Review

Life in the Years: Maximizing Physical and Cognitive Health in the Elderly

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Life in the Years: Maximizing Physical and Cognitive Health in the Elderly

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Abstract: Biomarker-based tests are capable of predicting one's biological age and mortality risk. To complement the suite of biomarker-based measurements, physical and cognitive performance tests can also improve the predictability of these measurement panels. Importantly, these measurements can be administered quite non-invasively and inexpensively, and training programs can be developed to improve parameters in aging. This will be a vital approach in improving the health of the aged and preventing massive healthcare expenditures at the end of life, which may become a serious fiscal issue if not addressed. This review touches on the ways people can measure function, the models that predict mortality based on this data, and the interventions that seek to improve these measures, subsequently extending lifespan and reducing mortality risk (as primary endpoints) and enhancing function and independence as secondary endpoints.

Keywords: Healthy aging; Biomarkers; Physical performance tests; Cognitive function; Metabolic health; Longevity interventions; Cardiovascular fitness; Musculoskeletal strength; Cognitive decline prevention; Quality of life in elderly

1. Introduction

Age distribution has been shifting upwards over the past few decades, creating both social and fiscal challenges. The economic consequences of an aging population drive political policies, influencing areas such as immigration, retirement age, and tax rates. These challenges are intensified when elderly individuals lack independence and the capacity to fulfill roles within their families, industries, and communities. Addressing the needs of an aging population requires a focus on building resilience in older adults to avoid substantial losses in quality of life for both the elderly and those who care for them.

2. Interventions for Improving Aging

Decline with age is not inevitable and can often be prevented or even reversed. Numerous interventions are available to support aging individuals, targeting various body systems. These include strategies to improve metabolic health, as well as enhancing physical and cognitive function.

Table 1. Physical measurements associated with aging and lifespan.

.	Physical marker		Prediction (Association with lifespan or health outcomes)
1.	Treadmill stress test	Cardiovascular fitness	All cause mortality [1,2]
2.	Sports participation	Overall physical activity	Lifespan [3]

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3.	Persistent vigorous activity	Overall physical activity	All cause mortality [4]
4.	Physical activity energy expenditure	Overall physical activity	All cause mortality [5]
5.	Leisure time physical activity	Overall physical activity	All cause mortality [6]
6.	Grip strength	Strength	All cause mortality [7–9] DunedinPoAm, PhenoAge and GrimAge clocks [10]
7.	Sitting rise test	Agility	All cause mortality [11]
8.	Gait speed	Agility, Cardiovascular fitness	All cause mortality [9]
9.	Leg strength	Strength, muscle mass	All cause mortality [9]
10.	Forced Expiratory Volume	Respiratory fitness	All cause mortality [9]
11.	VO2 max	Cardiovascular fitness	All cause mortality [9,12]

Table 2. Associations of cognitive tests with lifespan-associated measures. Cognitive tests.

Test	Predictability
Cognitive Function	Age [13]
Rate of cognitive decline	Mortality risk [14–36] Cardiovascular mortality [37]
Motoric Cognitive Function	Mortality Risk[38]

2.1. Metabolism

Poor metabolic function can contribute to a wide variety of illnesses. Those who are metabolically unwell (having metabolic multimorbidity) spend 52% more time as an inpatient in hospitals, have a 36% increased likelihood of not being able to perform activities of daily living (ADL)[39]. Metabolic dysregulation is comorbid with mental health disorders[40], cancer[41,42], neurodegenerative diseases[43,44].

Importantly, metabolic health can be readily changed through a shift in food consumption patterns. Any policy decision to tackle chronic disease must have food policy and agriculture at its core. Ultra processed foods (UPFs) comprise a larger proportion of people's diet now than before, often for reasons of convenience. These UPFs with an often poor nutritional profile crowd out whole foods in the diet [45], and consumption is associated with an increased risk of all-cause mortality, cardiovascular disease, hypertension, metabolic syndrome, obesity, depression, cancer, gastrointestinal disorders [46] and frailty among others[47]. Factors positively associated with UPF consumption are male sex, young age, smoking (only significant for females) and living alone[46,48]. UPFs have significant and wide-ranging deleterious impacts on health[49].

Aging decreases resting metabolic rate (RMR), which is partially attributable to losses in fat-free mass (FFM, i.e., muscle and bone), though there is a decline independent of FFM[50]. Additionally central adiposity increases as one ages[51], and metabolic changes occur regularly, leading experts to classify metabolic dysregulation as hallmarks of aging[52]. Excess body fat can also alter hormone balance, as adipose tissue can promote estrogen production[53].

There is also significant crosstalk between metabolic health and brain health, where metabolically unhealthy individual have lower brain volumes into old age than their metabolically fit counterparts[54]. When it comes to healthy aging, it is important to avoid insulin resistance, as this is a significant predictor of age-related disease[55]. Those who live to ages past 100 (centenarians) have better insulin sensitivity than their counterparts who die at younger ages [56].

Endurance exercise can reduce age-related declines in mitochondrial oxidative capacity in individuals[57]. Overall, it is important to maintain metabolic health throughout one's lifespan.

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Much as one's general fitness can be broken down into components of strength, speed, agility, balance, flexibility and more, one's metabolic health can be operationalized through meaningful metrics.

First, examining function, we would want a metabolic system to extract energy from food, enough to perform all Activities of Daily Living (ADL), as well as be able to perform athletically when required. The food that people eat should grow and repair their bodies, and be sufficient to power all of the necessary functions that contribute to the basal metabolic rate (BMR).

2.2. Endurance

Endurance exercise, as opposed to punctuated, vigorous exercise, involves exerting power over a longer duration of time at a lower intensity than acute bursts. While this would appear to have limited applicability outside of endurance sports, one major desire of people is to have sustained energy throughout the day. Typically, energy levels are high in the morning, low in the early afternoon, and then increasing again before dropping again at night. Higher Body mass index and waist circumference are associated with higher levels of fatigue [58].

Most studies of energy levels of people look at those which suffer from fatigue due to an illness, and not quotidian fatigue. Several dietary conditions have been investigated for their effect on fatigue in disease contexts, and some literature exists on the impact of diet on fatigue in the context of physical training.

In chronic fatigue syndrome (CFS), adoptees of a low sugar and low yeast diet decreased their fatigue significantly ($p=0.002$, difference measured by the Chalder fatigue score) from their baseline measured before the dietary intervention[59].

A study of breast cancer survivors found that fatigue was associated with fat consumption, and negatively associated with carbohydrate and fiber consumption[60]. A meta-analysis on Multiple Sclerosis (MS) related fatigue came to similar conclusions, finding diets high in greens and low in fat[61], such as a modified paleo diet, may improve MS-related fatigue[62]. The meta-analysis also demonstrated low-quality evidence supporting folate and magnesium for decreasing fatigue[63]. Carbohydrate intake is positively associated with physical capacity, while fat consumption is negatively associated with physical performance in a six minute walk test and VO2max tests[64]. Omega 3 improved VO2 max, and vitamin D was associated with a nonsignificant improvement in VO2max. Paleolithic diets and Mediterranean diets improved fatigue in MS patients [65], as well as anti-inflammatory diets[66].

Chronic fatigue syndrome (CFS) is another condition where people have difficulty with energy levels. A 2017 meta-analysis showed improvements in fatigue for nicotinamide adenine dinucleotide hydride (NADH), probiotics, high cocoa polyphenol rich chocolate, and a combination of NADH and coenzyme Q10[67]. Omega 3, D-ribose, polyphenols and a multivitamin supplement also have support for their therapeutic use in CFS[68,69].

In the case of cancer related fatigue, adoption of the Mediterranean diet was associated with a small-moderate decrease in fatigue levels[70]. High protein[71], carnitine[72,73], Omega-3[74], American Ginseng[75], Wisconsin Ginseng[76] and Astralagus membranacus[77] reduced fatigue[78]. Guarana had mixed positive effects[79] and nonsignificant effects[80,81].

For weightlifters in the midst of weight loss, high protein consumption helped with fatigue [82]. For non-athletes losing weight, higher vegetable consumption was associated with lower levels of fatigue[83].

2.3. Cognition

One of the most feared outcomes of aging is a loss of cognition. Many elderly people do suffer from dementia, whether in mild or severe forms. This can be attributed to several mechanisms, some of which can be mediated through diet and lifestyle. First, mitochondrial function often degrades, and aggregates can form in the cases of full-blown Alzheimer's disease. Other factors include decreased circulation, which can also precipitate hair loss.

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As people age, they often become more set in their ways and are less likely to actively learn new things, despite, in retirement, having more leisure time than during their working life. In fact, retirement can have very negative mental health consequences for seniors, as the inactivity and seclusion can harm neural pathways.

Furthermore, one commonality in old age is a reduction of one's social circle, as this often decreases as one increasingly becomes home bound. Old age homes may precipitate some social interaction in the common areas, but this is typically inadequate. Additionally, one social trend acting against senior cognitive health is that parents and children are decreasingly co-located in the same region, making visits more difficult.

The importance of regular social engagement for senior mental health has been studied, showing a significant impact of loneliness on senior health.

This impact often stretches back many years, where those with a more robust friend circle decades earlier also maintain a robust friend circle into old age. Therefore, the social circle is another 'biomarker' albeit unconventional, associated with successful aging. Here, relationships should be considered as a vital part of aging, as they present a vital support. Heart rate variability[84] and vagal nerve tone[85] are important biomarkers for stress tolerance.

Hobbies, including engagement with music[86], are associated with lower rates of cognitive decline and dementia[87–89]. Endurance exercise also prevents cognitive decline in older adults[90].

2.4. Cardiovascular and Pulmonary Health

Heart stroke volume from the heart increases with age, while heart rate decreases[91]. Maximum heart rate also decreases with age[92].

While total lung volume remains constant [93], respiratory strength decreases with age[94]. Aging causes a change in deep breathing where deep breathing is less able to increase the size of peripheral airways[95]

In addition, breath volume decreases with age, unless it is countervailed by physical activity.

Endurance exercise is excellent for aging people, as endurance exercise improves mitochondrial density[96] by enlargement of existing mitochondria[97,98].

can keep increasing, even as one grows older. The impacts of endurance exercise are cumulative, and people with histories of endurance exercise retain their endurance into advanced age.

Cardiopulmonary health can be assessed by the VO2 max test, which involves finding the maximal level of exertion and measuring the flow of oxygen at this level. VO2 max typically decreases with age, dropping more modestly in exercising individuals[99,100]

Given the trend of decreases in heart stroke volume and heart rate with increasing chronological age, VO2 max also declines with age, as it measures the combination of these factors along with respiratory capacity. It is important to retain VO2 max as one ages, and VO2 max helps with capacity to perform daily actions, such as walking up stairs. Additionally, endurance exercise also provides the metabolic benefits of increased mitochondrial density.

Another means by which older adults can improve their metabolic parameters is by cold exposure, which can facilitate the conversion of white adipose tissue to more metabolically active brown adipose tissue (BAT). This increases one's basal metabolic rate and the practice can also improve one's tolerance to cold. Older people, especially women, often feel cold at higher temperatures than their younger and male counterparts, so intentional cold exposure can help to alleviate this.

In addition to the cognitive benefits espoused above, periodic fasting can be important for metabolic parameters as well as improving cognitive function. Regular fasting can help to reduce blood sugar variation, which is a contributor to neurodegenerative diseases.

One common intervention that elderly people use is oxygen support. Approximately 1 in 5 people over the age of 70 have some form of chronic obstructive pulmonary disease[101]. Breathing pattern can impact the rates of respiratory illness, with mouth breathing contributing to the development of respiratory disorders[102,103]. One simple means of improving breathing performance is the practice of mouth taping, which involves taping one's mouth shut during sleep,

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preferably using a tape that does not leave a residue. Participants in a study experienced significant improvements in rates of snoring and decreases in rates of apnoea events[104].

Ideally, in healthy aging we would prevent the need for supplementary oxygen. Being on cannula oxygen is often bulky and cumbersome, though newer models have reduced the mass to <10lbs (~3kg)[105].

2.5. Musculoskeletal (Strength and Stability)

Musculoskeletal fitness and stability are very important for older individuals to maintain their independence and sovereignty as they age. Without their own mobility, they are dependent on a caregiver, either paid, a family or friend, for their transportation needs. Paid caregivers can be financially taxing, and the relational caregivers may strain the relationship if one asks too often, creating resentment.

Hip fractures are a major reason for senior death, the one-year mortality after a hip fracture is 24%[106]. Additionally, the sense of autonomy ties into many other positive health circuits. If one is mobile, they can reap the benefits of exercise and the outdoors. If people are left indoors without social interaction, an extreme case being solitary confinement, mental health degrades quickly, and physical deterioration is fast.

Generally, after a certain age, muscle mass declines by a few percentage points per year[107,108]. This can be combatted through resistance training to increase muscle mass and improve both stability (to prevent falls) and strength (to resist injury in the case of falls). Vitamin D is associated with musculoskeletal strength [109] and may be an important intervention for maintaining strength in old age.

2.6. Psychosocial

Maintaining a positive life outlook throughout times of stress is associated with decreases in inflammation and future depressive symptom onset[110], additionally, an optimistic spirit is associated with healthier behaviours[111–113]. Optimism is a significant predictor of positive health outcomes[114], and improved quality of life in individuals experiencing disease[115]. Optimism can also have a positive impact on people close to the optimistic individual, as a spouse's optimism is associated with the health of the other spouse[116]

Holding onto regret is a factor in lowered psychological well being in the aged [117,118], thought the emotional salience of missed opportunities is lesser in older people as opposed to young[119]. Forgiveness is also associated with increased well-being [120,121], including forgiveness of self[122]. Expressing and feeling gratitude is associated with life satisfaction [123–125].

Table 3. Intervention classes for maintaining physical function with age and means of training.

Training Type	Trend (absent training)	System	Associated tests and biomarkers	Training	Adaptations
Strength Training	Sarcopenia, muscle loss, bone loss	Musculoskeletal	Grip Strength[126]	Weightlifting	Increase in muscle mass and bone density
Endurance training	Lower VO2 max	Metabolic, cardiopulmonary	Resting Metabolic Rate, Creatine phosphokinase[127]	Running, swimming, walking, cycling, cross-country skiing, hiking, etc.	Increased mitochondrial size, greater ability to metabolize fat, increased (heart) stroke volume
Balance training	Poorer coordination	Musculoskeletal, nervous	Self-selected gait velocity [128], Chair rise test (timed 5 chair	Yoga	Neuromuscular control [130]

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			rises), Tandem standing and walking, timed up and go test, clinical gait analysis with special focus on regularity, mechanography [129]		
Flexibility	Decrease in joint flexion[131,132]	Musculoskeletal, tendons, fascia	Flexibility tests: Flexindex[132]	Yoga, Pilates	Improved flexibility and stability
Preservation of genomic integrity	Accumulation of mutations[133], accumulation of methylation, higher cancer rates[134]	Genomic Integrity	Telomere Length[135], Methylation level [136]	Low inflammation practices, avoiding carcinogenic exposures, possibly fasting[137]	Possible improved immune surveillance [138]
Cognition	Impairment on task switching[139], working and long-term memory [139]	Nervous	Cognitive tests[140]: Mini-Mental State Examination, Isaacs Set Test, Benton Visual Retention Test, Digit Symbol Substitution Test[141], Combined panel[142]	Equivocal evidence for transfer effects of cognitive training[143], Combined program (exercise, brain training and lecture)[144], Reading[145], Hobbies[146], Multilingualism[147], Dance[148], Social Activity [149], meditation[150]	Increased BDNF and neurogenesis[151]preservation of white matter

3. Conclusion

This review highlights the importance of identifying and utilizing biomarkers to guide interventions aimed at promoting healthy aging. By clearly defining the major target outcomes and establishing links between these biomarkers and specific interventions, we can better understand how to enhance lifespan and health span. The integration of biomarker testing with tailored interventions presents a comprehensive strategy to improve the degree of independence among the aging population.

Our findings suggest that addressing key areas such as metabolism, cognitive function, cardiovascular and pulmonary health, musculoskeletal strength, and emotional well-being can significantly contribute to healthier aging. Implementing these strategies can mitigate the crisis of

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age-related chronic diseases, reduce healthcare expenditures, and lessen the societal burden associated with an aging demographic.

Future research should focus on refining these interventions and exploring the synergistic effects of combining multiple approaches. Policymakers and healthcare providers can leverage these insights to develop more effective programs and policies that support healthy aging, ultimately enhancing the quality of life for elderly individuals and benefiting society as a whole.

Currently, a large number of people are entering advanced age in Western countries, motivating strategies for lifespan extension. Without the maintenance of good health into late adulthood, older people are more prone to age-related chronic diseases, which consume many resources late in life.

With the adoption of testing and intervention strategies, functional decline with age may be ameliorated and the crisis lessened. This work presents a strategy to improve the degree of independence in the aging population over the non-intervention strategy.

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References

1. Whelton, S.P.; McAuley, P.A.; Dardari, Z.; Orimoloye, O.A.; Michos, E.D.; Brawner, C.A.; Ehrman, J.K.; Keteyian, S.J.; Blaha, M.J.; Al-Mallah, M.H. Fitness and Mortality Among Persons 70 Years and Older Across the Spectrum of Cardiovascular Disease Risk Factor Burden: The FIT Project. *Mayo Clin Proc* **2021**, *96*, 2376–2385, doi:10.1016/j.mayocp.2020.12.039.
2. Kokkinos, P.; Faselis, C.; Samuel, I.B.H.; Pittaras, A.; Doumas, M.; Murphy, R.; Heimall, M.S.; Sui, X.; Zhang, J.; Myers, J. Cardiorespiratory Fitness and Mortality Risk Across the Spectra of Age, Race, and Sex. *Journal of the American College of Cardiology* **2022**, *80*, 598–609, doi:10.1016/j.jacc.2022.05.031.
3. Altulea, A.; Rutten, M.G.S.; Verdijk, L.B.; Demaria, M. Sport and Longevity: An Observational Study of International Athletes. *Geroscience* **2024**, doi:10.1007/s11357-024-01307-9.
4. Karvinen, S.; Waller, K.; Silvennoinen, M.; Koch, L.G.; Britton, S.L.; Kaprio, J.; Kainulainen, H.; Kujala, U.M. Physical Activity in Adulthood: Genes and Mortality. *Sci Rep* **2015**, *5*, 18259, doi:10.1038/srep18259.
5. Mok, A.; Khaw, K.-T.; Luben, R.; Wareham, N.; Brage, S. Physical Activity Trajectories and Mortality: Population Based Cohort Study. *BMJ* **2019**, *365*, l2323, doi:10.1136/bmj.l2323.
6. Saint-Maurice, P.F.; Coughlan, D.; Kelly, S.P.; Keadle, S.K.; Cook, M.B.; Carlson, S.A.; Fulton, J.E.; Matthews, C.E. Association of Leisure-Time Physical Activity Across the Adult Life Course With All-Cause and Cause-Specific Mortality. *JAMA Network Open* **2019**, *2*, e190355, doi:10.1001/jamanetworkopen.2019.0355.
7. Wu, Y.; Wang, W.; Liu, T.; Zhang, D. Association of Grip Strength With Risk of All-Cause Mortality, Cardiovascular Diseases, and Cancer in Community-Dwelling Populations: A Meta-Analysis of Prospective Cohort Studies. *J Am Med Dir Assoc* **2017**, *18*, 551.e17-551.e35, doi:10.1016/j.jamda.2017.03.011.
8. Bohannon, R.W. Grip Strength: An Indispensable Biomarker For Older Adults. *Clinical Interventions in Aging* **2019**, *14*, 1681, doi:10.2147/CIA.S194543.
9. McGreevy, K.M.; Radak, Z.; Torma, F.; Jokai, M.; Lu, A.T.; Belsky, D.W.; Binder, A.; Marioni, R.E.; Ferrucci, L.; Pośpiech, E.; et al. DNAmFitAge: Biological Age Indicator Incorporating Physical Fitness. *Aging* **2023**, *15*, 3904–3938, doi:10.18632/aging.204538.
10. Peterson, M.D.; Collins, S.; Meier, H.C.S.; Brahmsteadt, A.; Faul, J.D. Grip Strength Is Inversely Associated with DNA Methylation Age Acceleration. *Journal of Cachexia, Sarcopenia and Muscle* **2023**, *14*, 108–115, doi:10.1002/jcsm.13110.
11. Brito, L.B.B. de; Ricardo, D.R.; Araújo, D.S.M.S. de; Ramos, P.S.; Myers, J.; Araújo, C.G.S. de Ability to Sit and Rise from the Floor as a Predictor of All-Cause Mortality. *Eur J Prev Cardiol* **2014**, *21*, 892–898, doi:10.1177/2047487312471759.

12. Duizer, D. Cardiorespiratory Fitness Assessment and Treatment for Health Span and Lifespan. *CAND Journal* **2020**, *27*, 22–25, doi:10.54434/candj.76.
13. Statsenko, Y.; Habuza, T.; Charykova, I.; Gorkom, K.N.-V.; Zaki, N.; Almansoori, T.M.; Baylis, G.; Ljubisavljevic, M.; Belghali, M. Predicting Age From Behavioral Test Performance for Screening Early Onset of Cognitive Decline. *Front. Aging Neurosci.* **2021**, *13*, doi:10.3389/fnagi.2021.661514.
14. Aichele, S.; Rabbitt, P.; Ghisletta, P. Life Span Decrements in Fluid Intelligence and Processing Speed Predict Mortality Risk. *Psychol Aging* **2015**, *30*, 598–612, doi:10.1037/pag0000035.
15. Schupf, N.; Tang, M.-X.; Albert, S.M.; Costa, R.; Andrews, H.; Lee, J.H.; Mayeux, R. Decline in Cognitive and Functional Skills Increases Mortality Risk in Nondemented Elderly. *Neurology* **2005**, *65*, 1218–1226, doi:10.1212/01.wnl.0000180970.07386.cb.
16. Sachs, G.A.; Carter, R.; Holtz, L.R.; Smith, F.; Stump, T.E.; Tu, W.; Callahan, C.M. Cognitive Impairment: An Independent Predictor of Excess Mortality. *Ann Intern Med* **2011**, *155*, 300–308, doi:10.7326/0003-4819-155-5-201109060-00007.
17. Stump, T.E.; Callahan, C.M.; Hendrie, H.C. Cognitive Impairment and Mortality in Older Primary Care Patients. *Journal of the American Geriatrics Society* **2001**, *49*, 934–940, doi:10.1046/j.1532-5415.2001.49184.x.
18. LIU, I.Y.; LACROIX, A.Z.; WHITE, L.R.; KITTNER, S.J.; WOLF, P.A. COGNITIVE IMPAIRMENT AND MORTALITY: A STUDY OF POSSIBLE CONFOUNDERS. *American Journal of Epidemiology* **1990**, *132*, 136–143, doi:10.1093/oxfordjournals.aje.a115625.
19. van Gelder, B.M.; Tijhuis, M.A.R.; Kalmijn, S.; Giampaoli, S.; Kromhout, D. Decline in Cognitive Functioning Is Associated with a Higher Mortality Risk. *Neuroepidemiology* **2007**, *28*, 93–100, doi:10.1159/000098552.
20. Assari, S. Cognitive Test Score and 25-Year Mortality Risk; Does Race Matter? *Journal of Medical Research and Innovation* **2020**, *4*, e000213, doi:10.32892/jmri.213.
21. Pavlik, V.N.; de Moraes, S.A.; Szklo, M.; Knopman, D.S.; Mosley Jr., T.H.; Hyman, D.J. Relation between Cognitive Function and Mortality in Middle-Aged Adults: The Atherosclerosis Risk in Communities Study. *American Journal of Epidemiology* **2003**, *157*, 327–334, doi:10.1093/aje/kwf209.
22. Gale, C.R.; Martyn, C.N.; Cooper, C. Cognitive Impairment and Mortality in a Cohort of Elderly People. *BMJ* **1996**, *312*, 608–611, doi:10.1136/bmj.312.7031.608.
23. Griva, K.; Stygall, J.; Hankins, M.; Davenport, A.; Harrison, M.; Newman, S.P. Cognitive Impairment and 7-Year Mortality in Dialysis Patients. *American Journal of Kidney Diseases* **2010**, *56*, 693–703, doi:10.1053/j.ajkd.2010.07.003.
24. Baker, D.W.; Wolf, M.S.; Feinglass, J.; Thompson, J.A. Health Literacy, Cognitive Abilities, and Mortality Among Elderly Persons. *J GEN INTERN MED* **2008**, *23*, 723–726, doi:10.1007/s11606-008-0566-4.
25. Frith, E.; Addoh, O.; Mann, J.R.; Windham, B.G.; Loprinzi, P.D. Individual and Combined Associations of Cognitive and Mobility Limitations on Mortality Risk in Older Adults. *Mayo Clinic Proceedings* **2017**, *92*, 1494–1501, doi:10.1016/j.mayocp.2017.06.019.
26. Bosworth, H.B.; Schaie, K.W.; Willis, S.L. Cognitive and Sociodemographic Risk Factors for Mortality in the Seattle Longitudinal Study. *The Journals of Gerontology: Series B* **1999**, *54B*, P273–P282, doi:10.1093/geronb/54B.5.P273.
27. Shipley, B.A.; Der, G.; Taylor, M.D.; Deary, I.J. Cognition and All-Cause Mortality Across the Entire Adult Age Range: Health and Lifestyle Survey. *Psychosomatic Medicine* **2006**, *68*, 17, doi:10.1097/01.psy.0000195867.66643.0f.
28. Shipley, B.A.; Der, G.; Taylor, M.D.; Deary, I.J. Cognition and Mortality from the Major Causes of Death: The Health and Lifestyle Survey. *Journal of Psychosomatic Research* **2008**, *65*, 143–152, doi:10.1016/j.jpsychores.2008.02.017.
29. Holm, H.; Bachus, E.; Jujic, A.; Nilsson, E.D.; Wadström, B.; Molvin, J.; Minthon, L.; Fedorowski, A.; Nägga, K.; Magnusson, M. Cognitive Test Results Are Associated with Mortality and Rehospitalization in Heart Failure: Swedish Prospective Cohort Study. *ESC Heart Failure* **2020**, *7*, 2948–2955, doi:10.1002/ehf2.12909.
30. Perna, L.; Wahl, H.-W.; Mons, U.; Saum, K.-U.; Holleczek, B.; Brenner, H. Cognitive Impairment, All-Cause and Cause-Specific Mortality among Non-Demented Older Adults. *Age and Ageing* **2015**, *44*, 445–451, doi:10.1093/ageing/afu188.
31. Drew, D.A.; Weiner, D.E.; Tighiouart, H.; Scott, T.; Lou, K.; Kantor, A.; Fan, L.; Strom, J.A.; Singh, A.K.; Sarnak, M.J. Cognitive Function and All-Cause Mortality in Maintenance Hemodialysis Patients. *American Journal of Kidney Diseases* **2015**, *65*, 303–311, doi:10.1053/j.ajkd.2014.07.009.
32. Hayat, S.A.; Luben, R.; Dalzell, N.; Moore, S.; Hogervorst, E.; Matthews, F.E.; Wareham, N.; Brayne, C.; Khaw, K.-T. Understanding the Relationship between Cognition and Death: A within Cohort Examination of Cognitive Measures and Mortality. *Eur J Epidemiol* **2018**, *33*, 1049–1062, doi:10.1007/s10654-018-0439-z.
33. Kelman, H.R.; Thomas, C.; Kennedy, G.J.; Cheng, J. Cognitive Impairment and Mortality in Older Community Residents. *Am J Public Health* **1994**, *84*, 1255–1260, doi:10.2105/ajph.84.8.1255.

34. Dewey, M.E.; Saz, P. Dementia, Cognitive Impairment and Mortality in Persons Aged 65 and over Living in the Community: A Systematic Review of the Literature. *International Journal of Geriatric Psychiatry* **2001**, *16*, 751–761, doi:10.1002/gps.397.
35. Wilson, R.S.; Aggarwal, N.T.; Barnes, L.L.; Bienias, J.L.; Mendes de Leon, C.F.; Evans, D.A. Biracial Population Study of Mortality in Mild Cognitive Impairment and Alzheimer Disease. *Arch Neurol* **2009**, *66*, 767–772, doi:10.1001/archneurol.2009.80.
36. Gussekloo, J.; Westendorp, R.G.J.; Remarque, E.J.; Lagaay, A.M.; Heeren, T.J.; Knook, D.L. Impact of Mild Cognitive Impairment on Survival in Very Elderly People: Cohort Study. *BMJ* **1997**, *315*, 1053–1054, doi:10.1136/bmj.315.7115.1053.
37. O'Donnell, M.; Teo, K.; Gao, P.; Anderson, C.; Sleight, P.; Dans, A.; Marzona, I.; Bosch, J.; Probstfield, J.; Yusuf, S. Cognitive Impairment and Risk of Cardiovascular Events and Mortality. *European Heart Journal* **2012**, *33*, 1777–1786, doi:10.1093/eurheartj/ehs053.
38. Ayers, E.; Verghese, J. Motoric Cognitive Risk Syndrome and Risk of Mortality in Older Adults. *Alzheimer's & Dementia* **2016**, *12*, 556–564, doi:10.1016/j.jalz.2015.08.167.
39. Zhao, Y.; Zhang, P.; Lee, J.T.; Oldenburg, B.; Heusden, A. van; Haregu, T.N.; Wang, H. The Prevalence of Metabolic Disease Multimorbidity and Its Associations With Spending and Health Outcomes in Middle-Aged and Elderly Chinese Adults. *Frontiers in Public Health* **2021**, *9*.
40. Dunbar, J.A.; Reddy, P.; Davis-Lameloise, N.; Philpot, B.; Laatikainen, T.; Kilkkinen, A.; Bunker, S.J.; Best, J.D.; Vartiainen, E.; Kai Lo, S.; et al. Depression: An Important Comorbidity With Metabolic Syndrome in a General Population. *Diabetes Care* **2008**, *31*, 2368–2373, doi:10.2337/dc08-0175.
41. Yang, Y.; Mauldin, P.D.; Ebeling, M.; Hulsey, T.C.; Liu, B.; Thomas, M.B.; Camp, E.R.; Esnaola, N.F. Effect of Metabolic Syndrome and Its Components on Recurrence and Survival in Colon Cancer Patients. *Cancer* **2013**, *119*, 1512–1520.
42. Braun, S.; Bitton-Worms, K.; LeRoith, D. The Link between the Metabolic Syndrome and Cancer. *International journal of biological sciences* **2011**, *7*, 1003.
43. Pal, K.; Mukadam, N.; Petersen, I.; Cooper, C. Mild Cognitive Impairment and Progression to Dementia in People with Diabetes, Prediabetes and Metabolic Syndrome: A Systematic Review and Meta-Analysis. *Soc Psychiatry Psychiatr Epidemiol* **2018**, *53*, 1149–1160, doi:10.1007/s00127-018-1581-3.
44. Marseglia, A.; Darin-Mattsson, A.; Skoog, J.; Rydén, L.; Hadarsson-Bodin, T.; Kern, S.; Rydberg Sterner, T.; Shang, Y.; Zettergren, A.; Westman, E. Metabolic Syndrome Is Associated with Poor Cognition: A Population-Based Study of 70-Year-Old Adults without Dementia. *The Journals of Gerontology: Series A* **2021**, *76*, 2275–2283.
45. Martini, D.; Godos, J.; Bonaccio, M.; Vitaglione, P.; Grosso, G. Ultra-Processed Foods and Nutritional Dietary Profile: A Meta-Analysis of Nationally Representative Samples. *Nutrients* **2021**, *13*, 3390, doi:10.3390/nu13103390.
46. Schnabel, L.; Buscail, C.; Sabate, J.-M.; Bouchoucha, M.; Kesse-Guyot, E.; Allès, B.; Touvier, M.; Monteiro, C.A.; Hercberg, S.; Benamouzig, R.; et al. Association Between Ultra-Processed Food Consumption and Functional Gastrointestinal Disorders: Results From the French NutriNet-Santé Cohort. *Official journal of the American College of Gastroenterology | ACG* **2018**, *113*, 1217, doi:10.1038/s41395-018-0137-1.
47. Chen, X.; Zhang, Z.; Yang, H.; Qiu, P.; Wang, H.; Wang, F.; Zhao, Q.; Fang, J.; Nie, J. Consumption of Ultra-Processed Foods and Health Outcomes: A Systematic Review of Epidemiological Studies. *Nutrition Journal* **2020**, *19*, 86, doi:10.1186/s12937-020-00604-1.
48. Magalhães, V.; Severo, M.; Correia, D.; Torres, D.; Miranda, R.C. de; Rauber, F.; Levy, R.; Rodrigues, S.; Lopes, C. Associated Factors to the Consumption of Ultra-Processed Foods and Its Relation with Dietary Sources in Portugal. *Journal of Nutritional Science* **2021**, *10*, e89, doi:10.1017/jns.2021.61.
49. Lawrence, M.A.; Baker, P.I. Ultra-Processed Food and Adverse Health Outcomes. *BMJ* **2019**, *365*, l2289, doi:10.1136/bmj.l2289.
50. Poehlman, E.T.; Arciero, P.J.; Goran, M.I. Endurance Exercise in Aging Humans: Effects on Energy Metabolism. *Exercise and Sport Sciences Reviews* **1994**, *22*, 251.
51. Palmer, A.K.; Jensen, M.D. Metabolic Changes in Aging Humans: Current Evidence and Therapeutic Strategies. *J Clin Invest* **2022**, *132*, doi:10.1172/JCI158451.
52. López-Otín, C.; Blasco, M.A.; Partridge, L.; Serrano, M.; Kroemer, G. The Hallmarks of Aging. *Cell* **2013**, *153*, 1194–1217, doi:10.1016/j.cell.2013.05.039.
53. Nelson, L.R.; Bulun, S.E. Estrogen Production and Action. *Journal of the American Academy of Dermatology* **2001**, *45*, S116–S124.
54. Angoff, R.; Himali, J.J.; Maillard, P.; Aparicio, H.J.; Vasan, R.S.; Seshadri, S.; Beiser, A.S.; Tsao, C.W. Relations of Metabolic Health and Obesity to Brain Aging in Young to Middle-Aged Adults. *Journal of the American Heart Association* **2022**, *11*, e022107, doi:10.1161/JAHA.121.022107.
55. Facchini, F.S.; Hua, N.; Abbasi, F.; Reaven, G.M. Insulin Resistance as a Predictor of Age-Related Diseases. *The Journal of Clinical Endocrinology & Metabolism* **2001**, *86*, 3574–3578, doi:10.1210/jcem.86.8.7763.

56. Paolisso, G.; Gambardella, A.; Ammendola, S.; D'Amore, A.; Balbi, V.; Varricchio, M.; D'Onofrio, F. Glucose Tolerance and Insulin Action in Healthy Centenarians. *Am J Physiol* **1996**, *270*, E890-894, doi:10.1152/ajpendo.1996.270.5.E890.
57. Lanza, I.R.; Short, D.K.; Short, K.R.; Raghavakaimal, S.; Basu, R.; Joyner, M.J.; McConnell, J.P.; Nair, K.S. Endurance Exercise as a Countermeasure for Aging. *Diabetes* **2008**, *57*, 2933–2942, doi:10.2337/db08-0349.
58. Resnick, H.E.; Carter, E.A.; Aloia, M.; Phillips, B. Cross-Sectional Relationship of Reported Fatigue to Obesity, Diet, and Physical Activity: Results From the Third National Health and Nutrition Examination Survey. *Journal of Clinical Sleep Medicine* **2006**, *02*, 163–169, doi:10.5664/jcsm.26511.
59. Hobday, R.A.; Thomas, S.; O'Donovan, A.; Murphy, M.; Pinching, A.J. Dietary Intervention in Chronic Fatigue Syndrome. *Journal of Human Nutrition and Dietetics* **2008**, *21*, 141–149, doi:10.1111/j.1365-277X.2008.00857.x.
60. Guest, D.D.; Evans, E.M.; Rogers, L.Q. Diet Components Associated with Perceived Fatigue in Breast Cancer Survivors: Diet, Fatigue and Breast Cancer. *European Journal of Cancer Care* **2013**, *22*, 51–59, doi:10.1111/j.1365-2354.2012.01368.x.
61. Chase, E.; Chen, V.; Martin, K.; Lane, M.; Wooliscroft, L.; Adams, C.; Rice, J.; Silbermann, E.; Hollen, C.; Fryman, A.; et al. A Low-Fat Diet Improves Fatigue in Multiple Sclerosis: Results from a Randomized Controlled Trial. *Mult Scler* **2023**, *29*, 1659–1675, doi:10.1177/13524585231208330.
62. Pommerich, U.M.; Brincks, J.; Christensen, M.E. Is There an Effect of Dietary Intake on MS-Related Fatigue? – A Systematic Literature Review. *Multiple Sclerosis and Related Disorders* **2018**, *25*, 282–291, doi:10.1016/j.msard.2018.08.017.
63. Bitarafan, S.; Harirchian, M.-H.; Nafissi, S.; Sahraian, M.-A.; Togha, M.; Siassi, F.; Saedisomeolia, A.; Alipour, E.; Mohammadpour, N.; Chamary, M.; et al. Dietary Intake of Nutrients and Its Correlation with Fatigue in Multiple Sclerosis Patients. *Iran J Neurol* **2014**, *13*, 28–32.
64. Albrechtsen, M.T.; Langeskov-Christensen, M.; Jørgensen, M.L.K.; Dalgas, U.; Hansen, M. Is Diet Associated with Physical Capacity and Fatigue in Persons with Multiple Sclerosis? –Results from a Pilot Study. *Multiple Sclerosis and Related Disorders* **2020**, *40*, 101921, doi:10.1016/j.msard.2019.101921.
65. Snetselaar, L.G.; Cheek, J.J.; Fox, S.S.; Healy, H.S.; Schweizer, M.L.; Bao, W.; Kamholz, J.; Titcomb, T.J. Efficacy of Diet on Fatigue and Quality of Life in Multiple Sclerosis. *Neurology* **2023**, *100*, e357–e366, doi:10.1212/WNL.0000000000201371.
66. Mousavi-Shirazi-Fard, Z.; Mazloom, Z.; Izadi, S.; Fararouei, M. The Effects of Modified Anti-Inflammatory Diet on Fatigue, Quality of Life, and Inflammatory Biomarkers in Relapsing-Remitting Multiple Sclerosis Patients: A Randomized Clinical Trial. *International Journal of Neuroscience* **2021**, *131*, 657–665, doi:10.1080/00207454.2020.1750398.
67. Campagnolo, N.; Johnston, S.; Collatz, A.; Staines, D.; Marshall-Gradisnik, S. Dietary and Nutrition Interventions for the Therapeutic Treatment of Chronic Fatigue Syndrome/Myalgic Encephalomyelitis: A Systematic Review. *Journal of Human Nutrition and Dietetics* **2017**, *30*, 247–259, doi:10.1111/jhn.12435.
68. Maric, D.; Brkic, S.; Mikic, A.N.; Tomic, S.; Cebovic, T.; Turkulov, V. Multivitamin Mineral Supplementation in Patients with Chronic Fatigue Syndrome. *Medical science monitor: international medical journal of experimental and clinical research* **2014**, *20*, 47.
69. Bo, S.; Pisu, E. Role of Dietary Magnesium in Cardiovascular Disease Prevention, Insulin Sensitivity and Diabetes. *Current Opinion in Lipidology* **2008**, *19*, 50, doi:10.1097/MOL.0b013e3282f33ccc.
70. Kleckner, A.S.; Reschke, J.E.; Kleckner, I.R.; Magnuson, A.; Amitrano, A.M.; Culakova, E.; Shayne, M.; Netherby-Winslow, C.S.; Czap, S.; Janelsins, M.C.; et al. The Effects of a Mediterranean Diet Intervention on Cancer-Related Fatigue for Patients Undergoing Chemotherapy: A Pilot Randomized Controlled Trial. *Cancers* **2022**, *14*, 4202, doi:10.3390/cancers14174202.
71. Stobäus, N.; Müller, M.J.; Küpferling, S.; Schulzke, J.-D.; Norman, K. Low Recent Protein Intake Predicts Cancer-Related Fatigue and Increased Mortality in Patients with Advanced Tumor Disease Undergoing Chemotherapy. *Nutrition and Cancer* **2015**, *67*, 818–824, doi:10.1080/01635581.2015.1040520.
72. Gramignano, G.; Lusso, M.R.; Madeddu, C.; Massa, E.; Serpe, R.; Deiana, L.; Lamonica, G.; Dessì, M.; Spiga, C.; Astara, G.; et al. Efficacy of L-Carnitine Administration on Fatigue, Nutritional Status, Oxidative Stress, and Related Quality of Life in 12 Advanced Cancer Patients Undergoing Anticancer Therapy. *Nutrition* **2006**, *22*, 136–145, doi:10.1016/j.nut.2005.06.003.
73. Marx, W.; Teleni, L.; Opie, R.S.; Kelly, J.; Marshall, S.; Itsiopoulos, C.; Isenring, E. Efficacy and Effectiveness of Carnitine Supplementation for Cancer-Related Fatigue: A Systematic Literature Review and Meta-Analysis. *Nutrients* **2017**, *9*, 1224, doi:10.3390/nu9111224.
74. Alfano, C.M.; Imayama, I.; Neuhouser, M.L.; Kiecolt-Glaser, J.K.; Smith, A.W.; Meeske, K.; McTiernan, A.; Bernstein, L.; Baumgartner, K.B.; Ulrich, C.M.; et al. Fatigue, Inflammation, and ω-3 and ω-6 Fatty Acid Intake Among Breast Cancer Survivors. *JCO* **2012**, *30*, 1280–1287, doi:10.1200/JCO.2011.36.4109.
75. Barton, D.L.; Soori, G.S.; Bauer, B.A.; Sloan, J.A.; Johnson, P.A.; Figueras, C.; Duane, S.; Mattar, B.; Liu, H.; Atherton, P.J.; et al. Pilot Study of Panax Quinquefolius (American Ginseng) to Improve Cancer-Related

 doi:10.20944/preprints202411.0583.v1

Fatigue: A Randomized, Double-Blind, Dose-Finding Evaluation: NCCTG Trial N03CA. *Support Care Cancer* **2010**, *18*, 179–187, doi:10.1007/s00520-009-0642-2.

76. Barton, D.L.; Liu, H.; Dakhil, S.R.; Linquist, B.; Sloan, J.A.; Nichols, C.R.; McGinn, T.W.; Stella, P.J.; Seeger, G.R.; Sood, A.; et al. Wisconsin Ginseng (Panax Quinquefolius) to Improve Cancer-Related Fatigue: A Randomized, Double-Blind Trial, N07C2. *JNCI: Journal of the National Cancer Institute* **2013**, *105*, 1230–1238, doi:10.1093/jnci/djt181.
77. Liu, C.-H.; Tsai, C.-H.; Li, T.-C.; Yang, Y.-W.; Huang, W.-S.; Lu, M.-K.; Tseng, C.-H.; Huang, H.-C.; Chen, K.-F.; Hsu, T.-S.; et al. Effects of the Traditional Chinese Herb *Astragalus Membranaceus* in Patients with Poststroke Fatigue: A Double-Blind, Randomized, Controlled Preliminary Study. *Journal of Ethnopharmacology* **2016**, *194*, 954–962, doi:10.1016/j.jep.2016.10.058.
78. Inglis, J.E.; Lin, P.-J.; Kerns, S.L.; Kleckner, I.R.; Kleckner, A.S.; Castillo, D.A.; Mustian, K.M.; Peppone, L.J. Nutritional Interventions for Treating Cancer-Related Fatigue: A Qualitative Review. *Nutrition and Cancer* **2019**, *71*, 21–40, doi:10.1080/01635581.2018.1513046.
79. de Oliveira Campos, M.P.; Riechelmann, R.; Martins, L.C.; Hassan, B.J.; Casa, F.B.A.; Giglio, A.D. Guarana (Paullinia Cupana) Improves Fatigue in Breast Cancer Patients Undergoing Systemic Chemotherapy. *The Journal of Alternative and Complementary Medicine* **2011**, *17*, 505–512, doi:10.1089/acm.2010.0571.
80. da Costa Miranda, V.; Trufelli, D.C.; Santos, J.; Campos, M.P.; Nobuo, M.; da Costa Miranda, M.; Schlinder, F.; Riechelmann, R.; del Giglio, A. Effectiveness of Guaraná (Paullinia Cupana) for Postradiation Fatigue and Depression: Results of a Pilot Double-Blind Randomized Study. *The Journal of Alternative and Complementary Medicine* **2009**, *15*, 431–433, doi:10.1089/acm.2008.0324.
81. Sette, C.V. de M.; Ribas de Alcântara, B.B.; Schoueri, J.H.M.; Cruz, F.M.; Cubero, D. de I.G.; Pianowski, L.F.; Peppone, L.J.; Fonseca, F.; del Giglio, A. Purified Dry Paullinia Cupana (PC-18) Extract for Chemotherapy-Induced Fatigue: Results of Two Double-Blind Randomized Clinical Trials. *Journal of Dietary Supplements* **2018**, *15*, 673–683, doi:10.1080/19390211.2017.1384781.
82. Helms, E.R.; Zinn, C.; Rowlands, D.S.; Naidoo, R.; Cronin, J. High-Protein, Low-Fat, Short-Term Diet Results in Less Stress and Fatigue Than Moderate-Protein, Moderate-Fat Diet During Weight Loss in Male Weightlifters: A Pilot Study. *International Journal of Sport Nutrition and Exercise Metabolism* **2015**, *25*, 163–170, doi:10.1123/ijsnem.2014-0056.
83. Kaya Kaçar, H.; Avery, A.; Bennett, S.; McCullough, F. Dietary Patterns and Fatigue in Female Slimmers. *Nutrition & Food Science* **2020**, *50*, 1213–1227, doi:10.1108/NFS-02-2020-0051.
84. Kim, H.-G.; Cheon, E.-J.; Bai, D.-S.; Lee, Y.H.; Koo, B.-H. Stress and Heart Rate Variability: A Meta-Analysis and Review of the Literature. *Psychiatry Investig* **2018**, *15*, 235–245, doi:10.30773/pi.2017.08.17.
85. Porges, S.W. Vagal Tone: A Physiologic Marker of Stress Vulnerability. *Pediatrics* **1992**, *90*, 498–504, doi:10.1542/peds.90.3.498.
86. Fang, R.; Ye, S.; Huangfu, J.; Calimag, D.P. Music Therapy Is a Potential Intervention for Cognition of Alzheimer's Disease: A Mini-Review. *Transl Neurodegener* **2017**, *6*, 2, doi:10.1186/s40035-017-0073-9.
87. Matsumura, T.; Muraki, I.; Ikeda, A.; Yamagishi, K.; Shirai, K.; Yasuda, N.; Sawada, N.; Inoue, M.; Iso, H.; Brunner, E.J.; et al. Hobby Engagement and Risk of Disabling Dementia. *J Epidemiol* **2023**, *33*, 456–463, doi:10.2188/jea.JE20210489.
88. Sommerlad, A.; Sabia, S.; Livingston, G.; Kivimäki, M.; Lewis, G.; Singh-Manoux, A. Leisure Activity Participation and Risk of Dementia. *Neurology* 2020, *95*, e2803–e2815.
89. Kim, M.J.; Tsutsumimoto, K.; Doi, T.; Nakakubo, S.; Kurita, S.; Makizako, H.; Shimada, H. Relationships between Cognitive Leisure Activities and Cognitive Function in Older Adults with Depressive Symptoms: A Cross-Sectional Study. *BMJ Open* **2020**, *10*, e032679, doi:10.1136/bmjopen-2019-032679.
90. Muscari, A.; Giannoni, C.; Pierpaoli, L.; Berzigotti, A.; Maietta, P.; Foschi, E.; Ravaioli, C.; Poggiopollini, G.; Bianchi, G.; Magalotti, D.; et al. Chronic Endurance Exercise Training Prevents Aging-Related Cognitive Decline in Healthy Older Adults: A Randomized Controlled Trial. *International Journal of Geriatric Psychiatry* **2010**, *25*, 1055–1064, doi:10.1002/gps.2462.
91. Houghton, D.; Jones, T.W.; Cassidy, S.; Siervo, M.; MacGowan, G.A.; Trenell, M.I.; Jakovljevic, D.G. The Effect of Age on the Relationship between Cardiac and Vascular Function. *Mech Ageing Dev* **2016**, *153*, 1–6, doi:10.1016/j.mad.2015.11.001.
92. Tanaka, H.; Monahan, K.D.; Seals, D.R. Age-Predicted Maximal Heart Rate Revisited. *J Am Coll Cardiol* **2001**, *37*, 153–156, doi:10.1016/s0735-1097(00)01054-8.
93. Sharma, G.; Goodwin, J. Effect of Aging on Respiratory System Physiology and Immunology. *Clin Interv Aging* **2006**, *1*, 253–260.
94. Tolep, K.; Higgins, N.; Muza, S.; Criner, G.; Kelsen, S.G. Comparison of Diaphragm Strength between Healthy Adult Elderly and Young Men. *Am J Respir Crit Care Med* **1995**, *152*, 677–682, doi:10.1164/ajrccm.152.2.7633725.
95. Berry, R.B.; Pai, U.P.; Fairshter, R.D. Effect of Age on Changes in Flow Rates and Airway Conductance after a Deep Breath. *Journal of Applied Physiology* **1990**, *68*, 635–643, doi:10.1152/jappl.1990.68.2.635.

96. Booth, F.W.; Ruegsegger, G.N.; Toedebusch, R.G.; Yan, Z. Chapter Six - Endurance Exercise and the Regulation of Skeletal Muscle Metabolism. In *Progress in Molecular Biology and Translational Science*; Bouchard, C., Ed.; Molecular and Cellular Regulation of Adaptation to Exercise; Academic Press, 2015; Vol. 135, pp. 129–151.
97. Meinild Lundby, A.-K.; Jacobs, R.A.; Gehrig, S.; de Leur, J.; Hauser, M.; Bonne, T.C.; Flück, D.; Dandanell, S.; Kirk, N.; Kaech, A.; et al. Exercise Training Increases Skeletal Muscle Mitochondrial Volume Density by Enlargement of Existing Mitochondria and Not de Novo Biogenesis. *Acta Physiologica* **2018**, *222*, e12905, doi:10.1111/apha.12905.
98. Lundby, C.; Jacobs, R.A. Adaptations of Skeletal Muscle Mitochondria to Exercise Training. *Experimental Physiology* **2016**, *101*, 17–22, doi:10.1113/EP085319.
99. Kasch, F.W.; Boyer, J.L.; Camp, S.V.; Nettl, F.; Verity, L.S.; Wallace, J.P. Cardiovascular Changes with Age and Exercise. *Scandinavian Journal of Medicine & Science in Sports* **1995**, *5*, 147–151, doi:10.1111/j.1600-0838.1995.tb00028.x.
100. Skinner, J.S.; Gaskill, S.E.; Rankinen, T.; Leon, A.S.; Rao, D.C.; Wilmore, J.H.; Bouchard, C. Heart Rate versus %VO2max: Age, Sex, Race, Initial Fitness, and Training Response--HERITAGE. *Med Sci Sports Exerc* **2003**, *35*, 1908–1913, doi:10.1249/01.MSS.0000093607.57995.E3.
101. Buist, A.S.; McBurnie, M.A.; Vollmer, W.M.; Gillespie, S.; Burney, P.; Mannino, D.M.; Menezes, A.M.; Sullivan, S.D.; Lee, T.A.; Weiss, K.B.; et al. International Variation in the Prevalence of COPD (The BOLD Study): A Population-Based Prevalence Study. *The Lancet* **2007**, *370*, 741–750, doi:10.1016/S0140-6736(07)61377-4.
102. Izuhara, Y.; Matsumoto, H.; Nagasaki, T.; Kanemitsu, Y.; Murase, K.; Ito, I.; Oguma, T.; Muro, S.; Asai, K.; Tabara, Y.; et al. Mouth Breathing, Another Risk Factor for Asthma: The Nagahama Study. *Allergy* **2016**, *71*, 1031–1036, doi:10.1111/all.12885.
103. Triana, B.E.G.; Ali, A.H.; León, I.B.G. Mouth Breathing and Its Relationship to Some Oral and Medical Conditions: Physiopathological Mechanisms Involved. *Revista Habanera de Ciencias Médicas* **2016**, *15*, 200–212.
104. Lee, Y.-C.; Lu, C.-T.; Cheng, W.-N.; Li, H.-Y. The Impact of Mouth-Taping in Mouth-Breathers with Mild Obstructive Sleep Apnea: A Preliminary Study. *Healthcare* **2022**, *10*, 1755, doi:10.3390/healthcare10091755.
105. Home Oxygen Therapy Available online: https://www.nhs.uk/conditions/home-oxygen-treatment/ (accessed on 27 October 2023).
106. Pioli, G.; Barone, A.; Giusti, A.; Oliveri, M.; Pizzonia, M.; Razzano, M.; Palummeri, E. Predictors of Mortality after Hip Fracture: Results from 1-Year Follow-Up. *Aging Clin Exp Res* **2006**, *18*, 381–387, doi:10.1007/BF03324834.
107. Rogers, M.A.; Evans, W.J. Changes in Skeletal Muscle with Aging: Effects of Exercise Training. *Exerc Sport Sci Rev* **1993**, *21*, 65–102.
108. Keller, K.; Engelhardt, M. Strength and Muscle Mass Loss with Aging Process. Age and Strength Loss. *Muscles Ligaments Tendons J* **2014**, *3*, 346–350.
109. Montero-Odasso, M.; Duque, G. Vitamin D in the Aging Musculoskeletal System: An Authentic Strength Preserving Hormone. *Molecular Aspects of Medicine* **2005**, *26*, 203–219, doi:10.1016/j.mam.2005.01.005.
110. Aschbacher, K.; Epel, E.; Wolkowitz, O.M.; Prather, A.A.; Puterman, E.; Dhabhar, F.S. Maintenance of a Positive Outlook during Acute Stress Protects against Pro-Inflammatory Reactivity and Future Depressive Symptoms. *Brain, Behavior, and Immunity* **2012**, *26*, 346–352, doi:10.1016/j.bbi.2011.10.010.
111. Lipowski, M. Level of Optimism and Health Behavior in Athletes. *Med Sci Monit* **2012**, *18*, CR39–CR43, doi:10.12659/MSM.882200.
112. Ingledew, D.K.; Brunning, S. Personality, Preventive Health Behaviour and Comparative Optimism about Health Problems. *J Health Psychol* **1999**, *4*, 193–208, doi:10.1177/135910539900400213.
113. Mulkana, S.S.; Hailey, B.J. The Role of Optimism in Health-Enhancing Behavior. *American Journal of Health Behavior* **2001**, *25*, 388–395, doi:10.5993/AJHB.25.4.4.
114. Rasmussen, H.N.; Scheier, M.F.; Greenhouse, J.B. Optimism and Physical Health: A Meta-Analytic Review. *Annals of Behavioral Medicine* **2009**, *37*, 239–256, doi:10.1007/s12160-009-9111-x.
115. Mannix, M.M.; Feldman, J.M.; Moody, K. Optimism and Health-Related Quality of Life in Adolescents with Cancer. *Child: Care, Health and Development* **2009**, *35*, 482–488, doi:10.1111/j.1365-2214.2008.00934.x.
116. Kim, E.S.; Chopik, W.J.; Smith, J. Are People Healthier If Their Partners Are More Optimistic? The Dyadic Effect of Optimism on Health among Older Adults. *Journal of Psychosomatic Research* **2014**, *76*, 447–453, doi:10.1016/j.jpsychores.2014.03.104.
117. Isenberg, C. An Examination of Regret as Expressed in the Life Reflections of Older Adults : Predictors of Regret Intensity and Frequency, and Association with Well-Being. phd, Concordia University, 2007.
118. Jokisaari, M. Regrets and Subjective Well-Being: A Life Course Approach. *Journal of Adult Development* **2004**, *11*, 281–288, doi:10.1023/B:JADE.0000044531.11605.d5.
119. Brassen, S.; Gamer, M.; Peters, J.; Gluth, S.; Büchel, C. Don't Look Back in Anger! Responsiveness to Missed Chances in Successful and Nonsuccessful Aging. *Science* **2012**, *336*, 612–614, doi:10.1126/science.1217516.

 doi:10.20944/preprints202411.0583.v1

120. Bono, G.; McCullough, M.E.; Root, L.M. Forgiveness, Feeling Connected to Others, and Well-Being: Two Longitudinal Studies. *Pers Soc Psychol Bull* **2008**, *34*, 182–195, doi:10.1177/0146167207310025.
121. Allemand, M.; Hill, P.L.; Ghaemmaghami, P.; Martin, M. Forgivingness and Subjective Well-Being in Adulthood: The Moderating Role of Future Time Perspective. *Journal of Research in Personality* **2012**, *46*, 32–39, doi:10.1016/j.jrp.2011.11.004.
122. Macaskill, A. Differentiating Dispositional Self-Forgiveness from Other-Forgiveness: Associations with Mental Health and Life Satisfaction. *Journal of Social and Clinical Psychology* **2012**, *31*, 28–50, doi:10.1521/jscp.2012.31.1.28.
123. Robustelli, B.L.; Whisman, M.A. Gratitude and Life Satisfaction in the United States and Japan. *J Happiness Stud* **2018**, *19*, 41–55, doi:10.1007/s10902-016-9802-5.
124. Kong, F.; Ding, K.; Zhao, J. The Relationships Among Gratitude, Self-Esteem, Social Support and Life Satisfaction Among Undergraduate Students. *J Happiness Stud* **2015**, *16*, 477–489, doi:10.1007/s10902-014-9519-2.
125. Unanue, W.; Gomez Mella, M.E.; Cortez, D.A.; Bravo, D.; Araya-Véliz, C.; Unanue, J.; Van Den Broeck, A. The Reciprocal Relationship Between Gratitude and Life Satisfaction: Evidence From Two Longitudinal Field Studies. *Frontiers in Psychology* **2019**, *10*.
126. Cui, M.; Zhang, S.; Liu, Y.; Gang, X.; Wang, G. Grip Strength and the Risk of Cognitive Decline and Dementia: A Systematic Review and Meta-Analysis of Longitudinal Cohort Studies. *Frontiers in Aging Neuroscience* **2021**, *13*.
127. Kim, S.; Jazwinski, S.M. Quantitative Measures of Healthy Aging and Biological Age. *Healthy Aging Res* **2015**, *4*, 26, doi:10.12715/har.2015.4.26.
128. Hirase, T.; Okubo, Y.; Delbaere, K.; Menant, J.C.; Lord, S.R.; Sturnieks, D.L. Risk Factors for Falls and Fall-Related Fractures in Community-Living Older People with Pain: A Prospective Cohort Study. *International Journal of Environmental Research and Public Health* **2023**, *20*, 6040, doi:10.3390/ijerph20116040.
129. Runge, M.; Hunter, G. Determinants of Musculoskeletal Frailty and the Risk of Falls in Old Age. *J Musculoskelet Neuronal Interact* **2006**, *6*, 167–173.
130. Zech, A.; Hübscher, M.; Vogt, L.; Banzer, W.; Hänsel, F.; Pfeifer, K. Balance Training for Neuromuscular Control and Performance Enhancement: A Systematic Review. *Journal of Athletic Training* **2010**, *45*, 392–403, doi:10.4085/1062-6050-45.4.392.
131. Stathokostas, L.; McDonald, M.W.; Little, R.M.D.; Paterson, D.H. Flexibility of Older Adults Aged 55–86 Years and the Influence of Physical Activity. *Journal of Aging Research* **2013**, *2013*, e743843, doi:10.1155/2013/743843.
132. Araújo, C.G.S. de Flexibility Assessment: Normative Values for Flexitest from 5 to 91 Years of Age. *Arq. Bras. Cardiol.* **2008**, *90*, 280–287, doi:10.1590/S0066-782X2008000400008.
133. Wolters, S.; Schumacher, B. Genome Maintenance and Transcription Integrity in Aging and Disease. *Frontiers in Genetics* **2013**, *4*.
134. Hoeijmakers, J.H.J. DNA Damage, Aging, and Cancer. *New England Journal of Medicine* **2009**, *361*, 1475–1485, doi:10.1056/NEJMra0804615.
135. Sanders, J.L.; Newman, A.B. Telomere Length in Epidemiology: A Biomarker of Aging, Age-Related Disease, Both, or Neither? *Epidemiologic Reviews* **2013**, *35*, 112–131, doi:10.1093/epirev/mxs008.
136. Horvath, S.; Raj, K. DNA Methylation-Based Biomarkers and the Epigenetic Clock Theory of Ageing. *Nat Rev Genet* **2018**, *19*, 371–384, doi:10.1038/s41576-018-0004-3.
137. Brandhorst, S.; Longo, V.D. Fasting and Caloric Restriction in Cancer Prevention and Treatment. In *Metabolism in Cancer*; Cramer, T., A. Schmitt, C., Eds.; Recent Results in Cancer Research; Springer International Publishing: Cham, 2016; pp. 241–266 ISBN 978-3-319-42118-6.
138. Chow, M.T.; Möller, A.; Smyth, M.J. Inflammation and Immune Surveillance in Cancer. *Seminars in Cancer Biology* **2012**, *22*, 23–32, doi:10.1016/j.semcancer.2011.12.004.
139. Riddle, D.R. *Brain Aging: Models, Methods, and Mechanisms*; CRC Press, 2007; ISBN 978-1-00-061155-7.
140. Wild, K.; Howieson, D.; Webbe, F.; Seelye, A.; Kaye, J. Status of Computerized Cognitive Testing in Aging: A Systematic Review. *Alzheimer's & Dementia* **2008**, *4*, 428–437, doi:10.1016/j.jalz.2008.07.003.
141. Proust-Lima, C.; Amieva, H.; Dartigues, J.-F.; Jacqmin-Gadda, H. Sensitivity of Four Psychometric Tests to Measure Cognitive Changes in Brain Aging-Population–Based Studies. *American Journal of Epidemiology* **2007**, *165*, 344–350, doi:10.1093/aje/kwk017.
142. Belleville, S.; Fouquet, C.; Hudon, C.; Zomahoun, H.T.V.; Croteau, J.; Consortium for the Early Identification of Alzheimer's disease-Quebec Neuropsychological Measures That Predict Progression from Mild Cognitive Impairment to Alzheimer's Type Dementia in Older Adults: A Systematic Review and Meta-Analysis. *Neuropsychol Rev* **2017**, *27*, 328–353, doi:10.1007/s11065-017-9361-5.
143. Butler, M.; McCreedy, E.; Nelson, V.A.; Desai, P.; Ratner, E.; Fink, H.A.; Hemmy, L.S.; McCarten, J.R.; Barclay, T.R.; Brasure, M.; et al. Does Cognitive Training Prevent Cognitive Decline? *Ann Intern Med* **2018**, *168*, 63–68, doi:10.7326/M17-1531.

144. Kouzuki, M.; Kato, T.; Wada-Isoe, K.; Takeda, S.; Tamura, A.; Takanashi, Y.; Azumi, S.; Kojima, Y.; Maruyama, C.; Hayashi, M.; et al. A Program of Exercise, Brain Training, and Lecture to Prevent Cognitive Decline. *Annals of Clinical and Translational Neurology* **2020**, *7*, 318–328, doi:10.1002/acn3.50993.
145. Chang, Y.-H.; Wu, I.-C.; Hsiung, C.A. Reading Activity Prevents Long-Term Decline in Cognitive Function in Older People: Evidence from a 14-Year Longitudinal Study. *International Psychogeriatrics* **2021**, *33*, 63–74, doi:10.1017/S1041610220000812.
146. Fallahpour, M.; Borell, L.; Luborsky, M.; Nygård, L. Leisure-Activity Participation to Prevent Later-Life Cognitive Decline: A Systematic Review. *Scandinavian Journal of Occupational Therapy* **2016**, *23*, 162–197, doi:10.3109/11038128.2015.1102320.
147. Van den Noort, M.; Vermeire, K.; Bosch, P.; Staudte, H.; Krajenbrink, T.; Jaswetz, L.; Struys, E.; Yeo, S.; Barisch, P.; Perriard, B.; et al. A Systematic Review on the Possible Relationship Between Bilingualism, Cognitive Decline, and the Onset of Dementia. *Behavioral Sciences* **2019**, *9*, 81, doi:10.3390/bs9070081.
148. Muiños, M.; Ballesteros, S. Does Dance Counteract Age-Related Cognitive and Brain Declines in Middle-Aged and Older Adults? A Systematic Review. *Neuroscience & Biobehavioral Reviews* **2021**, *121*, 259–276, doi:10.1016/j.neubiorev.2020.11.028.
149. Marioni, R.E.; Proust-Lima, C.; Amieva, H.; Brayne, C.; Matthews, F.E.; Dartigues, J.-F.; Jacqmin-Gadda, H. Social Activity, Cognitive Decline and Dementia Risk: A 20-Year Prospective Cohort Study. *BMC Public Health* **2015**, *15*, 1089, doi:10.1186/s12889-015-2426-6.
150. Hoffman, L.; Hutt, R.; Yi Tsui, C.K.; Zorokong, K.; Marfeo, E. Meditation-Based Interventions for Adults With Dementia: A Scoping Review. *The American Journal of Occupational Therapy* **2020**, *74*, 7403205010p1-7403205010p14, doi:10.5014/ajot.2020.037820.
151. Xu, L.; Zhu, L.; Zhu, L.; Chen, D.; Cai, K.; Liu, Z.; Chen, A. Moderate Exercise Combined with Enriched Environment Enhances Learning and Memory through BDNF/TrkB Signaling Pathway in Rats. *International Journal of Environmental Research and Public Health* **2021**, *18*, 8283, doi:10.3390/ijerph18168283.
152. Preventing Functional Decline with Age: Biomarkers and Best Practices - [V1].