'allenamento. Anche l'attaccatura dei tendini sull'osso e la lunghezza dell'articolazione su cui il muscolo è ancorato (effetto leva), sono parametri congeniti e non modificabili. Per contro, le singole fibre muscolari sottoposte ad allenamento appropriato vanno incontro sia ad ipertrofia (aumento del volume) sia ad aumento della capacità contrattile (aumento della forza). Inoltre, l'allenamento può aumentare il numero di fibre muscolari che il soggetto può utilizzare contemporaneamente durante una contrazione, aumentando quindi la forza complessiva.
In conclusione, la forza muscolare è il frutto della predisposizione genetica e dell'allenamento mirato.

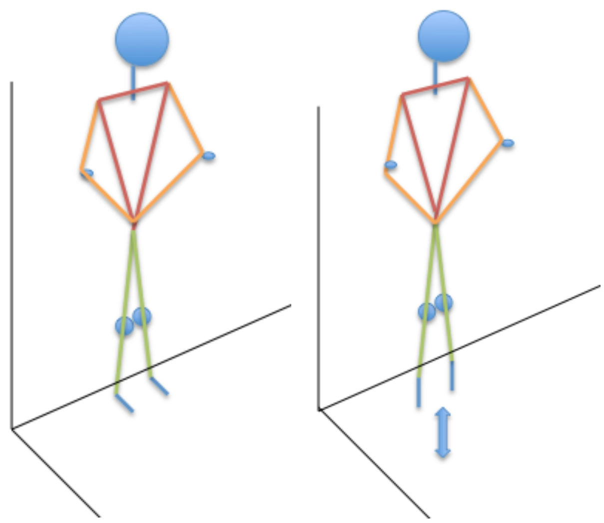


ESERCIZIO: In piedi. Braccia tese avanti a livello delle spalle con elastico rosso teso ma non tirato. Allargare le braccia per tirare l'elastico. Mantenere la posizione delle braccia allargate qualche secondo. Ripetere 10 volte.

ESERCIZI PER L'EQUILIBRIO:

L'equilibrio è importante anche per evitare le cadute che possono avere conseguenze importanti come le fratture.

Negli anziani, oltre all'equilibrio, le cadute possono avvenire per l'osteoporosi e il rallentamento dei riflessi. Dopo una caduta, si può diventare ansiosi e per paura, diminuire il movimento e l'attività in modo eccessivamente cauto, proprio per paura di cadere. Ciò contribuisce a ridurre la forza muscolare. Anche la capacità di equilibrio, come tutte le altre capacità coordinative, può essere migliorata attraverso un allenamento specifico.



ESERCIZIO: In piedi schiena rivolta al muro, a minima distanza, mani appoggiate sui fianchi. Sollevarsi sulle punte dei piedi. Mantenere la posizione 5 secondi. Ripetere 10 volte.

Mangiare sano è utile per mantenersi sani e attivi!

Secondo l'OMS, nutrizione adeguata e salute sono da considerarsi diritti umani fondamentali, molto correlati l'uno all'altro. **Uno stile di vita sano e una corretta alimentazione partecipano al mantenimento di un buono stato di salute, in ogni fascia di età.**

Gli alimenti di cui disponiamo sono tantissimi, e molte sono anche le vie per realizzare una dieta salutare associata ad uno stile di vita ugualmente salutare.

L'organismo umano ha bisogno di tutti i tipi di nutrienti per funzionare correttamente. Alcuni sono essenziali a garantirci l'energia di cui abbiamo bisogno, altri ad alimentare il continuo ricambio di cellule e altri elementi del corpo, altri a rendere possibili i processi fisiologici, altri ancora hanno funzioni protettive.

Per questa ragione l'alimentazione deve essere quanto più possibile varia ed equilibrata caratterizzata dall'assunzione bilanciata dei vari nutrienti. L'equilibrio alimentare non si costruisce su un unico pasto o su un unico giorno ma piuttosto su una continuità settimanale.

Un'alimentazione inadeguata oltre a incidere sul benessere psico-fisico, rappresenta uno dei principali fattori di rischio per l'insorgenza di numerose malattie croniche. Secondo l'OMS, circa 1/3 delle malattie cardiovascolari e dei tumori potrebbero essere evitati grazie a una equilibrata e sana alimentazione, la quale aiuta a prevenire e a trattare molte malattie croniche come l'obesità e il sovrappeso, l'ipertensione arteriosa, le malattie dell'apparato cardiocircolatorio, le malattie metaboliche, il diabete tipo 2. Inoltre, una sana alimentazione fortifica il sistema immunitario contribuendo a proteggere l'organismo da alcune malattie non direttamente legate alla nutrizione.

http://www.who.int/dietphysicalactivity/workplace/en/index.html

CONSIGLI UTILI PER UN'ALIMENTAZIONE SANA ED EQUILIBRATA:

- consultare sempre il proprio medico;
- controllare il peso;
- variare le scelte alimentari;

- evitare pasti abbondanti frazionando i pasti in più occasioni durante il giorno;
- non eccedere con il consumo di bevande alcoliche e non aggiungere eccessivamente sale alle pietanze;
- scegliere gli alimenti sulla base delle condizioni del proprio apparato masticatorio, anche per facilitare i processi digestivi;
- bere abbondantemente e frequentemente acqua (1.5 litri al giorno);
- limitare il consumo di grassi preferendo l'olio al burro o alla margarina;
- consumare spesso legumi, frutta e ortaggi freschi di stagione;
- mangiare almeno 2 volte la settimana la carne e il pesce
- cerchi di mangiare in compagnia

Per sentirsi meglio con sé stesso e gli altri, cerchi di seguire questi consigli:

1. Si mantenga attivo (in famiglia, col volontariato o con le iniziative di quartiere...), la sua esperienza può essere preziosa.

2. Coltivi gli affetti e le relazioni con gli altri e mantenga vivi i suoi interessi (amicizie, gite, viaggi, cinema, giardinaggio, lettura...).

3. Non è vero che non può imparare cose nuove, più si mantiene attivo e curioso più ne sarà capace.

4. In caso di difficoltà e/o disagi, legati allo stato psicologico, chieda chiarimenti e consigli ad uno specialista (psicologo o psicoterapeuta), soprattutto se ansia, depressione o riduzione della memoria la preoccupano.

UDITO

Le consigliamo di adottare piccoli accorgimenti per prevenire il rischio di compromettere l'udito, come ad esempio:

1. Non infili dita sporche nelle orecchie.

2. Non utilizzi cotton fioc per pulire l'interno dell'orecchio, sono dannosi.

3. Non introduca nelle orecchie oli caldi o freddi e rimedi erboristici.

4. In caso di necessità si rivolga sempre ad uno specialista.

IF WHISPER TEST FAILED ADD:

Inoltre, dovrebbe rivolgersi ad un professionista che potrà valutare in modo esaustivo le sue capacità uditive e consigliarla al meglio.

VISTA

Le consigliamo di continuare a prendersi cura dei suoi occhi, facendo particolare attenzione all'igiene (non toccare gli occhi con dita sporche ad esempio) e a non esitare ad andare da un oculista in caso di peggioramento!

IF V.A. 20/30, 20/40, 20/50, 20/70, 20/100, 20/200 DELETE ABOVE. IF V.A. = 20/20 O 20/25 DELETE BELOW

Sarebbe utile affidarsi ad un oculista per il trattamento di eventuali malattie oculari o per la prescrizione o revisione di lenti per gli occhiali.

Se fatica a leggere le consigliamo di utilizzare occhiali da lettura o lenti di ingrandimento (chieda un parere ad un oculista).

Potrebbe rivelarsi utile apportare dei piccoli cambiamenti in casa per prevenire il rischio di cadute, come ad esempio migliorare l'illuminazione, rimuovere oggetti e mobili d'intralcio lungo il cammino e segnare i bordi degli scalini con un nastro adesivo colorato, così che sia più facile

vederli.

Potrebbe inoltre rendere più visibili alcuni oggetti marcandoli con nastro adesivo colorato o comprandoli di colori sgargianti per non faticare a trovarli.

Mantenersi attivo mentalmente è molto importante per la sua salute e per il suo stile di vita. Ecco alcuni consigli:

1. Si assicuri di svolgere dell'attività fisica, un corpo in movimento aiuta il nostro cervello a mantenersi attivo.

2. Anche degli appropriati nutrienti sono rilevanti per le funzioni cognitive, in questo caso è consigliata la dieta mediterranea.

3. Faccia delle parole crociate quotidianamente e/o legga un giornale o un libro, è divertente e utile allo stesso tempo.

4. Si assicuri di dormire abbastanza, il nostro cervello ha bisogno di circa 7-8 ore di riposo per notte

GRAZIE!

APPENDIX C: TABLES OF THE RESULTS

TABLE C1. *Group comparisons (females vs. males) across demographic, cognitive, psychological, physiological, and functional variables at T0. Results are presented for independent-samples t-tests (t statistic, p-value, Cohen's d) and Mann–Whitney U tests (W statistic, p-value, rank-biserial correlation). FDR-adjusted p-values are provided for both tests (t_p_fdr, w_p_fdr). Significant results after FDR correction are highlighted in bold. Mean values are reported separately for females (MEAN_F) and males (MEAN_M).*

VARIABLE	MEAN_F	MEAN_M	T_STATISTIC	T_PVALUE	W_STATISTIC	W_PVALUE	COHEN_D	RANK_BISERIAL_R	T_P_FDR	W_P_FDR
AGE	72.610	73.947	-0.995	0.325	313.500	0.229	-0.248	0.195	0.638	0.585
BMI	25.052	25.807	-0.854	0.397	326.000	0.317	-0.199	0.163	0.638	0.596
DELTAHFA	-33.235	-8.635	-1.024	0.315	335.000	0.470	-0.317	0.118	0.638	0.700
DELTALF	16.188	13.495	0.318	0.753	386.000	0.929	0.098	-0.016	0.897	0.991
DELTALFA	62.755	210.246	-1.393	0.179	345.000	0.576	-0.518	0.092	0.572	0.729
DELTALFHF	1.566	2.510	-0.938	0.357	343.500	0.559	-0.295	0.096	0.638	0.729
DTCSWITCH	0.506	0.416	1.068	0.291	372.000	0.605	0.262	-0.088	0.638	0.744
ESS	6.275	6.000	0.260	0.796	365.500	0.819	0.061	0.038	0.909	0.904
FLUENCY	40.195	35.684	1.651	0.106	461.500	0.255	0.429	-0.185	0.428	0.585
FRAILTY	0.198	0.163	2.381	0.021	513.000	0.050	0.587	-0.317	0.207	0.355
GONOGO	1014.79	943.798	2.004	0.052	446.000	0.069	0.547	-0.304	0.267	0.404
GRIP	**19.39**	**33.976**	**-8.071**	**0.000**	**23.000**	**0.000**	**-2.667**	**0.941**	**0.000**	**0.000**
HADS_A	6.951	6.421	0.686	0.497	438.000	0.442	0.192	-0.125	0.723	0.700
HADS_D	5.073	4.947	0.166	0.869	387.000	0.974	0.046	0.006	0.948	0.996
HADS_TOT	12.024	11.368	0.566	0.575	435.500	0.468	0.163	-0.118	0.776	0.700
HEAR	0.570	0.454	1.185	0.243	461.000	0.253	0.314	-0.184	0.638	0.585
HFA_REST	192.004	101.241	2.325	0.024	455.000	0.302	0.465	-0.168	0.207	0.585
HFA_STAND	95.157	99.313	-0.108	0.915	382.000	0.981	-0.030	-0.005	0.948	0.996
HFNU_REST	53.348	46.487	1.301	0.204	468.000	0.215	0.397	-0.202	0.621	0.585
HFNU_STAND	35.818	31.061	0.897	0.377	438.000	0.351	0.262	-0.153	0.638	0.642
HTIME	90.205	93.647	-0.538	0.595	298.000	0.469	-0.158	0.124	0.777	0.700
IC	-0.042	0.153	-1.996	0.052	292.000	0.123	-0.489	0.250	0.267	0.563
IC_DT	-0.018	0.167	-1.963	0.055	299.000	0.153	-0.475	0.232	0.267	0.585
LFA_REST	143.132	137.105	0.116	0.908	389.000	1.000	0.027	0.001	0.948	1.000
LFA_STAND	140.814	144.398	-0.084	0.934	307.000	0.240	-0.021	0.192	0.948	0.585
LFHF_REST	0.935	1.498	-1.416	0.169	303.000	0.172	-0.459	0.222	0.570	0.585
LFHF_STAND	2.391	4.008	-1.540	0.136	310.500	0.263	-0.505	0.183	0.513	0.585
LFNU_REST	36.577	44.698	-1.441	0.160	301.500	0.164	-0.439	0.226	0.570	0.585
LFNU_STAND	51.574	58.193	-1.033	0.309	313.000	0.281	-0.298	0.176	0.638	0.585
LPA	35.768	37.516	-1.061	0.295	334.000	0.460	-0.280	0.121	0.638	0.700
MHC_SF	37.700	35.737	0.556	0.582	415.500	0.570	0.158	-0.093	0.776	0.729
MMSE	27.527	27.363	0.452	0.653	412.000	0.726	0.114	-0.058	0.804	0.845
MNA	25.951	27.263	-2.806	0.007	256.000	0.034	-0.658	0.343	0.112	0.269
MPA	27.400	26.889	0.241	0.811	398.500	0.770	0.063	-0.049	0.910	0.865
NPA	36.060	34.974	0.696	0.491	414.500	0.581	0.188	-0.091	0.723	0.729

PEF	**251.468**	**412.653**	**-6.390**	**0.000**	**72.000**	**0.000**	**-2.145**	**0.811**	**0.000**	**0.000**
PPB	2.088	1.889	0.743	0.461	429.000	0.431	0.194	-0.129	0.703	0.700
RAVLT_D	12.240	11.658	0.874	0.387	461.500	0.256	0.218	-0.185	0.638	0.585
RAVLT_I	54.937	50.568	1.951	0.058	510.500	0.055	0.520	-0.311	0.267	0.355
SENSORIAL_D	0.042	-0.173	1.199	0.237	471.000	0.198	0.301	-0.209	0.638	0.585
SIXMTW	484.014	545.839	-2.637	0.014	93.500	0.006	-0.871	0.523	0.180	0.083
SLEEP_EFFICIENCY	75.723	74.626	0.469	0.642	419.000	0.532	0.128	-0.103	0.804	0.729
SPPB	8.951	9.684	-1.650	0.107	291.000	0.113	-0.436	0.253	0.428	0.557
SSS	6.780	6.105	0.963	0.341	438.000	0.442	0.249	-0.125	0.638	0.700
STROOPDTC_FLEX_1	1.258	1.138	0.784	0.437	379.000	0.522	0.209	-0.108	0.683	0.729
STROOPDTC_FLEX_2	1.154	1.067	0.649	0.520	365.000	0.693	0.171	-0.067	0.740	0.821
STROOPDTC_INH_1	0.188	0.213	-0.304	0.763	310.000	0.581	-0.093	0.094	0.897	0.729
STROOPDTC_INH_2	0.133	0.169	-0.566	0.576	299.000	0.456	-0.170	0.126	0.776	0.700
SWAY_O_MAXDEV	16.072	18.549	-1.214	0.236	286.000	0.268	-0.390	0.185	0.638	0.585
SWAY_C_PL	335.905	424.401	-2.096	0.048	202.000	0.011	-0.724	0.425	0.267	0.115
SWAY_O_SPEED	11.191	14.049	-2.027	0.055	207.000	0.014	-0.701	0.410	0.267	0.126
SWAY_O_PL	515.188	775.509	-2.419	0.026	178.000	0.006	-0.924	0.463	0.207	0.083
TP_REST	888.88	1134.621	-0.856	0.398	322.000	0.287	-0.248	0.173	0.638	0.585
TP_STAND	746.156	591.503	1.016	0.314	377.000	0.968	0.227	0.008	0.638	0.996
TUGDTC	5.338	0.014	0.949	0.351	360.000	0.106	0.307	-0.283	0.638	0.557
TUGDTC_FAST	16.741	16.837	-0.010	0.992	346.000	0.183	-0.004	-0.234	0.992	0.585
VACUITY	0.701	0.680	0.294	0.770	408.500	0.647	0.082	-0.075	0.897	0.781
VPA	0.773	0.600	0.856	0.396	306.500	0.235	0.172	0.193	0.638	0.585
WAKE_EFFICIENCY	89.393	89.216	0.097	0.923	398.500	0.770	0.027	-0.049	0.948	0.865

TABLE C2. *Pairwise Spearman significant correlations among study variables at PRAISE T0 (age-adjusted data). For each pair we report Spearman's ρ, raw p-value and FDR-adjusted p-value (Benjamini–Hochberg). FDR-adjusted significant p values are highlighted in bold.*

VARIABLE 1	VARIABLE 2	SPEARMAN RHO	PVALUE	FDR PVALUE
BMI	GoNogo	-0.311	0.020	0.154
BMI	Locomotor_D	-0.268	0.039	0.252
BMI	MNA	**0.355**	**0.005**	**0.058**
BMI	PPB	**-0.346**	**0.008**	**0.078**
COGNITION_D	IC	**0.588**	**0.000**	**0.000**
COGNITION_D	IC_DT	**0.636**	**0.000**	**0.000**
DELTAHFA	Cognition_D	0.319	0.014	0.123
DELTAHFA	DualTask_D	**0.391**	**0.003**	**0.038**
DELTALF	DeltaHFa	**-0.581**	**0.000**	**0.000**
DELTALF	DeltaLFa	**0.571**	**0.000**	**0.000**
DELTALF	DeltaLFHF	**0.900**	**0.000**	**0.000**

DELTALF	DualTask_D	-0.270	0.045	0.277
DELTALF	HFa_stand	**-0.339**	**0.009**	**0.089**
DELTALF	HFnu_stand	**-0.689**	**0.000**	**0.000**
DELTALF	LFHF_stand	**0.736**	**0.000**	**0.000**
DELTALF	LFnu_stand	**0.766**	**0.000**	**0.000**
DELTALFHF	DeltaHFa	**-0.607**	**0.000**	**0.000**
DELTALFHF	DeltaLFa	**0.505**	**0.000**	**0.001**
DELTALFHF	DualTask_D	-0.288	0.031	0.215
DTCSWITCH	Cognition_D	**-0.417**	**0.002**	**0.021**
DTCSWITCH	DualTask_D	**-0.707**	**0.000**	**0.000**
DTCSWITCH	HFa_stand	-0.331	0.014	0.122
DTCSWITCH	IC	-0.290	0.030	0.212
DTCSWITCH	IC_DT	**-0.375**	**0.005**	**0.051**
DTCSWITCH	TP_stand	-0.346	0.010	0.098
DTCSWITCH	TugDTC	0.319	0.026	0.186
DTCSWITCH	TugDTC_fast	**0.561**	**0.000**	**0.001**
DUALTASK_D	Cognition_D	**0.490**	**0.000**	**0.003**
DUALTASK_D	IC	**0.376**	**0.004**	**0.047**
DUALTASK_D	IC_DT	**0.508**	**0.000**	**0.001**
ESS	Fluency	-0.269	0.039	0.256
ESS	IC	**-0.375**	**0.003**	**0.040**
ESS	IC_DT	**-0.371**	**0.004**	**0.043**
ESS	Sensorial_D	-0.306	0.019	0.147
ESS	TugDTC	**0.413**	**0.003**	**0.039**
ESS	VPA	0.316	0.016	0.132
FLUENCY	Cognition_D	**0.689**	**0.000**	**0.000**
FLUENCY	DTCSwitch	-0.278	0.038	0.249
FLUENCY	DualTask_D	0.307	0.020	0.154
FLUENCY	Hear	**0.347**	**0.007**	**0.070**
FLUENCY	HFa_rest	0.325	0.011	0.108
FLUENCY	HFa_stand	**0.401**	**0.002**	**0.022**
FLUENCY	IC	**0.426**	**0.001**	**0.011**
FLUENCY	IC_DT	**0.438**	**0.000**	**0.008**
FLUENCY	Sensorial_D	0.293	0.023	0.170
FLUENCY	TP_stand	**0.366**	**0.004**	**0.048**
FRAILTY	Grip	**-0.513**	**0.000**	**0.001**
FRAILTY	HADS_A	**0.442**	**0.000**	**0.007**
FRAILTY	HADS_TOT	**0.371**	**0.003**	**0.040**
FRAILTY	IC	**-0.448**	**0.000**	**0.006**
FRAILTY	IC_DT	**-0.425**	**0.001**	**0.011**
FRAILTY	LFHF_stand	-0.271	0.038	0.249
FRAILTY	Locomotor_D	-0.301	0.019	0.152
FRAILTY	MNA	**-0.421**	**0.001**	**0.012**
FRAILTY	Psychological_D	-0.319	0.013	0.117
FRAILTY	SixMTW	-0.358	0.020	0.154
FRAILTY	SPPB	**-0.372**	**0.003**	**0.040**

FRAILTY	Vacuity	-0.295	0.023	0.172
FRAILTY	Vitality_D	**-0.487**	**0.000**	**0.002**
GONOGO	PEF	-0.302	0.024	0.176
GONOGO	Vitality_D	**-0.407**	**0.002**	**0.026**
GRIP	GoNogo	-0.322	0.016	0.132
GRIP	IC	0.327	0.011	0.106
GRIP	IC_DT	0.321	0.013	0.115
GRIP	MNA	0.307	0.017	0.138
GRIP	PEF	**0.515**	**0.000**	**0.001**
GRIP	SixMTW	**0.481**	**0.001**	**0.018**
GRIP	SWAY_O_PL	0.269	0.046	0.280
GRIP	TugDTC	-0.300	0.035	0.233
GRIP	Vitality_D	**0.791**	**0.000**	**0.000**
HADS_A	HADS_TOT	**0.742**	**0.000**	**0.000**
HADS_A	HFa_rest	0.279	0.031	0.214
HADS_A	IC	**-0.338**	**0.008**	**0.083**
HADS_A	IC_DT	-0.306	0.018	0.141
HADS_A	Psychological_D	**-0.650**	**0.000**	**0.000**
HADS_D	HADS_TOT	**0.796**	**0.000**	**0.000**
HADS_D	IC	**-0.403**	**0.001**	**0.019**
HADS_D	IC_DT	-0.349	0.006	0.068
HADS_D	Psychological_D	**-0.797**	**0.000**	**0.000**
HADS_TOT	IC	**-0.471**	**0.000**	**0.003**
HADS_TOT	IC_DT	**-0.415**	**0.001**	**0.014**
HADS_TOT	Psychological_D	**-0.934**	**0.000**	**0.000**
HEAR	IC	**0.383**	**0.002**	**0.032**
HEAR	IC_DT	**0.381**	**0.003**	**0.034**
HEAR	LFa_rest	-0.257	0.047	0.286
HEAR	LFHF_rest	-0.310	0.016	0.132
HEAR	LFnu_rest	**-0.342**	**0.008**	**0.078**
HEAR	Sensorial_D	**0.653**	**0.000**	**0.000**
HFA_REST	Cognition_D	0.281	0.030	0.211
HFA_REST	HFa_stand	**0.621**	**0.000**	**0.000**
HFA_REST	HFnu_rest	0.331	0.010	0.098
HFA_REST	LFa_stand	**0.573**	**0.000**	**0.000**
HFA_REST	Locomotor_D	0.258	0.047	0.285
HFA_REST	TP_stand	**0.666**	**0.000**	**0.000**
HFA_STAND	Cognition_D	**0.465**	**0.000**	**0.005**
HFA_STAND	DeltaHFa	**0.641**	**0.000**	**0.000**
HFA_STAND	DeltaLFHF	**-0.433**	**0.001**	**0.010**
HFA_STAND	DualTask_D	0.370	0.005	0.058
HFA_STAND	HFnu_stand	**0.555**	**0.000**	**0.000**
HFA_STAND	LFHF_stand	**-0.495**	**0.000**	**0.002**
HFA_STAND	LFnu_stand	**-0.419**	**0.001**	**0.015**
HFNU_REST	DeltaLF	**0.460**	**0.000**	**0.005**
HFNU_REST	DeltaLFa	**0.456**	**0.000**	**0.006**

HFNU_REST	LFHF_rest	**-0.946**	**0.000**	**0.000**
HFNU_STAND	Cognition_D	0.320	0.014	0.122
HFNU_STAND	DeltaHFa	**0.602**	**0.000**	**0.000**
HFNU_STAND	DeltaLFa	-0.262	0.045	0.279
HFNU_STAND	DeltaLFHF	**-0.863**	**0.000**	**0.000**
HFNU_STAND	LFHF_stand	**-0.963**	**0.000**	**0.000**
HTIME	Cognition_D	-0.325	0.014	0.122
HTIME	IC	**-0.439**	**0.001**	**0.011**
HTIME	IC_DT	**-0.424**	**0.001**	**0.016**
HTIME	Sensorial_D	-0.308	0.020	0.154
HTIME	StroopDTC_Flex_2	0.337	0.014	0.122
HTIME	SWAY_C_PL	**0.405**	**0.003**	**0.033**
HTIME	SWAY_O_speed	**0.393**	**0.003**	**0.040**
HTIME	Vacuity	-0.289	0.031	0.213
IC_DT	IC	**0.982**	**0.000**	**0.000**
LFA_REST	DeltaLF	-0.304	0.020	0.152
LFA_REST	DeltaLFa	**-0.401**	**0.002**	**0.023**
LFA_REST	HFa_rest	**0.582**	**0.000**	**0.000**
LFA_REST	HFa_stand	**0.407**	**0.002**	**0.021**
LFA_REST	HFnu_rest	**-0.448**	**0.000**	**0.007**
LFA_REST	LFa_stand	**0.430**	**0.001**	**0.011**
LFA_REST	LFHF_rest	**0.529**	**0.000**	**0.000**
LFA_REST	LFnu_rest	**0.562**	**0.000**	**0.000**
LFA_REST	TP_stand	**0.404**	**0.002**	**0.022**
LFA_STAND	DeltaLFa	**0.534**	**0.000**	**0.000**
LFA_STAND	DeltaLFHF	0.314	0.016	0.132
LFA_STAND	HFa_stand	**0.595**	**0.000**	**0.000**
LFA_STAND	LFHF_stand	0.315	0.015	0.131
LFA_STAND	LFnu_stand	**0.362**	**0.005**	**0.056**
LFA_STAND	Locomotor_D	0.266	0.042	0.265
LFHF_REST	DeltaLF	**-0.488**	**0.000**	**0.002**
LFHF_REST	DeltaLFa	**-0.465**	**0.000**	**0.005**
LFHF_STAND	Cognition_D	-0.278	0.033	0.226
LFHF_STAND	DeltaHFa	**-0.583**	**0.000**	**0.000**
LFHF_STAND	DeltaLFa	0.339	0.009	0.089
LFHF_STAND	DeltaLFHF	**0.900**	**0.000**	**0.000**
LFNU_REST	DeltaLF	**-0.505**	**0.000**	**0.001**
LFNU_REST	DeltaLFa	**-0.448**	**0.000**	**0.007**
LFNU_REST	HFnu_rest	**-0.881**	**0.000**	**0.000**
LFNU_REST	LFHF_rest	**0.969**	**0.000**	**0.000**
LFNU_STAND	DeltaHFa	**-0.530**	**0.000**	**0.001**
LFNU_STAND	DeltaLFa	**0.376**	**0.004**	**0.041**
LFNU_STAND	DeltaLFHF	**0.900**	**0.000**	**0.000**
LFNU_STAND	HFnu_stand	**-0.914**	**0.000**	**0.000**
LFNU_STAND	LFHF_stand	**0.977**	**0.000**	**0.000**
LOCOMOTOR_D	IC	**0.563**	**0.000**	**0.000**

LOCOMOTOR_D	IC_DT	**0.550**	**0.000**	**0.000**
LPA	MPA	**-0.717**	**0.000**	**0.000**
LPA	VPA	**-0.504**	**0.000**	**0.001**
MHC_SF	HADS_A	-0.347	0.007	0.074
MHC_SF	HADS_D	**-0.586**	**0.000**	**0.000**
MHC_SF	HADS_TOT	**-0.583**	**0.000**	**0.000**
MHC_SF	IC	0.355	0.006	0.065
MHC_SF	IC_DT	0.327	0.012	0.109
MHC_SF	Psychological_D	**0.721**	**0.000**	**0.000**
MHC_SF	SixMTW	-0.320	0.042	0.264
MMSE	Cognition_D	**0.443**	**0.000**	**0.007**
MMSE	DeltaHFa	0.315	0.015	0.130
MMSE	DeltaLF	-0.258	0.049	0.292
MMSE	DeltaLFa	-0.257	0.049	0.293
MMSE	DeltaLFHF	-0.332	0.010	0.098
MMSE	DualTask_D	0.272	0.040	0.259
MMSE	HFnu_stand	0.300	0.021	0.157
MMSE	Htime	-0.294	0.026	0.188
MMSE	LFa_stand	-0.266	0.042	0.265
MMSE	LFHF_stand	-0.328	0.011	0.106
MMSE	LFnu_stand	-0.280	0.032	0.219
MMSE	NPA	-0.258	0.049	0.291
MMSE	RAVLT_D	**0.485**	**0.000**	**0.002**
MMSE	RAVLT_I	0.286	0.026	0.189
MMSE	StroopDTC_Flex_2	-0.268	0.046	0.283
MMSE	wake_efficiency	0.257	0.050	0.295
MNA	Cognition_D	0.301	0.019	0.152
MNA	GoNogo	-0.331	0.013	0.115
MNA	IC	**0.536**	**0.000**	**0.000**
MNA	IC_DT	**0.505**	**0.000**	**0.001**
MNA	Locomotor_D	0.259	0.046	0.280
MNA	SPPB	0.319	0.013	0.117
MNA	StroopDTC_Flex_2	-0.310	0.020	0.154
MNA	Vitality_D	**0.667**	**0.000**	**0.000**
MNA	wake_efficiency	0.260	0.047	0.285
MPA	SWAY_C_PL	0.321	0.016	0.132
MPA	SWAY_O_speed	0.316	0.017	0.141
MPA	VPA	**0.505**	**0.000**	**0.001**
MPA	wake_efficiency	**0.522**	**0.000**	**0.001**
NPA	MPA	**-0.581**	**0.000**	**0.000**
NPA	sleep_efficiency	**0.644**	**0.000**	**0.000**
NPA	SWAY_C_PL	**-0.431**	**0.001**	**0.013**
NPA	SWAY_O_speed	**-0.433**	**0.001**	**0.013**
NPA	SWAY_O_PL	-0.269	0.047	0.285
NPA	wake_efficiency	**-0.739**	**0.000**	**0.000**
PEF	IC	0.271	0.038	0.249

PEF	PPB	-0.300	0.022	0.166
PEF	sleep_efficiency	-0.290	0.028	0.195
PEF	Vitality_D	**0.753**	**0.000**	**0.000**
PPB	HFa_rest	0.320	0.014	0.122
PPB	HFnu_rest	0.322	0.013	0.118
PPB	Locomotor_D	**0.708**	**0.000**	**0.000**
PPB	TP_rest	0.336	0.009	0.094
PSYCHOLOGICAL_D	IC	**0.518**	**0.000**	**0.001**
PSYCHOLOGICAL_D	IC_DT	**0.458**	**0.000**	**0.005**
RAVLT_D	Cognition_D	**0.860**	**0.000**	**0.000**
RAVLT_D	DeltaHFa	**0.401**	**0.002**	**0.022**
RAVLT_D	DeltaLF	-0.282	0.030	0.213
RAVLT_D	DeltaLFHF	-0.325	0.012	0.110
RAVLT_D	DTCSwitch	-0.341	0.010	0.098
RAVLT_D	DualTask_D	**0.430**	**0.001**	**0.012**
RAVLT_D	Fluency	**0.453**	**0.000**	**0.005**
RAVLT_D	HFa_stand	**0.427**	**0.001**	**0.011**
RAVLT_D	HFnu_stand	**0.427**	**0.001**	**0.011**
RAVLT_D	Htime	-0.275	0.039	0.252
RAVLT_D	IC	**0.367**	**0.004**	**0.045**
RAVLT_D	IC_DT	**0.428**	**0.001**	**0.010**
RAVLT_D	LFHF_stand	**-0.377**	**0.003**	**0.039**
RAVLT_D	LFnu_stand	-0.328	0.011	0.106
RAVLT_D	TugDTC	-0.291	0.041	0.259
RAVLT_D	TugDTC_fast	-0.409	0.003	0.039
RAVLT_I	Cognition_D	**0.850**	**0.000**	**0.000**
RAVLT_I	DeltaHFa	0.311	0.017	0.138
RAVLT_I	DTCSwitch	-0.411	0.002	0.022
RAVLT_I	DualTask_D	**0.433**	**0.001**	**0.012**
RAVLT_I	Fluency	**0.498**	**0.000**	**0.001**
RAVLT_I	HFa_rest	0.276	0.033	0.225
RAVLT_I	HFa_stand	**0.452**	**0.000**	**0.006**
RAVLT_I	HFnu_stand	0.310	0.017	0.138
RAVLT_I	IC	**0.433**	**0.001**	**0.009**
RAVLT_I	IC_DT	**0.490**	**0.000**	**0.001**
RAVLT_I	LFa_stand	0.259	0.048	0.289
RAVLT_I	RAVLT_D	**0.822**	**0.000**	**0.000**
RAVLT_I	TP_stand	0.267	0.041	0.259
RAVLT_I	TugDTC	-0.301	0.034	0.229
RAVLT_I	TugDTC_fast	-0.381	0.006	0.068
SENSORIAL_D	IC	**0.592**	**0.000**	**0.000**
SENSORIAL_D	IC_DT	**0.594**	**0.000**	**0.000**
SENSORIAL_D	Locomotor_D	0.345	0.007	0.076
SIXMTW	LFnu_stand	0.312	0.047	0.285
SIXMTW	PEF	**0.468**	**0.002**	**0.023**
SIXMTW	TP_stand	0.350	0.025	0.182

SIXMTW	Vitality_D	0.385	0.012	0.110
SIXMTW	VPA	0.424	0.006	0.061
SLEEP_EFFICIENCY	SWAY_C_PL	-0.280	0.037	0.246
SLEEP_EFFICIENCY	SWAY_O_speed	-0.276	0.040	0.256
SPPB	GoNogo	-0.317	0.017	0.141
SPPB	IC	**0.607**	**0.000**	**0.000**
SPPB	IC_DT	**0.570**	**0.000**	**0.000**
SPPB	Locomotor_D	**0.726**	**0.000**	**0.000**
SPPB	Vitality_D	0.312	0.015	0.130
SSS	HADS_D	0.300	0.020	0.153
SSS	HFnu_stand	0.274	0.036	0.240
SSS	IC	-0.310	0.016	0.132
SSS	IC_DT	-0.279	0.031	0.215
SSS	Psychological_D	**-0.480**	**0.000**	**0.002**
SSS	SPPB	-0.263	0.042	0.265
SSS	wake_efficiency	-0.339	0.009	0.088
STROOPDTC_FLEX_1	DualTask_D	**-0.562**	**0.000**	**0.000**
STROOPDTC_FLEX_1	SixMTW	**0.439**	**0.004**	**0.042**
STROOPDTC_FLEX_1	StroopDTC_Flex_2	**0.846**	**0.000**	**0.000**
STROOPDTC_FLEX_2	DualTask_D	**-0.498**	**0.000**	**0.002**
STROOPDTC_FLEX_2	IC_DT	-0.270	0.045	0.277
STROOPDTC_FLEX_2	SixMTW	0.399	0.009	0.088
STROOPDTC_FLEX_2	SWAY_C_PL	0.318	0.017	0.141
STROOPDTC_FLEX_2	SWAY_O_speed	0.308	0.021	0.158
STROOPDTC_INH_1	PPB	-0.337	0.012	0.113
STROOPDTC_INH_1	StroopDTC_Inh_2	**0.694**	**0.000**	**0.000**
STROOPDTC_INH_2	Cognition_D	-0.300	0.025	0.182
STROOPDTC_INH_2	IC	-0.275	0.041	0.260
STROOPDTC_INH_2	IC_DT	-0.307	0.022	0.162
STROOPDTC_INH_2	LPA	0.326	0.015	0.129
STROOPDTC_INH_2	MPA	-0.284	0.036	0.238
STROOPDTC_INH_2	PPB	-0.355	0.008	0.082
SWAY_O_MAXDEV	HFnu_rest	0.273	0.040	0.259
SWAY_O_MAXDEV	Locomotor_D	**-0.387**	**0.003**	**0.039**
SWAY_O_MAXDEV	SWAY_O_speed	**0.415**	**0.001**	**0.020**
SWAY_C_PL	Locomotor_D	-0.313	0.018	0.142
SWAY_C_PL	Sensorial_D	-0.350	0.008	0.082
SWAY_C_PL	SWAY_O_maxDev	**0.409**	**0.002**	**0.022**
SWAY_C_PL	SWAY_O_speed	**0.998**	**0.000**	**0.000**
SWAY_C_PL	SWAY_O_PL	**0.798**	**0.000**	**0.000**
SWAY_C_PL	Vitality_D	0.299	0.024	0.177
SWAY_O_SPEED	Locomotor_D	-0.309	0.020	0.152
SWAY_O_SPEED	Sensorial_D	-0.354	0.007	0.075
SWAY_O_SPEED	Vitality_D	0.296	0.026	0.186
SWAY_O_PL	LFa_stand	0.339	0.012	0.109
SWAY_O_PL	Sensorial_D	-0.281	0.036	0.240

SWAY_O_PL	SWAY_O_maxDev	**0.432**	**0.001**	**0.014**
SWAY_O_PL	SWAY_O_speed	**0.801**	**0.000**	**0.000**
SWAY_O_PL	Vitality_D	0.333	0.013	0.114
TP_REST	HFa_rest	**0.683**	**0.000**	**0.000**
TP_REST	HFa_stand	**0.433**	**0.001**	**0.011**
TP_REST	LFa_rest	**0.677**	**0.000**	**0.000**
TP_REST	LFa_stand	**0.523**	**0.000**	**0.001**
TP_REST	Locomotor_D	0.324	0.012	0.110
TP_REST	TP_stand	**0.529**	**0.000**	**0.001**
TP_STAND	Cognition_D	0.302	0.020	0.154
TP_STAND	DeltaLFa	0.265	0.043	0.265
TP_STAND	HFa_stand	**0.631**	**0.000**	**0.000**
TP_STAND	LFa_stand	**0.660**	**0.000**	**0.000**
TP_STAND	Locomotor_D	0.277	0.034	0.233
TUGDTC	Cognition_D	-0.358	0.011	0.106
TUGDTC	DeltaHFa	**-0.482**	**0.001**	**0.009**
TUGDTC	DeltaLF	0.292	0.042	0.265
TUGDTC	DualTask_D	**-0.637**	**0.000**	**0.000**
TUGDTC	HFa_stand	**-0.422**	**0.003**	**0.034**
TUGDTC	IC	**-0.475**	**0.001**	**0.009**
TUGDTC	IC_DT	**-0.548**	**0.000**	**0.001**
TUGDTC	Sensorial_D	-0.319	0.024	0.177
TUGDTC	TugDTC_fast	**0.623**	**0.000**	**0.000**
TUGDTC_FAST	Cognition_D	**-0.408**	**0.003**	**0.040**
TUGDTC_FAST	DeltaHFa	**-0.481**	**0.001**	**0.009**
TUGDTC_FAST	DeltaLFHF	0.300	0.036	0.241
TUGDTC_FAST	DualTask_D	**-0.820**	**0.000**	**0.000**
TUGDTC_FAST	HFa_stand	**-0.452**	**0.001**	**0.017**
TUGDTC_FAST	IC	-0.336	0.018	0.141
TUGDTC_FAST	IC_DT	**-0.456**	**0.001**	**0.014**
TUGDTC_FAST	LFHF_stand	0.303	0.034	0.233
TUGDTC_FAST	TP_stand	-0.340	0.017	0.141
VACUITY	IC	**0.365**	**0.005**	**0.050**
VACUITY	IC_DT	**0.375**	**0.003**	**0.040**
VACUITY	NPA	0.310	0.018	0.142
VACUITY	Sensorial_D	**0.670**	**0.000**	**0.000**
VACUITY	SWAY_C_PL	**-0.385**	**0.003**	**0.040**

TABLE C3. *Node-level centrality metrics for all variables in the thresholded correlation network (|r| ≥ 0.40) of raw data at PRAISE T0. Degree = number of edges; Strength = sum of absolute edge weights; Betweenness = proportion of shortest paths passing through the node (using distance = 1/weight); Closeness = inverse of average path length to all other nodes; Eigenvector = importance based on connections to other central nodes; Community = Louvain cluster assignment.*

VARIABLE	DEGREE	STRENGTH	BETWEENNESS	CLOSENESS	EIGENVECTOR	COMMUNITY
AGE	4	1.901	0.046	0.164	0.059	1
MMSE	2	1.045	0.028	0.159	0.072	1
SSS	2	0.931	0.000	0.155	0.101	1
MHC_SF	3	1.914	0.000	0.140	0.082	1
SPPB	4	2.489	0.000	0.186	0.300	1
HTIME	3	1.374	0.000	0.169	0.178	1
HADS_A	2	1.273	0.000	0.132	0.058	1
HADS_D	4	2.584	0.000	0.157	0.156	1
HADS_TOT	5	3.390	0.001	0.159	0.170	1
PPB	1	0.708	0.000	0.150	0.043	1
PSYCHOLOGICAL_D	7	4.507	0.061	0.171	0.270	1
LOCOMOTOR_D	6	3.654	0.075	0.190	0.290	1
IC	17	9.123	0.245	0.231	0.800	1
FRAILTY	6	2.961	0.130	0.184	0.255	2
GRIP	4	2.510	0.000	0.157	0.091	2
MNA	3	1.576	0.000	0.173	0.203	2
GONOGO	1	0.425	0.000	0.129	0.023	2
SIXMTW	6	3.098	0.172	0.153	0.080	2
PEF	3	1.818	0.000	0.154	0.061	2
VITALITY_D	8	4.588	0.083	0.184	0.259	2
BMI	0	0.000	0.000	NA	0.000	3
ESS	2	0.805	0.000	0.160	0.125	4
RAVLT_I	9	4.899	0.001	0.202	0.740	4
RAVLT_D	8	4.280	0.059	0.192	0.634	4
FLUENCY	6	2.999	0.000	0.190	0.513	4
DTCSWITCH	5	2.535	0.000	0.176	0.394	4
STROOPDTC_FLEX_1	2	1.471	0.000	0.150	0.093	4
STROOPDTC_FLEX_2	2	1.434	0.000	0.148	0.089	4
TUGDTC	7	3.701	0.147	0.209	0.567	4
TUGDTC_FAST	9	4.750	0.034	0.204	0.710	4
DUALTASK_D	9	5.268	0.060	0.200	0.619	4
COGNITION_D	9	5.407	0.137	0.212	0.802	4
IC_DT	18	9.660	0.312	0.235	0.902	4
STROOPDTC_INH_1	1	0.642	0.000	0.642	0.000	5

STROOPDTC_INH_2	1	0.642	0.000	0.642	0.000	5
HEAR	2	1.095	0.000	0.156	0.113	6
VACUITY	1	0.685	0.000	0.143	0.034	6
SWAY_C_PL	2	1.804	0.000	0.116	0.007	6
SWAY_O_PL	3	2.053	0.000	0.115	0.009	6
SWAY_O_MAXDEV	3	1.325	0.010	0.141	0.032	6
SWAY_O_SPEED	4	2.607	0.054	0.130	0.026	6
SENSORIAL_D	5	2.943	0.107	0.180	0.235	6
NPA	3	1.943	0.030	0.089	0.000	7
LPA	2	1.353	0.000	0.102	0.001	7
MPA	4	2.506	0.088	0.105	0.001	7
VPA	3	1.672	0.141	0.122	0.009	7
SLEEP_EFFICIENCY	1	0.653	0.000	0.079	0.000	7
WAKE_EFFICIENCY	2	1.252	0.000	0.088	0.000	7
TP_REST	5	2.955	0.000	0.136	0.253	8
LFA_REST	9	4.545	0.012	0.136	0.328	8
HFA_REST	5	3.110	0.000	0.146	0.282	8
LFNU_REST	5	3.402	0.001	0.119	0.256	8
HFNU_REST	5	3.229	0.000	0.116	0.242	8
LFHF_REST	5	3.465	0.000	0.118	0.257	8
TP_STAND	5	2.885	0.000	0.147	0.274	8
LFA_STAND	6	3.402	0.004	0.147	0.303	8
HFA_STAND	16	7.925	0.140	0.181	1.000	8
DELTALFA	7	3.590	0.003	0.124	0.338	8
DELTALF	9	5.724	0.094	0.145	0.788	9
LFNU_STAND	6	4.553	0.000	0.145	0.834	9
HFNU_STAND	7	5.025	0.026	0.156	0.892	9
LFHF_STAND	6	4.650	0.000	0.147	0.850	9
DELTALFHF	7	5.118	0.002	0.147	0.870	9
DELTAHFA	9	4.916	0.152	0.176	0.842	9

TABLE C4. *Pairwise Spearman significant correlations among study variables at PRAISE HRV T0 (age-adjusted data). For each pair we report Spearman's ρ, raw p-value and FDR-adjusted p-value (Benjamini–Hochberg). FDR-adjusted significant p values are highlighted in bold.*

VARIABLE 1	VARIABLE 2	SPEARMAN RHO	PVALUE	FDR PVALUE
BMI	ESS	0.403	0.027	0.257
BMI	MNA	0.507	0.004	0.069
BMI	PEF	0.496	0.005	0.082
BMI	RAVLT_D	-0.451	0.014	0.164

BMI	TugDTC_fast	0.422	0.040	0.329
DELTAHF	HFa_stand	0.447	0.014	0.164
DELTAHF	HFnu_stand	**0.619**	**0.000**	**0.011**
DELTAHF	LFHF_stand	**-0.601**	**0.001**	**0.016**
DELTAHF	LFnu_stand	**-0.604**	**0.001**	**0.015**
DELTAHFA	DeltaHF	**0.654**	**0.000**	**0.004**
DELTAHFA	DeltaLF	**-0.598**	**0.001**	**0.017**
DELTAHFA	DeltaLFHF	**-0.696**	**0.000**	**0.001**
DELTAHFA	HFa_stand	**0.613**	**0.000**	**0.012**
DELTAHFA	HFnu_stand	**0.668**	**0.000**	**0.003**
DELTAHFA	LFHF_stand	**-0.657**	**0.000**	**0.004**
DELTAHFA	LFnu_stand	**-0.660**	**0.000**	**0.004**
DELTALF	DeltaHF	**-0.865**	**0.000**	**0.000**
DELTALF	DeltaLFHF	**0.829**	**0.000**	**0.000**
DELTALF	HFa_stand	-0.514	0.004	0.067
DELTALF	HFnu_stand	**-0.572**	**0.001**	**0.027**
DELTALF	LFHF_stand	**0.636**	**0.000**	**0.007**
DELTALF	LFnu_stand	**0.669**	**0.000**	**0.003**
DELTALFA	DeltaHF	-0.457	0.012	0.149
DELTALFA	DeltaLF	**0.547**	**0.002**	**0.040**
DELTALFA	DeltaLFHF	0.370	0.044	0.344
DELTALFHF	DeltaHF	**-0.788**	**0.000**	**0.000**
DELTALFHF	HFa_stand	**-0.726**	**0.000**	**0.000**
DELTALFHF	HFnu_stand	**-0.867**	**0.000**	**0.000**
DELTALFHF	LFHF_stand	**0.895**	**0.000**	**0.000**
DELTALFHF	LFnu_stand	**0.889**	**0.000**	**0.000**
DELTALFHF	TP_stand	-0.414	0.023	0.231
DTCSWITCH	DeltaLFHF	0.442	0.019	0.199
DTCSWITCH	HFnu_stand	-0.403	0.034	0.292
DTCSWITCH	LFHF_stand	0.470	0.012	0.153
DTCSWITCH	LFnu_stand	0.414	0.029	0.270
DTCSWITCH	StroopDTC_Inh_1	0.484	0.010	0.130
DTCSWITCH	StroopDTC_Inh_2	**0.591**	**0.001**	**0.027**
ESS	Fluency	-0.455	0.013	0.155
ESS	HADS_D	0.370	0.044	0.344
ESS	Hear	**-0.565**	**0.001**	**0.027**
ESS	Htime	0.455	0.015	0.170
ESS	RAVLT_I	-0.534	0.003	0.051
FLUENCY	DeltaHFa	0.435	0.018	0.198
FLUENCY	DeltaLF	-0.384	0.040	0.326
FLUENCY	DeltaLFHF	-0.414	0.025	0.243
FLUENCY	HFnu_stand	0.376	0.044	0.344
FLUENCY	LFHF_stand	-0.484	0.008	0.110
FLUENCY	LFnu_stand	**-0.547**	**0.002**	**0.040**
FLUENCY	SixMTW	-0.541	0.017	0.184
FLUENCY	VPA	-0.375	0.050	0.368

FLUENCY	wake_efficiency	0.374	0.050	0.368
FRAILTY	Grip	-0.468	0.009	0.125
FRAILTY	HADS_TOT	0.390	0.033	0.290
FRAILTY	HFnu_stand	0.386	0.035	0.296
FRAILTY	StroopDTC_Inh_1	0.463	0.013	0.155
GRIP	HFnu_rest	-0.490	0.007	0.095
GRIP	LFHF_rest	0.443	0.014	0.164
GRIP	LFnu_rest	0.461	0.011	0.141
GRIP	PEF	0.394	0.031	0.273
GRIP	StroopDTC_Inh_1	-0.443	0.019	0.202
HADS_A	HADS_TOT	**0.743**	**0.000**	**0.000**
HADS_A	HFa_rest	0.443	0.014	0.164
HADS_D	HADS_TOT	**0.801**	**0.000**	**0.000**
HADS_D	TP_stand	0.457	0.011	0.141
HADS_TOT	HFa_rest	0.524	0.003	0.051
HADS_TOT	LFa_stand	0.415	0.023	0.230
HADS_TOT	TP_stand	0.415	0.023	0.230
HEAR	DeltaHFa	0.384	0.036	0.301
HEAR	DeltaLFa	0.372	0.043	0.343
HEAR	LFa_rest	-0.405	0.027	0.251
HEAR	LFHF_rest	-0.422	0.020	0.212
HEAR	LFnu_rest	-0.436	0.016	0.177
HFA_REST	DeltaLFHF	-0.463	0.010	0.131
HFA_REST	HFa_stand	**0.767**	**0.000**	**0.000**
HFA_REST	HFnu_stand	0.474	0.009	0.121
HFA_REST	LFa_stand	**0.684**	**0.000**	**0.002**
HFA_REST	LFHF_stand	-0.415	0.023	0.231
HFA_REST	TP_stand	**0.737**	**0.000**	**0.000**
HFA_STAND	HFnu_stand	**0.785**	**0.000**	**0.000**
HFA_STAND	LFHF_stand	**-0.709**	**0.000**	**0.001**
HFA_STAND	LFnu_stand	**-0.664**	**0.000**	**0.004**
HFNU_REST	DeltaHF	**-0.672**	**0.000**	**0.003**
HFNU_REST	DeltaLF	**0.552**	**0.002**	**0.037**
HFNU_REST	DeltaLFa	0.454	0.012	0.153
HFNU_REST	LFHF_rest	**-0.900**	**0.000**	**0.000**
HFNU_STAND	LFHF_stand	**-0.928**	**0.000**	**0.000**
LFA_REST	DeltaHF	0.432	0.018	0.195
LFA_REST	DeltaLF	**-0.563**	**0.001**	**0.031**
LFA_REST	DeltaLFa	**-0.687**	**0.000**	**0.002**
LFA_REST	DeltaLFHF	-0.396	0.030	0.271
LFA_REST	HFa_rest	**0.725**	**0.000**	**0.001**
LFA_REST	HFa_stand	**0.538**	**0.002**	**0.046**
LFA_REST	LFa_stand	**0.661**	**0.000**	**0.004**
LFA_REST	LFHF_rest	0.509	0.004	0.067
LFA_REST	LFnu_rest	**0.538**	**0.002**	**0.046**
LFA_REST	TP_stand	**0.562**	**0.001**	**0.031**

LFA_STAND	HFa_stand	**0.719**	**0.000**	**0.001**
LFHF_REST	DeltaHF	**0.573**	**0.001**	**0.024**
LFHF_REST	DeltaLF	**-0.568**	**0.001**	**0.027**
LFHF_REST	DeltaLFa	**-0.558**	**0.001**	**0.030**
LFNU_REST	DeltaHF	0.507	0.005	0.076
LFNU_REST	DeltaLF	-0.526	0.003	0.055
LFNU_REST	DeltaLFa	**-0.556**	**0.002**	**0.034**
LFNU_REST	HFnu_rest	**-0.840**	**0.000**	**0.000**
LFNU_REST	LFHF_rest	**0.983**	**0.000**	**0.000**
LFNU_STAND	HFnu_stand	**-0.879**	**0.000**	**0.000**
LFNU_STAND	LFHF_stand	**0.980**	**0.000**	**0.000**
LPA	MPA	**-0.779**	**0.000**	**0.000**
LPA	VPA	**-0.566**	**0.001**	**0.030**
MHC_SF	HADS_D	**-0.563**	**0.001**	**0.027**
MHC_SF	HADS_TOT	**-0.528**	**0.003**	**0.049**
MHC_SF	sleep_efficiency	-0.403	0.030	0.271
MMSE	Fluency	0.504	0.005	0.082
MMSE	RAVLT_D	0.541	0.002	0.046
MMSE	RAVLT_I	0.378	0.043	0.343
MMSE	SixMTW	-0.629	0.003	0.051
MMSE	wake_efficiency	**0.603**	**0.001**	**0.015**
MNA	DeltaLF	**-0.560**	**0.001**	**0.029**
MNA	DeltaLFHF	-0.369	0.045	0.344
MPA	VPA	0.401	0.031	0.273
MPA	wake_efficiency	0.492	0.007	0.097
NPA	MPA	-0.456	0.013	0.155
NPA	sleep_efficiency	**0.754**	**0.000**	**0.000**
NPA	wake_efficiency	**-0.616**	**0.000**	**0.011**
PPB	HFa_rest	0.405	0.029	0.270
PPB	LFa_rest	0.443	0.016	0.177
PPB	LFa_stand	0.392	0.035	0.298
PPB	TP_rest	0.508	0.005	0.077
RAVLT_D	DeltaHFa	0.385	0.039	0.326
RAVLT_D	DeltaLF	-0.403	0.030	0.271
RAVLT_D	DeltaLFHF	-0.401	0.031	0.273
RAVLT_D	Fluency	0.520	0.004	0.064
RAVLT_D	HFnu_stand	0.497	0.006	0.091
RAVLT_D	LFHF_stand	-0.461	0.012	0.149
RAVLT_D	LFnu_stand	-0.483	0.008	0.111
RAVLT_D	TugDTC_fast	-0.415	0.049	0.368
RAVLT_D	VPA	-0.388	0.041	0.334
RAVLT_I	DeltaLF	-0.444	0.016	0.176
RAVLT_I	DeltaLFHF	-0.491	0.007	0.098
RAVLT_I	Fluency	**0.549**	**0.002**	**0.040**
RAVLT_I	HFa_stand	0.406	0.029	0.270
RAVLT_I	HFnu_stand	**0.572**	**0.001**	**0.027**

RAVLT_I	LFHF_stand	-0.494	0.006	0.095
RAVLT_I	LFnu_stand	-0.499	0.006	0.088
RAVLT_I	RAVLT_D	**0.837**	**0.000**	**0.000**
RAVLT_I	VPA	-0.383	0.044	0.344
SLEEP_EFFICIENCY	SWAY_O_PL	-0.458	0.015	0.170
SLEEP_EFFICIENCY	SWAY_O_Speed	-0.458	0.015	0.170
SPPB	LFa_stand	0.365	0.048	0.359
SSS	HADS_D	0.396	0.030	0.271
SSS	PEF	-0.412	0.024	0.231
SSS	wake_efficiency	-0.371	0.048	0.359
STROOPDTC_FLEX_1	StroopDTC_Flex_2	**0.924**	**0.000**	**0.000**
STROOPDTC_INH_1	LPA	**0.595**	**0.001**	**0.027**
STROOPDTC_INH_1	PPB	-0.428	0.026	0.249
STROOPDTC_INH_1	StroopDTC_Inh_2	**0.809**	**0.000**	**0.000**
STROOPDTC_INH_2	DeltaLF	0.403	0.034	0.292
STROOPDTC_INH_2	LPA	**0.652**	**0.000**	**0.007**
STROOPDTC_INH_2	MPA	**-0.556**	**0.003**	**0.047**
STROOPDTC_INH_2	StroopDTC_Flex_2	0.382	0.046	0.350
SWAY_C_PL	SWAY_O_Speed	**0.821**	**0.000**	**0.000**
SWAY_O_MAXDEV	DeltaHF	-0.581	0.001	0.027
SWAY_O_MAXDEV	DeltaLF	**0.572**	**0.001**	**0.031**
SWAY_O_MAXDEV	DeltaLFa	0.421	0.024	0.231
SWAY_O_MAXDEV	DeltaLFHF	0.525	0.003	0.059
SWAY_O_MAXDEV	HFnu_rest	0.486	0.008	0.113
SWAY_O_MAXDEV	LFHF_rest	-0.470	0.010	0.132
SWAY_O_MAXDEV	LFnu_rest	-0.421	0.024	0.231
SWAY_O_PL	SWAY_C_PL	**0.821**	**0.000**	**0.000**
SWAY_O_PL	SWAY_O_Speed	**1.000**	**0.000**	**0.000**
TP_REST	DeltaLF	-0.469	0.010	0.129
TP_REST	DeltaLFa	-0.467	0.010	0.131
TP_REST	DeltaLFHF	-0.412	0.024	0.231
TP_REST	HFa_rest	**0.732**	**0.000**	**0.000**
TP_REST	HFa_stand	**0.604**	**0.001**	**0.015**
TP_REST	LFa_rest	**0.842**	**0.000**	**0.000**
TP_REST	LFa_stand	**0.701**	**0.000**	**0.001**
TP_REST	TP_stand	**0.663**	**0.000**	**0.004**
TP_STAND	HFa_stand	**0.616**	**0.000**	**0.011**
TP_STAND	HFnu_stand	0.399	0.030	0.271
TP_STAND	LFa_stand	**0.582**	**0.001**	**0.024**
TP_STAND	LFHF_stand	-0.366	0.047	0.359
TUGDTC	DeltaHF	-0.552	0.006	0.088
TUGDTC	DeltaHFa	-0.557	0.005	0.083
TUGDTC	DeltaLF	**0.622**	**0.001**	**0.031**
TUGDTC	DeltaLFHF	**0.619**	**0.002**	**0.032**
TUGDTC	HFa_stand	-0.426	0.039	0.326
TUGDTC	HFnu_stand	-0.505	0.013	0.155

TUGDTC	LFHF_stand	0.516	0.011	0.140
TUGDTC	LFnu_stand	0.459	0.025	0.243
TUGDTC	TugDTC_fast	0.472	0.021	0.217
TUGDTC	Vacuity	-0.473	0.020	0.208
TUGDTC_FAST	DeltaHF	-0.423	0.040	0.329
TUGDTC_FAST	DeltaHFa	-0.470	0.022	0.224
TUGDTC_FAST	DeltaLF	0.419	0.043	0.342
TUGDTC_FAST	DeltaLFHF	0.422	0.041	0.334
TUGDTC_FAST	LFHF_stand	0.444	0.031	0.273
TUGDTC_FAST	LFnu_stand	0.437	0.034	0.292
TUGDTC_FAST	NPA	-0.423	0.045	0.344
TUGDTC_FAST	sleep_efficiency	-0.478	0.022	0.227

TABLE C5. *PRAISE HRV T0 (N =30) age-adjusted data. W statistic and t test between subject level clustering (Chapter 3.1.2.2). Significant p values are highlighted in yellow, FRD-adjusted significant p values are reported in green.*

VARIABLE	MEAN CL1	MEANCL2	T TEST	T PVALUE	W STATISTIC	W PVALUE	T PFDR	W PFDR
L_FNU_STAND	41.482	74.267	-8.850	0.000	2.000	0.000	0.000	0.000
H_FNU_STAND	43.911	18.760	8.948	0.000	220.000	0.000	0.000	0.000
DELTA_LFHF_TERZILI	1.375	2.714	-7.567	0.000	12.000	0.000	0.000	0.000
DELTA_LF_TERZILI	1.500	2.571	-4.576	0.000	32.000	0.000	0.001	0.003
DELTA_LFHF	0.226	3.835	-5.105	0.000	1.000	0.000	0.002	0.000
LFHF_STAND	1.008	4.971	-4.721	0.000	1.000	0.000	0.004	0.000
DELTA_HF	-11.865	-35.218	4.013	0.000	192.000	0.001	0.004	0.003
DELTA_LF	7.257	35.317	-3.871	0.001	29.000	0.000	0.005	0.002
H_FA_STAND	197.360	31.859	3.534	0.003	205.000	0.000	0.019	0.000
DELTA_H_FA	-0.110	-70.264	3.187	0.005	199.000	0.000	0.034	0.001
FRAILTY	0.214	0.159	2.726	0.012	169.000	0.018	0.069	0.077
TP_STAND_LFHF	379.298	150.118	2.653	0.015	172.000	0.012	0.080	0.062
RAVLT_I	57.653	51.221	2.483	0.020	160.000	0.017	0.088	0.077
FLUENCY	45.933	36.571	2.501	0.019	160.000	0.017	0.088	0.077
TP_REST	1486.744	733.286	2.178	0.041	153.000	0.093	0.172	0.278
RAVLT_D	12.991	11.236	2.098	0.046	151.500	0.044	0.182	0.156
TUG_DTC	-3.360	12.849	-2.096	0.057	27.000	0.011	0.210	0.061
DTC_SWITCH	0.319	0.493	-1.817	0.088	65.000	0.142	0.291	0.374
VLF_REST	979.561	471.877	1.829	0.083	137.000	0.313	0.291	0.570
STROOP_DTC_INH_2	0.116	0.250	-1.768	0.093	71.000	0.235	0.294	0.549
L_FA_REST	184.797	100.244	1.650	0.112	140.000	0.257	0.322	0.550

TP_REST_LFHF	464.431	249.451	1.668	0.108	155.000	0.077	0.322	0.256
SPPB	8.938	9.786	-1.575	0.127	75.500	0.127	0.324	0.349
STROOP_DTC_INH_1	0.141	0.267	-1.597	0.128	76.000	0.339	0.324	0.577
HEAR	0.633	0.420	1.599	0.121	149.000	0.123	0.324	0.349
MHC_SF	42.375	36.214	1.444	0.160	138.500	0.279	0.341	0.550
TUG_DTC_FAST	5.279	26.725	-1.512	0.162	33.000	0.031	0.341	0.113
H_FA_REST	279.634	149.207	1.447	0.160	166.000	0.025	0.341	0.097
TP_STAND	1000.057	611.497	1.455	0.157	153.000	0.093	0.341	0.278
L_FA_STAND	181.938	118.259	1.467	0.154	145.000	0.179	0.341	0.452
HADS_A	7.500	6.000	1.276	0.212	141.500	0.224	0.432	0.543
MNA	27.000	26.286	1.237	0.227	139.500	0.257	0.433	0.550
SWAY_C_MAX_DEV	15.631	17.394	-1.237	0.227	79.000	0.270	0.433	0.550
MMSE	27.619	27.129	1.064	0.299	136.500	0.317	0.538	0.570
VPA	0.927	0.464	1.077	0.299	114.500	0.693	0.538	0.860
GRIP	21.270	23.663	-1.009	0.322	85.000	0.275	0.549	0.550
STROOP_DTC_FLEX_2	0.930	1.125	-1.026	0.317	79.000	0.413	0.549	0.651
LPA	35.087	37.429	-0.961	0.345	83.500	0.359	0.573	0.596
STROOP_DTC_FLEX_1	0.978	1.147	-0.907	0.375	86.000	0.618	0.605	0.846
HADS_TOT	12.500	11.071	0.837	0.410	137.000	0.307	0.646	0.570
SIX_MTW	484.300	508.350	-0.761	0.460	35.000	0.335	0.707	0.577
L_FNU_REST	34.225	38.950	-0.705	0.487	97.000	0.552	0.713	0.809
LFHF_REST	0.783	1.136	-0.723	0.479	103.000	0.724	0.713	0.860
VACUITY	0.671	0.728	-0.581	0.566	98.500	0.585	0.810	0.837
VLF_STAND	557.329	452.164	0.527	0.602	121.000	0.723	0.843	0.860
BMI	25.839	25.306	0.449	0.657	124.000	0.633	0.845	0.848
ESS	5.938	6.714	-0.478	0.636	91.500	0.403	0.845	0.651
HTIME	82.467	84.492	-0.450	0.657	96.500	0.982	0.845	0.983
MPA	28.400	26.943	0.471	0.642	117.000	0.616	0.845	0.846
SSS	6.000	6.357	-0.385	0.704	107.500	0.866	0.870	0.941
PEF	279.523	288.629	-0.273	0.788	115.500	0.901	0.870	0.946
WAKE_EFFICIENCY	89.600	88.836	0.332	0.743	106.000	0.983	0.870	0.983
PPB	2.020	1.914	0.290	0.774	109.500	0.861	0.870	0.941
SWAY_C_PL	342.400	354.327	-0.328	0.746	114.000	0.715	0.870	0.860
SWAY_O_PL	551.027	570.518	-0.283	0.779	104.000	0.983	0.870	0.983
SWAY_O_SPEED	11.407	11.805	-0.328	0.746	114.000	0.715	0.870	0.860
H_FNU_REST	55.776	53.978	0.306	0.762	117.000	0.854	0.870	0.941
NPA	35.587	35.150	0.204	0.840	114.000	0.711	0.912	0.860
AGE	72.188	71.857	0.185	0.855	116.000	0.884	0.913	0.944
GO_NOGO	960.884	955.200	0.140	0.890	104.000	0.786	0.919	0.917
DELTA_L_FA	104.465	116.980	-0.154	0.879	93.000	0.448	0.919	0.688
HADS_D	5.000	5.071	-0.064	0.949	129.000	0.487	0.963	0.730
SLEEP_EFFICIENCY	75.180	75.029	0.047	0.963	111.000	0.813	0.963	0.931

TABLE C6. *Pairwise Spearman significant correlations among study variables at PRAISE T1. For each pair we report Spearman's ρ, raw p-value and FDR-adjusted p-value (Benjamini–Hochberg). FDR-adjusted significant p values are highlighted in bold.*

VARIABLE1	VARIABLE2	SPEARMAN RHO	P VALUE	FDR P VALUE
BMI	Grip	0.383	0.024	0.253
BMI	MNA	0.431	0.010	0.148
DELTAHFA	DeltaLF	-0.435	0.031	0.293
DELTAHFA	DeltaLFHF	-0.495	0.013	0.176
DELTALF	DeltaLFHF	**0.856**	**0.000**	**0.000**
DELTALF	HFnu_stand	**-0.665**	**0.000**	**0.015**
DELTALF	LFa_stand	0.477	0.017	0.214
DELTALF	LFHF_stand	**0.622**	**0.001**	**0.035**
DELTALF	LFnu_stand	0.569	0.003	0.077
DELTALFA	DeltaLF	0.487	0.015	0.191
DELTALFA	DeltaLFHF	0.481	0.016	0.207
DELTALFA	HFnu_stand	-0.455	0.023	0.252
DELTALFA	IC_Dtglobal	0.564	0.007	0.120
DELTALFA	IC_global	0.443	0.040	0.343
DELTALFA	LFa_stand	0.501	0.012	0.163
DELTALFA	LFHF_stand	0.410	0.043	0.353
DELTALFA	LFnu_stand	0.492	0.013	0.181
DT_ICDOMAIN	IC_Dtglobal	**0.697**	**0.000**	**0.001**
DTCSWITCH	DeltaLfa	-0.573	0.003	0.074
DTCSWITCH	DT_Icdomain	**-0.639**	**0.000**	**0.006**
DTCSWITCH	Hear	-0.388	0.023	0.252
DTCSWITCH	HFnu_stand	0.523	0.008	0.126
DTCSWITCH	IC_Dtglobal	-0.493	0.005	0.092
DTCSWITCH	LFa_stand	-0.547	0.005	0.103
DTCSWITCH	LFHF_stand	-0.498	0.012	0.168
DTCSWITCH	LFnu_stand	**-0.606**	**0.002**	**0.048**
DTCSWITCH	PPB	-0.378	0.031	0.293
DTCSWITCH	StroopDTC_Flex_1	0.513	0.002	0.052
DTCSWITCH	StroopDTC_Flex_2	0.463	0.006	0.104
DTCSWITCH	TugDTC_fast	0.392	0.030	0.289
DTCSWITCH	Vitality_IC	-0.352	0.049	0.372
DTCSWITCH	wake_efficiency	0.346	0.049	0.372
ESS	DeltaLfa	-0.426	0.035	0.316
ESS	DeltaLFHF	-0.465	0.020	0.242
ESS	Fluency	-0.357	0.038	0.332
ESS	HFnu_stand	0.428	0.034	0.315
ESS	IC_Dtglobal	-0.519	0.002	0.060
ESS	IC_global	-0.396	0.025	0.261
ESS	LFHF_stand	-0.431	0.033	0.305
ESS	LFnu_stand	-0.408	0.044	0.356

ESS	StroopDTC_Inh_1	0.413	0.014	0.183
ESS	StroopDTC_Inh_2	**0.581**	**0.000**	**0.010**
FLUENCY	Cognition_IC	**0.602**	**0.000**	**0.013**
FLUENCY	Hear	0.346	0.049	0.372
FLUENCY	HFnu_rest	0.551	0.004	0.088
FLUENCY	IC_Dtglobal	**0.559**	**0.001**	**0.034**
FLUENCY	IC_global	**0.561**	**0.001**	**0.034**
FLUENCY	LFHF_rest	-0.420	0.037	0.326
FLUENCY	NPA	-0.364	0.040	0.343
FLUENCY	StroopDTC_Flex_1	-0.341	0.048	0.371
FLUENCY	StroopDTC_Flex_2	-0.358	0.038	0.328
FLUENCY	wake_efficiency	0.407	0.021	0.243
FRAILTY	DeltaHFa	-0.435	0.030	0.288
FRAILTY	Grip	-0.484	0.003	0.074
FRAILTY	HADS_A	0.348	0.041	0.346
FRAILTY	HADS_D	0.505	0.002	0.054
FRAILTY	HADS_TOT	**0.587**	**0.000**	**0.009**
FRAILTY	IC_Dtglobal	**-0.565**	**0.001**	**0.026**
FRAILTY	IC_global	**-0.569**	**0.001**	**0.024**
FRAILTY	Locomotor_IC	**-0.544**	**0.001**	**0.039**
FRAILTY	Psy_IC	-0.359	0.044	0.356
FRAILTY	SPPB	**-0.587**	**0.000**	**0.009**
FRAILTY	Vitality_IC	-0.459	0.008	0.128
GRIP	Cognition_IC	-0.466	0.008	0.124
GRIP	PEF	0.500	0.004	0.084
GRIP	SPPB	0.371	0.028	0.285
GRIP	TugDTC_fast	-0.514	0.004	0.077
GRIP	Vitality_IC	**0.751**	**0.000**	**0.000**
HADS_A	HADS_TOT	**0.808**	**0.000**	**0.000**
HADS_A	IC_Dtglobal	-0.388	0.028	0.285
HADS_A	IC_global	-0.381	0.031	0.295
HADS_A	Psy_IC	**-0.722**	**0.000**	**0.000**
HADS_A	StroopDTC_Flex_2	0.339	0.047	0.362
HADS_D	HADS_TOT	**0.656**	**0.000**	**0.001**
HADS_D	IC_Dtglobal	-0.441	0.012	0.163
HADS_D	IC_global	-0.464	0.007	0.121
HADS_D	Psy_IC	-0.517	0.002	0.060
HADS_D	Visual_acuity	-0.381	0.024	0.253
HADS_TOT	DeltaLfa	-0.457	0.021	0.243
HADS_TOT	IC_Dtglobal	-0.480	0.005	0.104
HADS_TOT	IC_global	-0.518	0.002	0.060
HADS_TOT	Psy_IC	**-0.840**	**0.000**	**0.000**
HEAR	LFa_rest	-0.530	0.008	0.124
HEAR	Sensorial_IC	**0.539**	**0.002**	**0.050**
HFA_REST	HFa_stand	**0.750**	**0.000**	**0.001**
HFA_REST	LFa_stand	0.509	0.010	0.152

HFA_REST	TP_stand	0.562	0.004	0.085
HFNU_REST	DeltaLF	0.533	0.007	0.117
HFNU_REST	DeltaLFHF	0.424	0.036	0.323
HFNU_REST	LFHF_rest	**-0.944**	**0.000**	**0.000**
HFNU_STAND	DeltaLFHF	**-0.834**	**0.000**	**0.000**
HFNU_STAND	DT_Icdomain	-0.431	0.047	0.362
HFNU_STAND	LFHF_stand	**-0.964**	**0.000**	**0.000**
HTIME	DeltaLfa	-0.507	0.011	0.155
HTIME	DT_Icdomain	-0.414	0.021	0.243
HTIME	Fluency	-0.365	0.034	0.314
HTIME	HFnu_stand	0.523	0.008	0.126
HTIME	IC_Dtglobal	-0.453	0.011	0.160
HTIME	LFHF_stand	-0.528	0.007	0.121
HTIME	LFnu_stand	-0.600	0.002	0.052
HTIME	Locomotor_IC	-0.428	0.016	0.210
HTIME	Visual_acuity	0.439	0.009	0.143
IC_DTGLOBAL	IC_global	**0.875**	**0.000**	**0.000**
LFA_REST	HFa_rest	0.597	0.002	0.054
LFA_REST	HFa_stand	0.553	0.005	0.094
LFA_REST	HFnu_rest	-0.412	0.042	0.348
LFA_REST	LFa_stand	0.542	0.006	0.108
LFA_REST	TP_stand	0.441	0.029	0.285
LFA_STAND	HFa_stand	**0.626**	**0.001**	**0.034**
LFA_STAND	HFnu_stand	-0.440	0.029	0.286
LFA_STAND	IC_Dtglobal	0.485	0.023	0.252
LFA_STAND	LFHF_stand	0.537	0.006	0.113
LFA_STAND	LFnu_stand	0.583	0.003	0.063
LFHF_REST	DeltaLF	-0.530	0.006	0.113
LFHF_STAND	DeltaLFHF	**0.781**	**0.000**	**0.000**
LFNU_REST	DeltaLF	-0.466	0.020	0.241
LFNU_REST	HFnu_rest	**-0.822**	**0.000**	**0.000**
LFNU_REST	LFHF_rest	**0.891**	**0.000**	**0.000**
LFNU_REST	Locomotor_IC	0.524	0.012	0.170
LFNU_STAND	DeltaLFHF	**0.728**	**0.000**	**0.003**
LFNU_STAND	DT_Icdomain	0.504	0.018	0.223
LFNU_STAND	HFnu_stand	**-0.928**	**0.000**	**0.000**
LFNU_STAND	IC_Dtglobal	0.431	0.047	0.362
LFNU_STAND	LFHF_stand	**0.965**	**0.000**	**0.000**
LFNU_STAND	Locomotor_IC	0.435	0.043	0.353
LOCOMOTOR_IC	IC_Dtglobal	0.398	0.024	0.255
LOCOMOTOR_IC	IC_global	0.408	0.021	0.243
LPA	MPA	-0.408	0.019	0.235
LPA	sleep_efficiency	-0.385	0.028	0.281
LPA	wake_efficiency	0.403	0.021	0.243
MHC_SF	HADS_A	-0.413	0.014	0.183
MHC_SF	HADS_D	-0.478	0.004	0.080

MHC_SF	HADS_TOT	**-0.542**	**0.001**	**0.026**
MHC_SF	NPA	-0.392	0.024	0.253
MHC_SF	Psy_IC	**0.781**	**0.000**	**0.000**
MMSE	Cognition_IC	0.472	0.006	0.113
MMSE	Locomotor_IC	-0.406	0.021	0.243
MMSE	RAVLT_D	0.343	0.044	0.356
MNA	DT_Icdomain	0.480	0.005	0.104
MNA	HADS_D	-0.403	0.017	0.210
MNA	IC_Dtglobal	**0.741**	**0.000**	**0.000**
MNA	IC_global	**0.707**	**0.000**	**0.000**
MNA	PPB	0.345	0.049	0.372
MNA	Psy_IC	0.363	0.041	0.348
MNA	Sensorial_IC	0.401	0.023	0.252
MNA	Vitality_IC	**0.622**	**0.000**	**0.007**
MPA	sleep_efficiency	-0.402	0.021	0.243
MPA	VPA	0.523	0.002	0.055
NPA	Cognition_IC	-0.407	0.026	0.272
NPA	MPA	**-0.684**	**0.000**	**0.001**
NPA	sleep_efficiency	**0.731**	**0.000**	**0.000**
NPA	wake_efficiency	**-0.613**	**0.000**	**0.009**
PEF	Cognition_IC	-0.377	0.045	0.356
PEF	HFa_rest	0.509	0.010	0.152
PEF	HFa_stand	**0.615**	**0.001**	**0.040**
PEF	TP_rest	**0.658**	**0.000**	**0.018**
PEF	Vitality_IC	**0.645**	**0.000**	**0.009**
PPB	HFa_stand	0.497	0.015	0.191
PPB	IC_Dtglobal	0.383	0.037	0.328
PSY_IC	IC_Dtglobal	0.446	0.011	0.160
PSY_IC	IC_global	0.521	0.003	0.062
RAVLT_D	Cognition_IC	**0.631**	**0.000**	**0.005**
RAVLT_D	NPA	-0.387	0.026	0.269
RAVLT_D	Sensorial_IC	-0.354	0.047	0.362
RAVLT_D	sleep_efficiency	-0.399	0.022	0.243
RAVLT_I	Cognition_IC	**0.591**	**0.000**	**0.014**
RAVLT_I	DeltaLF	0.397	0.049	0.372
RAVLT_I	Fluency	0.453	0.007	0.120
RAVLT_I	RAVLT_D	**0.703**	**0.000**	**0.000**
RAVLT_I	StroopDTC_Flex_1	-0.340	0.046	0.362
RAVLT_I	StroopDTC_Flex_2	-0.445	0.007	0.121
RAVLT_I	SWAY_O_maxDev	-0.383	0.023	0.252
RAVLT_I	wake_efficiency	0.401	0.021	0.243
SLEEP_EFFICIENCY	HFa_rest	-0.468	0.022	0.249
SLEEP_EFFICIENCY	HFa_stand	-0.543	0.007	0.118
SLEEP_EFFICIENCY	TP_rest	-0.551	0.006	0.110
SLEEP_EFFICIENCY	wake_efficiency	-0.367	0.036	0.326
SPPB	Htime	-0.372	0.030	0.293

SPPB	IC_Dtglobal	0.430	0.014	0.187
SPPB	IC_global	0.411	0.019	0.236
SPPB	LFnu_rest	0.475	0.017	0.210
SPPB	LFnu_stand	0.425	0.034	0.315
SPPB	Locomotor_IC	**0.975**	**0.000**	**0.000**
SSS	MHC_SF	-0.483	0.003	0.075
SSS	Psy_IC	**-0.615**	**0.000**	**0.008**
SSS	SWAY_C_PL	-0.354	0.037	0.326
SSS	SWAY_O_maxDev	-0.358	0.035	0.316
STROOPDTC_FLEX_1	Cognition_IC	-0.357	0.046	0.361
STROOPDTC_FLEX_1	DT_Icdomain	**-0.743**	**0.000**	**0.000**
STROOPDTC_FLEX_1	IC_Dtglobal	-0.388	0.029	0.286
STROOPDTC_FLEX_1	LFa_stand	-0.473	0.018	0.223
STROOPDTC_FLEX_1	StroopDTC_Flex_2	**0.893**	**0.000**	**0.000**
STROOPDTC_FLEX_1	TugDTC	0.485	0.006	0.111
STROOPDTC_FLEX_2	DT_Icdomain	**-0.746**	**0.000**	**0.000**
STROOPDTC_FLEX_2	HFnu_stand	0.419	0.038	0.330
STROOPDTC_FLEX_2	IC_Dtglobal	-0.451	0.010	0.152
STROOPDTC_FLEX_2	LFa_stand	-0.461	0.022	0.243
STROOPDTC_FLEX_2	LFnu_stand	-0.422	0.037	0.326
STROOPDTC_FLEX_2	TugDTC	0.389	0.031	0.295
STROOPDTC_INH_1	DT_Icdomain	-0.461	0.008	0.130
STROOPDTC_INH_1	sleep_efficiency	-0.353	0.045	0.356
STROOPDTC_INH_1	StroopDTC_Inh_2	**0.858**	**0.000**	**0.000**
STROOPDTC_INH_1	TugDTC	0.386	0.033	0.305
STROOPDTC_INH_1	VPA	0.400	0.022	0.245
STROOPDTC_INH_2	DT_Icdomain	-0.507	0.003	0.077
STROOPDTC_INH_2	IC_Dtglobal	-0.403	0.023	0.252
STROOPDTC_INH_2	LFnu_stand	-0.412	0.042	0.349
STROOPDTC_INH_2	StroopDTC_Flex_2	0.346	0.042	0.351
STROOPDTC_INH_2	VPA	0.365	0.037	0.328
SWAY_C_PL	SWAY_O_Speed	**0.817**	**0.000**	**0.000**
SWAY_O_PL	SWAY_C_PL	**0.829**	**0.000**	**0.000**
SWAY_O_PL	SWAY_O_Speed	**0.987**	**0.000**	**0.000**
TP_REST	HFa_rest	**0.772**	**0.000**	**0.001**
TP_REST	HFa_stand	**0.743**	**0.000**	**0.002**
TP_REST	LFa_rest	**0.781**	**0.000**	**0.000**
TP_REST	LFa_stand	0.538	0.006	0.111
TP_REST	TP_stand	0.504	0.011	0.160
TP_STAND	HFa_stand	0.557	0.004	0.090
TP_STAND	IC_Dtglobal	0.431	0.047	0.362
TP_STAND	LFa_stand	**0.647**	**0.001**	**0.023**
TUGDTC	DeltaLF	0.408	0.044	0.356
TUGDTC	DT_Icdomain	**-0.689**	**0.000**	**0.004**
TUGDTC	TugDTC_fast	0.365	0.045	0.356
TUGDTC_FAST	DT_Icdomain	**-0.592**	**0.001**	**0.035**

TUGDTC_FAST	IC_Dtglobal	-0.550	0.003	0.066
TUGDTC_FAST	IC_global	-0.389	0.042	0.348
TUGDTC_FAST	PPB	-0.401	0.029	0.286
TUGDTC_FAST	TP_stand	-0.540	0.006	0.110
TUGDTC_FAST	Vitality_IC	-0.444	0.019	0.233
VISUAL_ACUITY	DeltaLFHF	-0.519	0.008	0.126
VISUAL_ACUITY	HFa_stand	0.424	0.035	0.316
VISUAL_ACUITY	LFa_rest	0.546	0.005	0.094
VISUAL_ACUITY	Locomotor_IC	-0.389	0.028	0.284
VISUAL_ACUITY	Sensorial_IC	**0.663**	**0.000**	**0.002**
VISUAL_ACUITY	TP_rest	0.496	0.012	0.163
VITALITY_IC	IC_Dtglobal	0.522	0.002	0.060
VITALITY_IC	IC_global	0.527	0.002	0.058
VPA	Psy_IC	-0.400	0.029	0.288
WAKE_EFFICIENCY	Cognition_IC	0.410	0.025	0.263
WAKE_EFFICIENCY	HFa_rest	0.427	0.039	0.332
WAKE_EFFICIENCY	HFnu_rest	**0.650**	**0.001**	**0.026**
WAKE_EFFICIENCY	LFHF_rest	-0.594	0.002	0.058
WAKE_EFFICIENCY	LFnu_rest	-0.571	0.004	0.086

APPENDIX D: FIGURES

FIGURE D1. *Correlation network of age-adjusted variables (PRAISE T0) at threshold |r| ≥ 0.35. Each node represents a variable, with node size proportional to node strength (sum of absolute edge weights). Node colour indicates community membership as identified by the Louvain algorithm. Edges represent pairwise absolute correlations exceeding the threshold, with thickness proportional to the correlation strength.*

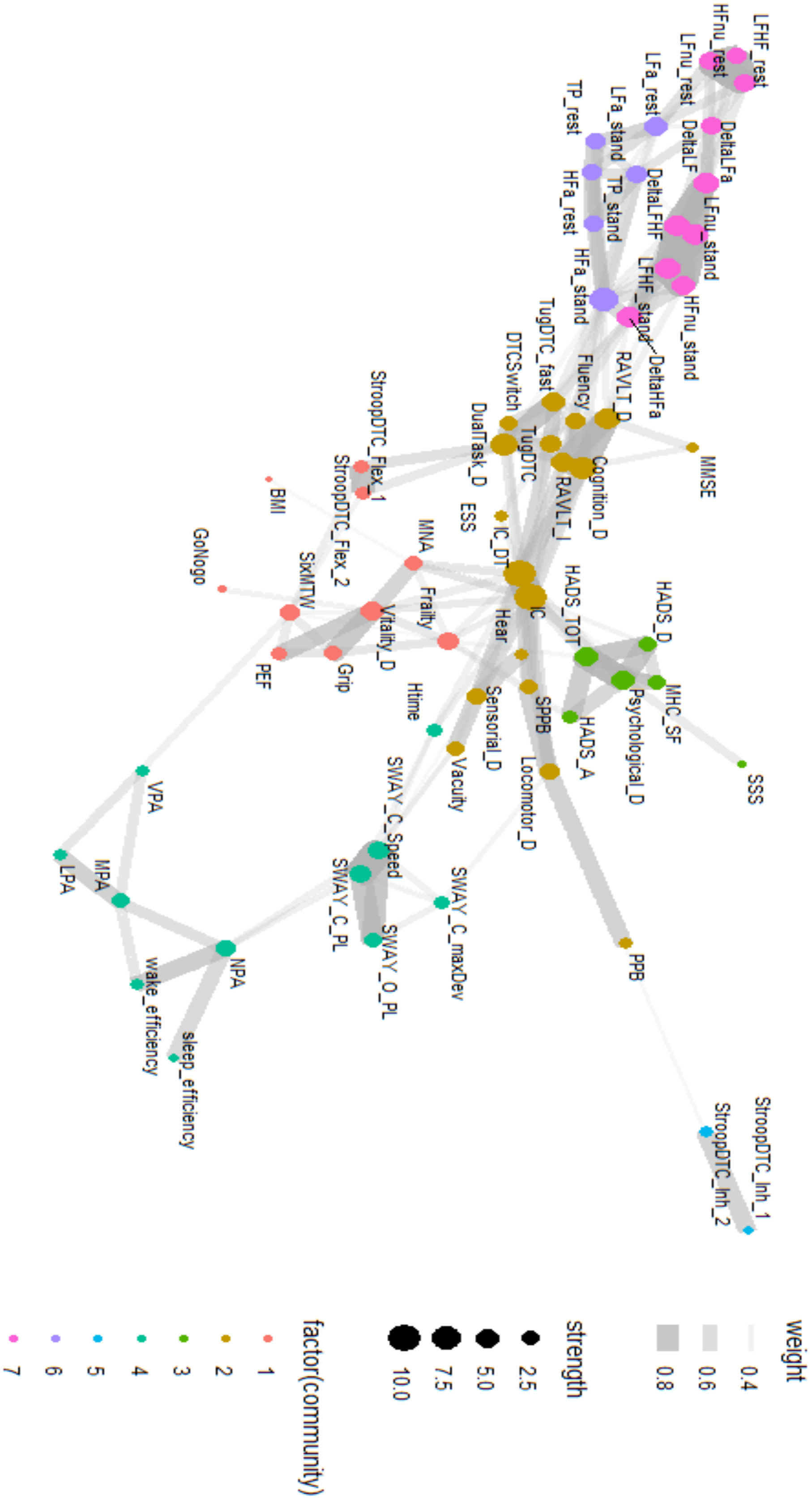


FIGURE D2. *Correlation network of raw variables (PRAISE T0) at threshold |r| ≥ 0.4.*

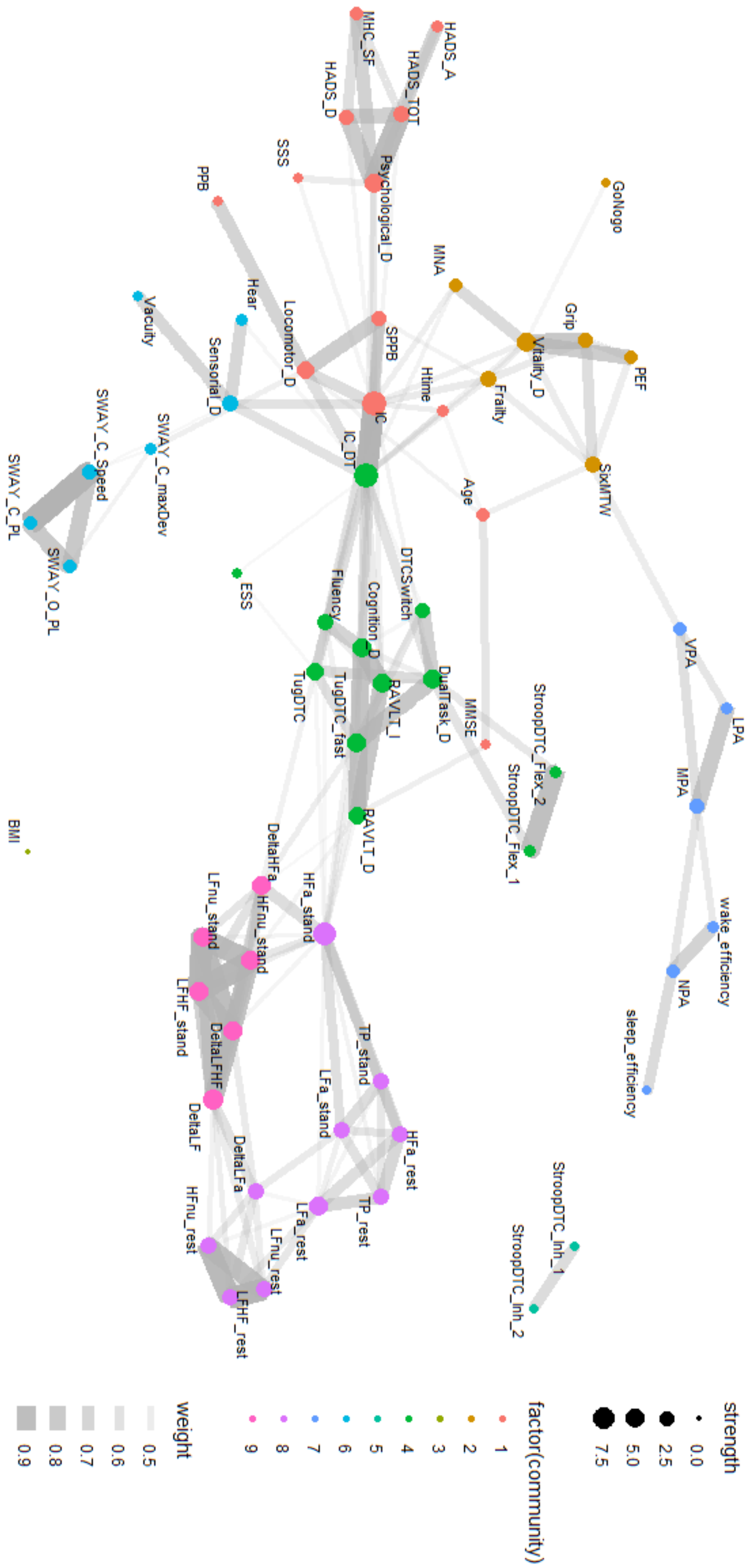
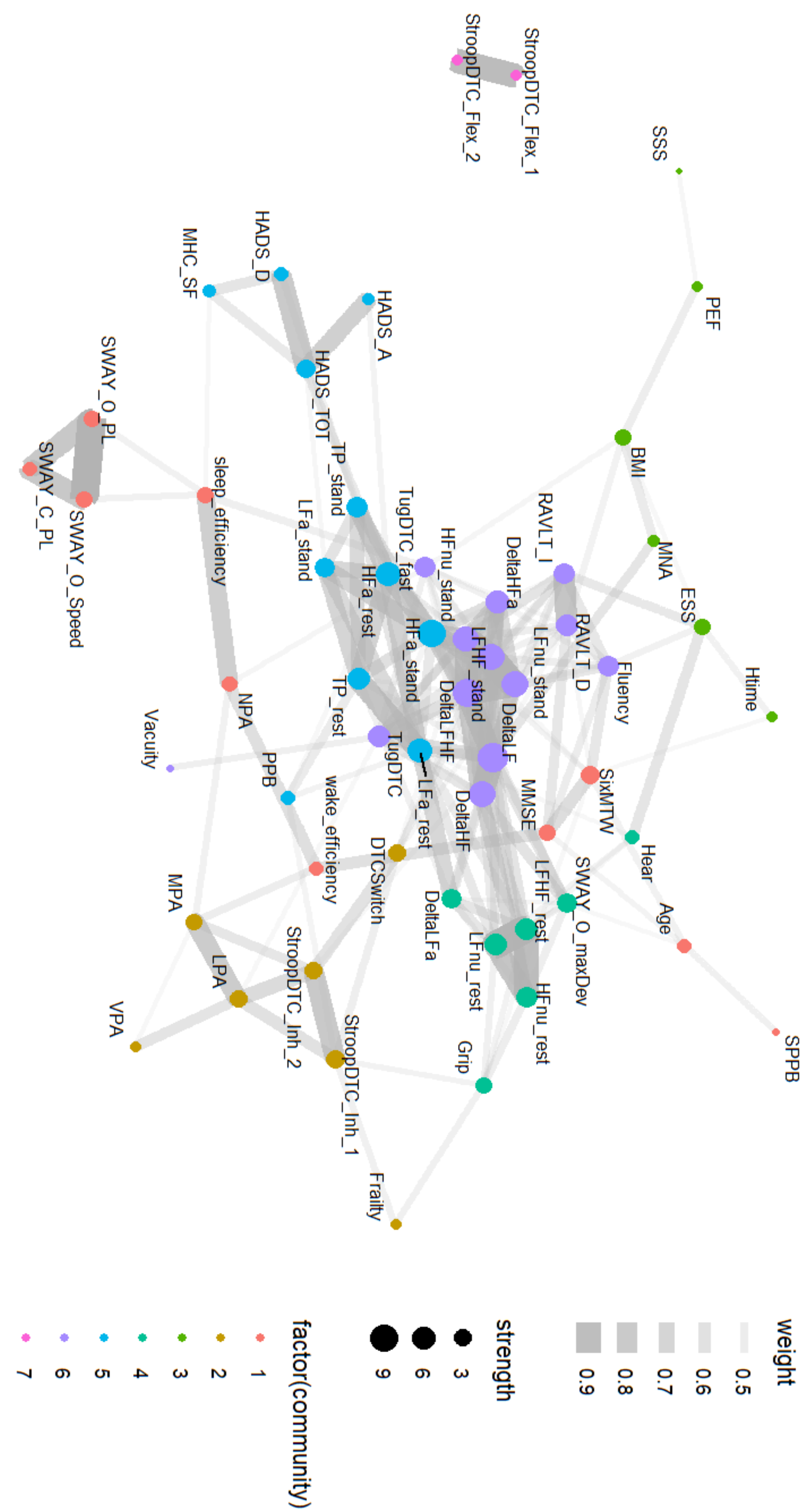


FIGURE D3. *Correlation network of raw variables (PRAISE HRV T0) at threshold |r| ≥ 0.4*



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