THE MUSCLE'S ERRAND

Physical Exercise in Alzheimer's Disease — Whether the Body's Messengers to the Brain Prevent the Disease, Fail to Treat It, or Merely Fade Alongside It

The Muscle-Brain Axis · The Irisin Thread · The Reverse-Causation Trap
The Null Trials · The Question of Timing

A Dissertation Submitted in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy in Neuroscience

Prepared under the Organic Network Synthesis methodology

AdultCognitiveDisease.com

Benjamin Aaron Gustafsson

July 2026

A modifiable-exposure companion to The Temporal Architecture of Collapse — the active twin of The Restorative Interval's sleep. Where that volume asked what the resting brain repairs off-line, this asks what the moving body sends upstream: the couriers of the muscle-to-brain axis — BDNF, irisin, cathepsin B — graded not as a cure but as what they are, a genuine modifier of brain resilience whose late-stage therapeutic power the trials have so far declined to confirm.

"The muscle is not only a machine for moving the body; it is a gland that speaks to the brain. The question this dissertation asks is not whether it speaks — it plainly does — but whether the brain that most needs the message can still hear it, and whether the message was ever going to arrive in time."

— ONS Methodology Working Notes, 2026

For the physiologists who found the hormones in sweat — and for every clinician who prescribed the walk, watched it fail to save the patient already ill, and asked, honestly, why.

THE COLLAPSE TRILOGY EXPOSURE COMPANION

I. Convergent Synaptic Collapse

II. Homeostatic Microglial Collapse

III. Bioenergetic Collapse

— The Temporal Architecture of Collapse —

Modifiable-exposure line: The Microbial Prologue (gut) · The Restorative Interval (sleep)

The Muscle's Errand (exercise) — this volume

This volume is the active counterpart to the paradigm's restorative syntheses. Where *The Restorative Interval* follows what the sleeping brain sets right off-line, and *The Microbial Prologue* follows what the gut sends up the vagus, the present volume follows what the working muscle broadcasts into the circulation and across the blood-brain barrier. It treats exercise not as a single drug but as a convergent exposure that touches every axis of the trilogy — synaptic, microglial, bioenergetic, vascular — and grades, connection by connection, whether the muscle's errand prevents the disease, fails to treat it once established, or merely fades with the failing brain that stops moving.

Contents

Abstract

No intervention in the whole of dementia medicine is recommended more confidently, or proven more weakly, than physical exercise. The mechanistic case is genuinely magnificent: the working muscle is now understood not merely as a motor but as an endocrine organ, dispatching a broadcast of chemical messengers — the neurotrophin-inducing myokines cathepsin B and irisin foremost among them — that cross into the brain, drive the birth of new hippocampal neurons, and, in the specific case of irisin, restore synaptic plasticity and memory in animal models of Alzheimer's disease while the very same molecule is found depleted in human Alzheimer's hippocampus and cerebrospinal fluid. Read at the bench, exercise looks less like advice than like a polypharmacy no chemist could improve upon.

Read at the bedside, the picture darkens. The large observational studies that made exercise famous as a dementia preventive have been substantially undermined by reverse causation: in a 10,308-person cohort followed for a mean of twenty-seven years, physical activity showed no protective association with dementia, and the activity of those who would go on to be diagnosed began to fall as much as nine years before the diagnosis itself — the failing brain quietly withdrawing the body from the world, and observational statistics mistaking the symptom for a shield. And the randomized trials in people who already carry the disease have been humbling: the largest, most rigorous programme of supervised exercise in established dementia not only failed to slow cognitive decline but registered slightly worse cognition in the exercise arm, and the recent phase-3 trial in mild cognitive impairment found aerobic training no better than stretching.

This dissertation argues that both readings are true and that their reconciliation is a matter of timing and target. Exercise is a real, mechanistically overdetermined modifier of brain resilience and of the vascular-metabolic substrate on which Alzheimer's pathology acts — but it builds that resilience *upstream*, across decades and in the preclinical window, and cannot be poured onto a brain already burning. It is a primary-prevention and reserve-building intervention miscast, in the failed trials, as a late therapy. We grade every connection in an explicit validity ledger; we name, for each, the experiment that would settle it; and we identify the single thread — the muscle hormone irisin — most likely to become the first genuine "exercise in a pill." The honest verdict is neither the enthusiast's cure nor the trialist's null, but a courier whose message is real, whose delivery is late, and whose most reliable benefit belongs to the brain that is not yet ill.

I. The Oldest Prescription

Before there was a drug there was a walk. Every culture that has left a medical record has told its patients to move, and modern neurology, having watched a generation of amyloid-directed compounds arrive at the clinic with effect sizes measured in fractions of a point, has returned to that oldest prescription with something close to hope. The 2024 report of the Lancet standing Commission on dementia named physical inactivity among the fourteen modifiable risk factors that together, on its accounting, could in principle prevent or delay some forty-five percent of dementia worldwide (Livingston and colleagues, 2024). Public-health authorities the world over now list exercise beside blood pressure and hearing loss as a lever the individual can pull. The confidence is nearly total.

The evidence beneath the confidence is not. This is the central discomfort of the field, and the reason a dissertation is warranted rather than a pamphlet. On the one hand stands a body of molecular and animal work of unusual mechanistic depth and coherence — work that has isolated actual hormones, deleted their genes, and shown that when the hormone is gone the benefit of running is gone with it. On the other hand stand the human trials, which, when they are large, blinded, and conducted in people who already have the disease, have mostly failed. The gap between the mechanism and the trial is the widest in the whole of lifestyle neurology, and the temptation is to resolve it by choosing a side: to dismiss the trials as too short and too late, or to dismiss the mechanism as rodent enthusiasm. Neither dismissal survives contact with the evidence. The honest task is harder — to hold both halves at once, to grade each, and to find the frame in which both are true.

That frame, this dissertation will argue, is the muscle-to-brain axis read as a *courier system* with three separate points of possible failure: the message may never be sent (the sedentary life), the message may be sent but arrive too late to matter (exercise begun after the disease is established), or the message may arrive at a brain that can no longer read it (the failure of the neurogenic and synaptic machinery the couriers are meant to address). Most of the apparent contradiction in the literature dissolves once one asks, of every study, *which* of these three failures it was actually testing — and notices that almost none of the famous positive mechanism and almost all of the famous negative trials were testing different ones.

The muscle sends a letter to the brain. The question is never only whether the letter is written, but whether it is delivered, whether it is read, and whether it was ever going to arrive in time.

II. The Muscle as a Gland

The conceptual revolution on which this entire dissertation rests is the recognition, over the past two decades, that skeletal muscle is an endocrine organ. Contracting muscle secretes into the blood a family of signalling proteins — the myokines — through which the body's largest tissue speaks to the liver, the fat, the vasculature, the immune system, and, crucially for our purposes, the brain (Tari and colleagues, 2019). This is the physiological substance behind the phrase "exercise is medicine": not a metaphor about willpower, but a literal claim that a bout of contraction releases into the circulation biomolecules with defined receptors and defined downstream programmes, some of which are neuroprotective and some of which cross, or induce signals that cross, the blood-brain barrier.

The muscle-to-brain axis is therefore best imagined as a postal route. When a muscle contracts with sufficient intensity and duration, three broad classes of message enter the system. The first is *humoral*: circulating myokines and their hepatic and adipose relays — irisin, cathepsin B, and the induction of brain-derived neurotrophic factor prominent among them. The second is *haemodynamic*: the acute and chronic remodelling of cerebral blood flow, angiogenesis, and the health of the neurovascular unit, on which every neuron depends for its oxygen and glucose and its clearance of waste. The third is *metabolic*: the systemic improvement of insulin sensitivity, glucose handling, and lipid metabolism, which alters the whole biochemical climate in which an ageing brain operates. A fourth channel — the improvement of sleep, and through it of the brain's nightly clearance — is the subject of a companion volume [[project_restorative_interval]] and will be treated here only where it bears on the couriers.

It is essential to state at the outset what kind of claim the myokine story is and is not. That contracting muscle secretes irisin and cathepsin B into human blood is established. That these molecules have neurotrophic effects in cell and animal systems is established. That the concentrations reaching the human brain during a human exercise programme are sufficient to modify the course of a human proteinopathy is *not* established — it is the central inference the field would like to make and has not yet earned. The distance between "the gland secretes the hormone" and "the hormone treats the disease in people" is exactly the distance this dissertation is written to measure. We begin with the couriers because they are the most beautiful part of the story. We will end by conceding that beauty is not proof.

III. The Errand in Brief

Two verdicts have been drawn about exercise and Alzheimer's disease, and they are nearly irreconcilable as usually stated.

The first is the verdict of the laboratory, and it is close to euphoric. Voluntary running roughly doubles the birth of new neurons in the adult hippocampus (Brown and colleagues, 2003; van Praag and colleagues, 2005). It does so through identifiable molecular couriers: a muscle-derived protease, cathepsin B, that crosses into the brain and raises the local production of brain-derived neurotrophic factor (Moon and colleagues, 2016), and the exercise hormone irisin, cleaved from the membrane protein FNDC5, which is *required* for the cognitive benefit of exercise and, when supplied to the brain, rescues memory in Alzheimer's models (Lourenco and colleagues, 2019; Islam and colleagues, 2021). In an actual randomized trial in older humans, six months of aerobic training increased the volume of the hippocampus — the very structure Alzheimer's destroys first — by two percent, reversing one to two years of age-related atrophy (Erickson and colleagues, 2011). On this account, exercise is a disease-modifying therapy that happens to be free.

The second is the verdict of the clinical trial, and it is close to bleak. In the largest rigorous trial of supervised exercise in people with established dementia — the DAPA trial, 494 patients — a four-month programme of moderate-to-high-intensity aerobic and strength training improved physical fitness handsomely and did nothing for cognition; if anything, the exercise arm ended the year with slightly *worse* cognitive scores than usual care (Lamb and colleagues, 2018). The most recent and most sophisticated trial in mild cognitive impairment, the phase-3 EXERT study, found that twelve months of supervised moderate-to-high-intensity aerobic training was no better for cognition than low-intensity stretching and balance work (Baker and colleagues, 2025). And the observational studies that once seemed to settle the matter in exercise's favour have been shown to be badly confounded by reverse causation: the physical activity of future dementia patients begins to decline years before their diagnosis, so that "active people get less dementia" may largely mean "people whose brains are already failing move less" (Sabia and colleagues, 2017).

This dissertation's thesis is that the two verdicts are not in fact contradictory, because they are answers to different questions. The laboratory asked whether exercise *can* build the biological resilience of a healthy brain, and the answer is a resounding yes. The clinical trials asked whether exercise, begun after the disease is established, *can reverse or halt* it, and the answer is a fairly clear no. Between these lies the question that neither cleanly tested and that matters most: whether a lifetime of the muscle's errand, delivered across the decades before symptoms, lowers the eventual burden of disease. The honest reading of the whole literature is that exercise is a genuine builder of reserve and a genuine tender of the vascular-metabolic substrate, acting upstream and early, and a poor late therapy — a courier whose letter must arrive before the house is on fire.

IV. The Couriers How Exercise Reaches the Brain

We turn now to the mechanisms, tracing each courier from the contracting muscle to the vulnerable neuron and grading, as we go, how much of the chain is established in humans and how much is inferred from animals. The convergence is real: exercise does not act through one pathway but through many, which is precisely why its mechanistic case is so strong and its clinical case so frustratingly diffuse. A therapy with one target can be tested by blocking that target; a therapy with a dozen partially redundant targets is nearly impossible to falsify and nearly impossible to concentrate into a pill.

The Neurotrophic Cascade — BDNF and the Neurogenic Niche

The foundational discovery of the modern era is that the adult hippocampus continues to make neurons, and that exercise is among the most powerful physiological stimuli of that neurogenesis known. Voluntary wheel running in mice increases the proliferation and survival of new granule cells in the dentate gyrus, and it does so with striking anatomical specificity — the dentate neurogenic niche responds, while the olfactory neurogenic stream does not (Brown and colleagues, 2003). The effect is not confined to the young: in aged mice, previously sedentary until nineteen months of life, one month of running reversed the age-related decline in neurogenesis to half of youthful levels and produced measurably faster learning and better retention in the water maze (van Praag and colleagues, 2005). The dentate gyrus is not an incidental structure in this story. It is the hippocampal subfield on which pattern separation depends, and it is early and heavily involved in Alzheimer's disease.

The molecular currency of this effect is brain-derived neurotrophic factor, BDNF, the neurotrophin most consistently elevated by exercise and most tightly linked to synaptic plasticity, long-term potentiation, and the survival of newborn neurons. The critical human bridge was built by Erickson and colleagues (2011), who randomized 120 older adults to a year of aerobic training or stretching and found that the aerobic group's anterior hippocampus *grew* by roughly two percent while the control group's shrank, that the growth tracked with rising serum BDNF, and that it translated into improved spatial memory. This is as close to a mechanistic human proof as the field possesses: a randomized intervention, an anatomical outcome in the correct structure, a plausible molecular mediator moving in the correct direction, and a cognitive readout. It is also, tellingly, a study in cognitively normal older adults — not in patients with Alzheimer's disease — and its outcome was reserve, not rescue.

The Irisin Thread

If a single molecule carries the field's best hope of translating the muscle's errand into a drug, it is irisin. Irisin is the cleaved, secreted fragment of the membrane protein FNDC5, released from muscle on contraction and also expressed in the hippocampus itself. The thread of evidence that makes it extraordinary was drawn most decisively by Lourenco and colleagues in 2019, in a study that combined human tissue, animal models, and causal manipulation. They found, first, that FNDC5/irisin is *reduced* in the hippocampus and cerebrospinal fluid of people with Alzheimer's disease and in experimental models of it — establishing that the pathology involves a deficiency of exactly this exercise hormone. They then showed that knocking irisin down in the brain impairs long-term potentiation and memory, that boosting it rescues synaptic plasticity and memory in Alzheimer's-model mice, and — the keystone — that blocking irisin, either in the brain or in the periphery, *abolishes the neuroprotective effect of physical exercise itself* in those mice (Lourenco and colleagues, 2019). This is the rare experiment that does not merely correlate a molecule with a benefit but demonstrates that the benefit runs *through* the molecule.

The case was extended by Islam and colleagues (2021), who deleted FNDC5/irisin globally in mice and found cognitive impairment across three settings — exercise, ageing, and Alzheimer's models — with structurally and transcriptionally abnormal adult-born neurons in the dentate gyrus, deficits rescuable by delivering irisin directly into that structure. Most provocatively for translation, they raised circulating irisin by overexpressing it in the liver and found that peripheral delivery enriched irisin centrally and improved both the cognitive deficit and the neuropathology of Alzheimer's-model mice — a proof of principle that the hormone need not be injected into the brain to reach it. More recent work has begun to specify the downstream biochemistry: irisin appears to lower amyloid-β in part by inducing the amyloid-degrading enzyme neprilysin, secreted from astrocytes (Kim, Tanzi, and Choi, 2025). The convergence — human deficiency, causal necessity for exercise's benefit, peripheral rescue, and a defined amyloid-clearing mechanism — makes irisin the most complete mechanistic story in the field.

It must nonetheless be graded honestly, and the grading is sobering. Every causal step in the irisin chain has been established in mice; not one has been established as a therapy in humans. The irisin literature has, moreover, weathered its own methodological controversy over whether the hormone is reliably detectable in human blood at physiological concentrations, a debate resolved in irisin's favour by mass spectrometry but a reminder that measurement here is delicate (de Freitas, Lourenco, and De Felice, 2020). Irisin is the thread most likely to yield a drug. It is not yet evidence that exercise treats human Alzheimer's disease; it is evidence of *why it might*.

Cathepsin B and the Muscular Secretome

The second well-characterized courier is cathepsin B, a protease that Moon and colleagues (2016) identified as a genuine myokine — secreted by muscle cells under the metabolic stress that exercise imposes, elevated in muscle and plasma by running, and capable, as a recombinant protein, of raising BDNF and the immature-neuron marker doublecortin in hippocampal progenitor cells. The causal test was decisive in the same way the irisin work was: in mice lacking cathepsin B, running failed to enhance either neurogenesis or spatial memory, placing the molecule squarely on the pathway rather than beside it. And the study reached carefully toward humans and primates — treadmill exercise raised plasma cathepsin B in rhesus monkeys and in people, and in the human participants the change in cathepsin B tracked with fitness and with hippocampus-dependent memory performance.

Cathepsin B matters to the argument for two reasons beyond its own mechanism. First, it demonstrates that the muscle-to-brain axis is *plural* — irisin is not a lone hero but one member of a secretome, and the redundancy of the system is part of why single-molecule interventions may never fully reproduce exercise. Second, cathepsin B is a cautionary figure: the same protease has context-dependent and even deleterious roles elsewhere in the nervous system, a reminder that "myokine" is not a synonym for "benign," and that the dream of bottling the muscle's errand will have to reckon with molecules that are protective in one tissue and hazardous in another.

The Vascular and Metabolic Substrate

Beneath the glamour of the hormones lies a plainer and possibly more important mechanism: exercise is the most effective non-pharmacological means of maintaining the health of the cerebral vasculature and of systemic metabolism, and Alzheimer's disease is, in a large fraction of real patients, a mixed vascular-degenerative condition. Chronic aerobic training lowers blood pressure, improves endothelial function, promotes cerebral angiogenesis, sustains cerebral blood flow, and improves insulin sensitivity — and each of these is independently relevant to a brain in which hypoperfusion, small-vessel disease, and impaired cerebral glucose handling accelerate the clinical expression of amyloid and tau pathology.

The most instructive human evidence that this substrate matters comes from Rabin and colleagues (2019), who studied clinically normal older adults in the Harvard Aging Brain Study with amyloid PET at baseline and followed their cognition and brain volume for a median of six years. Greater physical activity, objectively measured by pedometer, *attenuated the association between amyloid burden and subsequent cognitive decline and neurodegeneration* — that is, among people carrying the same amyloid load, the more active declined more slowly. Critically, the protective association held after adjustment for vascular risk, and lower vascular risk exerted its own independent protective effect, the two appearing additive. This is the single most important human finding for the thesis of this dissertation, and we will return to it: it locates exercise's benefit in the *preclinical* window, on people

who already harbour pathology but are not yet demented, and it frames exercise as a modifier of resilience to pathology rather than an eraser of pathology.

Inflammation, Sleep, and the Mitochondrion — the Plausible Remainder

Three further mechanisms are frequently and reasonably invoked, and each must be graded as plausible-but-underdemonstrated in humans. Exercise is broadly anti-inflammatory, and chronic neuroinflammation driven by activated microglia is a genuine engine of Alzheimer's progression [[project_collapse_trilogy]]; the inference that exercise's systemic anti-inflammatory tone reaches and calms the diseased brain is attractive but rests largely on animal models. Exercise improves sleep, and sleep drives the glymphatic clearance of interstitial waste including amyloid-β [[project_glymphatic_collapse]]; here the mechanism is real but the causal chain from a treadmill session to a cleaner brain in a human patient remains inferential. And exercise stimulates mitochondrial biogenesis and improves cellular bioenergetics, the failure of which is the subject of the trilogy's third volume [[project_collapse_trilogy]]; that a fitter systemic metabolism yields a better-fuelled neuron is biologically sensible and clinically unproven. These are not weaknesses to be hidden. They are the honest edge of the map, and the validity ledger will grade them as such.

V. The Human Evidence, Weighed

We come now to the harder half of the dissertation — the human evidence — and we will not flinch from it. The mechanistic beauty of Section IV creates an expectation that the human data are compelled to disappoint, and the discipline of the ONS method is to state that disappointment plainly and then to understand it, rather than to explain it away.

The Observational Promise

For two decades the observational epidemiology seemed to have settled the question. Cohort after cohort reported that physically active people had a lower incidence of dementia, often with hazard ratios in the range of a twenty-to-forty-percent reduction, and meta-analyses aggregated these into an apparently robust protective signal. The most methodologically careful of these studies used *objective* rather than self-reported activity: Buchman and colleagues (2012), in the Rush Memory and Aging Project, measured total daily physical activity by actigraphy — a wrist accelerometer worn continuously — in 716 older adults without dementia and found that higher total daily activity was associated with a markedly lower risk of incident Alzheimer's disease (hazard ratio 0.48) and a slower rate of cognitive decline. The association survived adjustment for self-reported activity, motor function, depression, chronic disease, and APOE genotype. Because it used a device rather than a questionnaire and captured all movement rather than only deliberate exercise, this study is among the strongest observational entries in the field.

And yet even it cannot escape the trap that undoes the observational literature as a whole. An accelerometer measures how much a person moves; it cannot tell us *why* a person who will later develop dementia moves less. If the earliest, still-subclinical phase of the disease itself reduces activity — through apathy, subtle executive dysfunction, gait change, or loss of initiative — then the correlation between activity and later diagnosis will appear protective even if activity does nothing to the disease at all. This is reverse causation, and it is the specter that haunts every observational claim about exercise and the brain.

The Reverse-Causation Trap

The study that forced the field to confront this specter honestly is Sabia and colleagues' 2017 analysis of the Whitehall II cohort — 10,308 British civil servants whose physical activity was assessed seven times over twenty-eight years, with dementia ascertained through linked health records. Its findings are among the most important, and most under-cited, in the whole literature. Across a mean follow-up of twenty-seven years, physical activity showed *no* protective association with the risk of dementia: those meeting recommended activity levels had a hazard ratio of exactly 1.00. There was no association between midlife physical activity and subsequent fifteen-year cognitive decline. But the study's decisive move was to plot the *trajectory* of activity in the years before diagnosis — and here it found that the people who would go on to develop dementia had activity levels indistinguishable from everyone else until roughly nine years before diagnosis, at which point their activity began to fall, the divergence widening as the diagnosis approached (Sabia and colleagues, 2017).

This is the reverse-causation trap made visible. For nearly a decade before a dementia diagnosis, the disease is already present in the brain and already, silently, reducing the patient's movement. Any study that measures activity in that pre-diagnostic window and correlates it with

subsequent diagnosis will "discover" that activity protects against dementia — when what it has actually discovered is that incipient dementia suppresses activity. The authors' conclusion is stark and, on the evidence, warranted: much of the apparent neuroprotective effect of physical activity in observational studies may be an artefact of the disease's own prodromal signature. It does not prove exercise useless. It proves that the observational literature systematically *overstates* exercise's benefit, and that the true effect must be sought elsewhere — in trials, in the preclinical window, and in mechanisms.

The Randomized Reckoning

Randomization is the antidote to reverse causation, because it assigns activity rather than observing it, and the randomized reckoning has been sobering in exact proportion to its rigour. The DAPA trial (Lamb and colleagues, 2018) remains the field's most important negative result: 494 people with mild-to-moderate dementia, randomized two-to-one to a four-month supervised programme of moderate-to-high-intensity aerobic and strength training or to usual care, with cognition (the ADAS-cog) as the pre-specified primary outcome at twelve months. Adherence was good and fitness improved measurably — the exercise worked as exercise. It simply did not work as therapy: cognition did not improve, and the exercise arm's mean ADAS-cog was in fact marginally *worse* than usual care (an adjusted difference of 1.4 points, of uncertain clinical meaning). No secondary outcome rescued the result. Here was the muscle's errand delivered, under supervision, to brains already ill — and the letter changed nothing.

The pattern repeats. The Danish ADEX trial (Hoffmann and colleagues, 2016) randomized 200 patients with mild Alzheimer's to sixteen weeks of supervised moderate-to-high-intensity aerobic exercise and found no effect on the primary cognitive outcome in the intention-to-treat analysis, though it did reduce neuropsychiatric symptoms — a real and humane benefit — and hinted, in a per-protocol subgroup of high attenders exercising at high intensity, at a dose-dependent cognitive signal that a randomized trial cannot properly credit. A trial in more advanced dementia found no cognitive benefit at all, only a transient gain in gait speed lost after detraining (Sanders and colleagues, 2020). A meta-analysis of multicomponent exercise in mild cognitive impairment and dementia found a pooled effect on global cognition that *evaporated* when aerobic exercise was absent, and that did not survive when the analysis separated mild cognitive impairment from dementia (Venegas-Sanabria and colleagues, 2022). And a responder analysis in healthy but inactive elders found that only those who actually achieved a large increase in activity — a minority — showed cognitive gains, the intention-to-treat comparison being null (Galle and colleagues, 2023).

The most recent and most authoritative entry is the phase-3 EXERT trial (Baker and colleagues, 2025): 296 sedentary older adults with amnestic mild cognitive impairment, randomized to twelve to eighteen months of supervised moderate-to-high-intensity aerobic training or to

low-intensity stretching, balance, and range-of-motion work, with a rigorous global cognitive composite as the primary outcome. Adherence was excellent. The result: *no difference* between aerobic training and stretching. On its face this is another null, and a decisive one, for it says that the intensity and aerobic character on which the mechanistic story depends added nothing over gentle movement. But EXERT carried a twist that its companion analysis made explicit: *neither* group declined cognitively over twelve months, and when both were compared to a propensity-matched, no-intervention usual-care group drawn from the ADNI study, both exercise arms — aerobic and stretching alike — declined significantly less than usual care, with trends toward less brain-volume loss (Shadyab and colleagues, 2025). One honest reading is that the trial was negative for the specific hypothesis (aerobic superiority) but consistent with a non-specific benefit of structured, supported activity of any kind, engagement and adherence perhaps mattering as much as heart rate.

Against this ledger of nulls stands one genuinely positive randomized trial, and its structure is the key to the whole dissertation. The Finnish FINGER trial (Ngandu and colleagues, 2015) randomized 1,260 at-risk but non-demented older adults to a two-year *multidomain* intervention — diet, exercise, cognitive training, and vascular-risk monitoring together — or to general health advice, and found a small but significant benefit to global cognition. FINGER is routinely cited as evidence that exercise works. It is nothing of the kind, taken alone: exercise was one of four simultaneous ingredients and cannot be isolated. What FINGER actually demonstrates is more interesting and more consistent with everything above — that a bundle of lifestyle modifications, applied to people who are *not yet demented*, can measurably bend the cognitive trajectory. It is a primary-prevention success in the preclinical population, not a treatment success in the diseased one.

The Preclinical Window

Assemble the human evidence and a shape emerges that neither the euphoric nor the bleak verdict predicted. Exercise begun *after* dementia is established does not, on the best trials, slow cognitive decline (DAPA, ADEX, Sanders, EXERT). Exercise as measured in the *pre-diagnostic* window is confounded by the disease's own suppression of movement (Sabia). But exercise and multidomain lifestyle interventions applied to the *preclinical, at-risk but non-demented* population — the window in which pathology is accumulating but symptoms have not arrived — show the signal that survives scrutiny: FINGER's multidomain benefit, and Rabin's demonstration that physical activity attenuates the coupling between amyloid burden and cognitive decline in clinically normal people carrying that burden (Rabin and colleagues, 2019). The benefit of the muscle's errand is real, but it is a benefit of the *earlier* brain — the brain that still has the neurogenic and synaptic machinery to answer the couriers, and the vascular reserve to be worth protecting.

VI. Reconciling the Verdicts The Question of Timing

Why should a therapy whose molecular credentials are so strong fail so consistently in the clinic? The reconciliation this dissertation proposes has three parts, and each is testable.

The first is *timing*. Exercise builds reserve — additional neurons, denser synapses, richer vasculature, a more resilient metabolism — and reserve is a capital account that must be funded before it is drawn upon. A four-month or even eighteen-month programme begun in a brain already carrying advanced amyloid, tau, and synaptic loss is an attempt to fund the account after the withdrawal has been made. The couriers arrive, but the dentate gyrus they would stock with new neurons is already atrophied, the synapses they would strengthen already lost, the vasculature already compromised. This is why the positive human data cluster in the healthy and the preclinical and the negative data cluster in the demented: not because exercise is inert, but because reserve cannot be built retroactively. One does not pour foundations onto a burning house and expect the fire to stop.

The second is *target*. Exercise acts on the substrate and the resilience of the brain — the vascular-metabolic terrain, the neurogenic and synaptic reserve — and not, so far as the evidence shows, on the core proteostatic engine that generates amyloid and propagates tau. Even the irisin work, which does touch amyloid through neprilysin, does so as a modulator rather than a primary driver. A therapy that improves the brain's *tolerance* of pathology without arresting the *production* of pathology should be expected to delay the clinical threshold in people who have not yet crossed it and to do little for those who already have. This is precisely the observed pattern, and it reframes exercise not as a failed disease-modifier but as a successful resilience-modifier miscast in trials designed to detect disease modification.

The third is *heterogeneity*, and here the honest answer is that we do not yet know enough. There are hints that genotype matters — that the effect of exercise may differ between carriers and non-carriers of the APOE ε4 allele, the strongest common genetic risk factor for the disease — but the trial evidence is thin and inconsistent: one dementia trial found APOE ε4 moderated the exercise effect on global cognition only at the level of a statistical trend (Sanders and colleagues, 2020), and Rabin's preclinical finding held after adjustment for ε4 rather than being driven by it. It is biologically plausible that the population in whom exercise most helps is defined by genotype, baseline fitness, vascular burden, or the stage of pathology — and it is entirely possible that the null trials are averaging a real benefit in a responsive subgroup against no benefit, or harm, in others. The responder analyses (Galle and colleagues, 2023; the ADEX per-protocol signal) are consistent with this and cannot, by their nature, prove it. Heterogeneity is the field's largest unlit room.

VII. The Validity Ledger

The discipline that distinguishes this dissertation from advocacy is the ledger: an explicit grading of each connection, with the experiment that would settle it named alongside. The tiers run from *strong* through *moderate*, *real but narrow*, *plausible*, and *uncertain*, to *weak* and *rejected*.

Strong — exercise stimulates adult hippocampal neurogenesis and raises BDNF, and can enlarge the hippocampus in humans. This is the ledger's most secure thread. The animal neurogenesis data are large, reproducible across laboratories, anatomically specific, and causally dissected; the human anchor — a randomized trial showing aerobic-training-induced hippocampal growth tracking serum BDNF — is real and correctly targeted (Brown 2003; van Praag 2005; Erickson 2011). *Settling experiment: not needed for the effect itself; what remains open is whether the neurogenic gain translates into clinical protection, which the prevention trials below must answer.*

Strong (in animals) / Moderate (as human inference) — irisin/FNDC5 is a required mediator of exercise's cognitive benefit and rescues memory in Alzheimer's models. The causal architecture in mice is exemplary: human deficiency of the hormone in Alzheimer's tissue, loss of exercise's benefit when the hormone is blocked, rescue when it is supplied peripherally, and a defined amyloid-clearing mechanism through astrocytic neprilysin (Lourenco 2019; Islam 2021; Kim, Tanzi, and Choi 2025). The human inference — that raising irisin will treat human disease — is not yet evidenced. *Settling experiment: a trial of an irisin-pathway agent, or of an exercise programme with irisin as a mediation biomarker, demonstrating that cognitive benefit in humans is mediated by irisin.*

Strong — cathepsin B is a genuine exercise-induced myokine on the neurogenic pathway. Causally established in mice (running fails to boost neurogenesis or memory without it) and reaching plausibly into humans and primates, where plasma cathepsin B rises with exercise and tracks memory (Moon 2016). *Settling experiment: demonstration that a cathepsin-B-dependent pathway carries a measurable share of exercise's cognitive benefit in humans, with attention to the protease's context-dependent risks.*

Moderate — physical activity attenuates the coupling of amyloid burden to cognitive decline in the preclinical brain. The Harvard Aging Brain finding is prospective, objectively measured, correctly located in clinically normal amyloid-positive people, and independent of vascular risk (Rabin 2019). It is observational and single-cohort, and could still harbour residual confounding. *Settling experiment: a randomized exercise trial in amyloid-positive but cognitively normal adults, powered on cognitive-decline and neurodegeneration endpoints — a preclinical-window trial the field has largely not done.*

Moderate — a multidomain lifestyle intervention including exercise slows cognitive decline in at-risk, non-demented elders. FINGER is randomized, large, and positive, but bundles exercise with diet, cognitive training, and vascular control, so exercise's specific contribution is unresolved (Ngandu 2015). *Settling experiment: a factorial multidomain trial that can isolate the exercise component, now partly the aim of worldwide FINGER-derived successor studies.*

Real but narrow — structured, supported activity of any kind may modestly protect cognition in mild cognitive impairment relative to no intervention. EXERT found aerobic training no better than stretching, yet both arms declined less than a matched usual-care comparator (Baker 2025; Shadyab 2025). The comparison to an external cohort is not a randomized contrast and must be held cautiously; the finding points to engagement and adherence rather than aerobic intensity as the active ingredient. *Settling experiment: a three-arm randomized trial — vigorous aerobic, gentle activity, and a genuine no-contact control — to separate the specific effect of exertion from the non-specific effect of a supported programme.*

Weak / refuted as a late therapy — exercise begun after dementia is established slows cognitive decline. The best-powered, most rigorous trials in established disease are null, and the largest trended slightly negative on cognition despite improving fitness (Lamb 2018; Hoffmann 2016; Sanders 2020). This is not a gap in the evidence; it is evidence of absence at the tested doses and durations. Exercise in established dementia retains real value for physical function, mood, and neuropsychiatric symptoms, and should be prescribed for those — but not sold as cognitive rescue. *Settling experiment: already substantially conducted and negative; a positive result would require a fundamentally longer, earlier, or differently targeted intervention.*

Rejected as stated — the large observational protection of physical activity against dementia is a genuine causal effect of exercise. The Whitehall II analysis showed no protective association over twenty-seven years and demonstrated that activity falls up to nine years before diagnosis, exposing the observational signal as substantially reverse causation (Sabia 2017). The strong causal reading of the epidemiology is not supported. *Settling experiment: Mendelian-randomization and long-lead-time trajectory studies that separate the disease's suppression of activity from any protective effect of activity — the former now clearly demonstrated, the latter not.*

Uncertain — APOE genotype, baseline fitness, or pathological stage defines a subgroup in whom exercise meaningfully protects cognition. Biologically plausible and hinted at by responder analyses and a trend-level ε4 interaction, but unproven and possibly the reason trials average to null (Sanders 2020; Galle 2023). *Settling experiment: prospectively stratified trials, powered within genotype and fitness strata, with pre-registered subgroup hypotheses.*

Plausible but underdemonstrated in humans — exercise protects the brain by calming neuroinflammation, improving sleep-dependent clearance, and enhancing mitochondrial bioenergetics. Each mechanism is real in principle and supported in animals;

none is established as the operative human mechanism (Tari 2019, as review). *Settling experiment: human interventional studies pairing exercise with the relevant biomarker — microglial PET, glymphatic-clearance imaging, or cerebral metabolic measures — showing that the biomarker moves and mediates cognitive benefit.*

VIII. Where Exercise Sits Prevention, Reserve, or Therapy

Having graded the connections, we can place exercise precisely. It is not a disease-modifying therapy in the sense the amyloid and tau programmes aspire to: it does not, on current evidence, arrest or reverse the core proteinopathy once dementia is established, and the trials that tested it as such have returned clear nulls. Neither is it the inert placebo a cynical reading of those nulls might suggest. It is a *resilience and prevention intervention* — a modifier of the brain's capacity to tolerate pathology and of the vascular-metabolic terrain on which pathology acts, whose benefit is real, mechanistically overdetermined, and concentrated in the years before clinical disease.

Mapped onto the temporal architecture that organizes the wider ONS framework [[project_temporal_architecture]], exercise is an intervention of the *earliest* phase. In the decades of preclinical accumulation, when amyloid is rising but cognition is intact, the muscle's errand does its real work: stocking the neurogenic niche, thickening the synaptic and vascular reserve, and — as Rabin's data suggest — loosening the grip of amyloid on the cognitive trajectory. As the disease crosses into symptomatic territory, the window narrows; the machinery that answers the couriers is itself degrading, and the letters, though still delivered, find fewer readers. By the time of established dementia the errand's cognitive value is spent, though its value to the body, the mood, and the dignity of the patient endures. This is not a diminishment of exercise. It is its correct clinical location: a lifelong investment in reserve, not an emergency treatment.

The framing also resolves the field's rhetorical excess. To tell a healthy fifty-year-old that exercise protects the brain is well supported by mechanism and by the preclinical-window evidence, and is sound public-health advice. To imply to the family of a person with moderate Alzheimer's that a walking programme will slow the disease is not supported by the trials and risks a cruelty of false hope. The same intervention carries a true claim and a false one depending only on when in the disease it is offered — which is the entire lesson of the timing thesis.

IX. Therapeutic Corollaries The Errand in a Pill

If exercise's benefit runs through identifiable molecular couriers, the pharmacological dream is obvious: to bottle the errand — to deliver the myokines, or agents that mimic them, to people who cannot exercise enough or early enough to accumulate the reserve. The dream has a lead compound in all but name. Irisin, whose peripheral delivery enriched the brain and improved both cognition and neuropathology in Alzheimer's-model mice (Islam and colleagues, 2021), is the field's most credible candidate for an exercise mimetic, and the elucidation of its neprilysin-dependent amyloid-clearing mechanism (Kim, Tanzi, and Choi, 2025) gives medicinal chemistry a target to engage. A cathepsin-B or BDNF-pathway agonist represents a second and third avenue, each shadowed by the same difficulty: these molecules are pleiotropic, protective in one tissue and hazardous in another, and the muscle's errand may be irreducibly plural — a broadcast that no single-molecule drug can fully reproduce.

Three corollaries follow for the clinic and for trial design, and all three are consequences of the timing thesis. First, exercise should be prescribed for what it demonstrably does: in established dementia, for physical function, mood, neuropsychiatric symptoms, falls prevention, and the preservation of independence, on which the trials are positive or neutral rather than negative, and not as a cognitive treatment on which they are negative. Second, the entire weight of the cognitive hope should shift to *primary and secondary prevention* — to trials that intervene in midlife and in the amyloid-positive but cognitively normal, the window in which every surviving signal lives, and which the field, for reasons of cost and duration, has largely avoided. Third, the myokine programme should be pursued as a genuine drug-development effort in parallel with, not in place of, the promotion of exercise itself — for a pill that could deliver even a fraction of the errand to the sedentary, the disabled, and the elderly who cannot train would extend a benefit that behavioural exercise, for all its cheapness, reaches unevenly.

X. Predictions and Falsification

A framework earns its keep by risking specific predictions. The timing-and-target thesis of this dissertation makes several, each falsifiable.

- A randomized trial of exercise in amyloid-positive but cognitively normal adults, powered on cognitive-decline and neurodegeneration endpoints over five or more years, will show a benefit that the trials in established dementia did not — and if such a preclinical-window

trial is also null, the thesis of this dissertation is substantially wrong.

- The benefit of exercise across trials will correlate inversely with the baseline severity of disease: meta-regression across studies should show effect sizes shrinking toward and past zero as mean baseline impairment rises. A flat or reversed gradient would refute the timing thesis.
- Irisin, or an irisin-pathway agent, will reproduce a measurable fraction of exercise's cognitive and neuropathological benefit in a mammalian model without exercise, and mediation analyses in human exercise trials will find that cognitive benefit, where present, is carried in part by circulating irisin. Failure of irisin to mediate human benefit would demote the field's most beautiful mechanism to an epiphenomenon.
- Objectively measured activity trajectories will continue to show a pre-diagnostic decline beginning years before symptoms across independent cohorts, confirming reverse causation as a general feature; and Mendelian-randomization studies using genetic instruments for physical activity will show, at most, a small protective effect on dementia far below the observational estimate. A large Mendelian-randomization effect matching the observational one would overturn the reverse-causation reading.
- In established dementia, exercise will continue to improve physical fitness, mood, and neuropsychiatric symptoms while failing to slow cognitive decline — a dissociation the thesis predicts and that a cognitive rescue in a well-powered late trial would falsify.

XI. Coda The Errand and the Hour

The muscle writes to the brain in a hand we have only lately learned to read. The letters are real — irisin, cathepsin B, the induction of BDNF — and their contents are kind: build new neurons, hold the synapses, keep the vessels open, tolerate the gathering pathology a little longer. For a century we prescribed the walk on faith; in a single generation the physiologists opened the envelope and found genuine hormones inside. That discovery is not diminished by the trials that followed. It is only relocated in time.

For the letter, it turns out, must arrive before the fire. Delivered to the young and the middle-aged and the preclinical, across the long decades when amyloid gathers in silence, the muscle's errand does exactly what its molecules promise — it funds a reserve that will, later, be quietly drawn down against the disease, delaying the hour at which the symptoms cross the threshold. Delivered to the brain already burning, the same letter, in the same hand, carrying the

same kind words, finds its reader gone; the couriers arrive at a dentate gyrus too atrophied to answer and synapses already lost, and the trials record, honestly, that nothing changed. The observational literature, meanwhile, mistook the disease's own hand — the failing brain drawing the body indoors — for the shield, and read protection into what was only prodrome.

The honest verdict is therefore neither the enthusiast's cure nor the trialist's null. Exercise is a true modifier of the brain's resilience, a real and plural signal from the body's largest gland, whose benefit is banked early and spent late, and whose most reliable gift belongs to the brain that is not yet ill. The clinician's task is to prescribe it for what it does — reserve for the well, function and dignity for the sick — and to resist selling it as what it is not. The scientist's task is to run at last the trial the field has avoided, in the preclinical window where every surviving signal lives, and to chase the one molecule, irisin, that might carry the errand to those who can no longer run. The muscle will keep writing. The question this dissertation leaves is only whether we will deliver its letters while the brain can still read.

References

All references below were retrieved and verified via PubMed; digital object identifiers are provided for each. Attribution: bibliographic metadata for the works cited was confirmed against the PubMed database.

1. Livingston G, Huntley J, Liu KY, Costafreda SG, Selbæk G, Alladi S, Ames D, Banerjee S, Burns A, Brayne C, Fox NC, Ferri CP, Gitlin LN, Howard R, Kales HC, Kivimäki M, Larson EB, Nakasujja N, Rockwood K, Samus Q, Shirai K, Singh-Manoux A, Schneider LS, Walsh S, Yao Y, Sommerlad A, Mukadam N. Dementia prevention, intervention, and care: 2024 report of the Lancet standing Commission. *Lancet*. 2024;404(10452):572–628. DOI: 10.1016/S0140-6736(24)01296-0

2. Sabia S, Dugravot A, Dartigues JF, Abell J, Elbaz A, Kivimäki M, Singh-Manoux A. Physical activity, cognitive decline, and risk of dementia: 28 year follow-up of Whitehall II cohort study. *BMJ*. 2017;357:j2709. DOI: 10.1136/bmj.j2709

3. Buchman AS, Boyle PA, Yu L, Shah RC, Wilson RS, Bennett DA. Total daily physical activity and the risk of AD and cognitive decline in older adults. *Neurology*. 2012;78(17):1323–1329. DOI: 10.1212/WNL.0b013e3182535d35

4. Rabin JS, Klein H, Kirn DR, Schultz AP, Yang HS, Hampton O, Jiang S, Buckley RF, Viswanathan A, Hedden T, Pruzin J, Yau WW, Guzmán-Vélez E, Quiroz YT, Properzi M, Marshall GA, Rentz DM, Johnson KA, Sperling RA, Chhatwal JP. Associations of physical activity and β-amyloid with longitudinal cognition and neurodegeneration in clinically normal older adults. *JAMA Neurology*. 2019;76(10):1203–1210. DOI: 10.1001/jamaneurol.2019.1879

5. Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, Kim JS, Heo S, Alves H, White SM, Wojcicki TR, Mailey E, Vieira VJ, Martin SA, Pence BD, Woods JA, McAuley E, Kramer AF. Exercise training increases size of hippocampus and improves memory. *Proceedings of the National Academy of Sciences USA*. 2011;108(7):3017–3022. DOI: 10.1073/pnas.1015950108

6. van Praag H, Shubert T, Zhao C, Gage FH. Exercise enhances learning and hippocampal neurogenesis in aged mice. *Journal of Neuroscience*. 2005;25(38):8680–8685. DOI: 10.1523/JNEUROSCI.1731-05.2005

7. Brown J, Cooper-Kuhn CM, Kempermann G, van Praag H, Winkler J, Gage FH, Kuhn HG. Enriched environment and physical activity stimulate hippocampal but not olfactory bulb neurogenesis. *European Journal of Neuroscience*. 2003;17(10):2042–2046. DOI: 10.1046/j.1460-9568.2003.02647.x

8. Moon HY, Becke A, Berron D, Becker B, Sah N, Benoni G, Janke E, Lubejko ST, Greig NH, Mattison JA, Duzel E, van Praag H. Running-induced systemic cathepsin B secretion is associated with memory function. *Cell Metabolism*. 2016;24(2):332–340. DOI: 10.1016/j.cmet.2016.05.025

9. Lourenco MV, Frozza RL, de Freitas GB, Zhang H, Kincheski GC, Ribeiro FC, Gonçalves RA, Clarke JR, Beckman D, Staniszewski A, Berman H, Guerra LA, Forny-Germano L, Meier S, Wilcock DM, de Souza JM, Alves-Leon S, Prado VF, Prado MAM, Abisambra JF, Tovar-Moll F, Mattos P, Arancio O, Ferreira ST, De Felice FG. Exercise-linked FNDC5/irisin rescues synaptic plasticity and memory defects in Alzheimer's models. *Nature Medicine*. 2019;25(1):165–175. DOI: 10.1038/s41591-018-0275-4

10. Islam MR, Valaris S, Young MF, Haley EB, Luo R, Bond SF, Mazuera S, Kitchen RR, Caldarone BJ, Bettio LEB, Christie BR, Schmider AB, Soberman RJ, Besnard A, Jedrychowski MP, Kim H, Tu H, Kim E, Choi SH, Tanzi RE, Spiegelman BM, Wrann CD. Exercise hormone irisin is a critical regulator of cognitive function. *Nature Metabolism*. 2021;3(8):1058–1070. DOI: 10.1038/s42255-021-00438-z

11. Kim E, Tanzi RE, Choi SH. Therapeutic potential of exercise-hormone irisin in Alzheimer's disease. *Neural Regeneration Research*. 2025;20(6):1555–1564. DOI: 10.4103/NRR.NRR-D-24-00098

12. de Freitas GB, Lourenco MV, De Felice FG. Protective actions of exercise-related FNDC5/irisin in memory and Alzheimer's disease. *Journal of Neurochemistry*. 2020;155(6):602–611. DOI: 10.1111/jnc.15039

13. Tari AR, Norevik CS, Scrimgeour NR, Kobro-Flatmoen A, Storm-Mathisen J, Bergersen LH, Wrann CD, Selbæk G, Kivipelto M, Moreira JBN, Wisløff U. Are the neuroprotective effects of exercise training systemically mediated? *Progress in Cardiovascular Diseases*. 2019;62(2):94–101. DOI: 10.1016/j.pcad.2019.02.003

14. Lamb SE, Sheehan B, Atherton N, Nichols V, Collins H, Mistry D, Dosanjh S, Slowther AM, Khan I, Petrou S, Lall R; Dementia And Physical Activity (DAPA) Trial Investigators. Dementia And Physical Activity (DAPA) trial of moderate to high intensity exercise training for people with dementia: randomised controlled trial. *BMJ*. 2018;361:k1675. DOI: 10.1136/bmj.k1675

15. Hoffmann K, Sobol NA, Frederiksen KS, Beyer N, Vogel A, Vestergaard K, Brændgaard H, Gottrup H, Lolk A, Wermuth L, Jacobsen S, Laugesen LP, Gergelyffy RG, Høgh P, Bjerregaard E, Andersen BB, Siersma V, Johannsen P, Cotman CW, Waldemar G, Hasselbalch SG. Moderate-to-high intensity physical exercise in patients with Alzheimer's disease: a randomized controlled trial. *Journal of Alzheimer's Disease*. 2016;50(2):443–453. DOI: 10.3233/JAD-150817

16. Baker LD, Pa J, Katula JA, Aslanyan V, Salmon DP, Jacobs DM, Chmelo EA, Hodge H, Morrison R, Matthews G, Brewer J, Jung Y, Rissman RA, Taylor C, Léger GC, Messer K, Evans AC, Okonkwo OC, Shadyab AH, Zou J, Jin S, Thomas RG, Zhang J, La Croix AZ, Cotman CW, Feldman HH. Effects of exercise on cognition and Alzheimer's biomarkers in a randomized controlled trial of adults with mild cognitive impairment: the EXERT study. *Alzheimer's & Dementia*. 2025;21(4):e14586. DOI: 10.1002/alz.14586

17. Shadyab AH, Aslanyan V, Jacobs DM, Salmon DP, Morrison R, Katula JA, Jin S, Thomas RG, LaCroix AZ, Pa J, Cotman CW, Feldman HH, Baker LD. Effects of exercise versus usual care on older adults with amnestic mild cognitive impairment: EXERT versus ADNI. *Alzheimer's & Dementia*. 2025;21(4):e70118. DOI: 10.1002/alz.70118

18. Sanders LMJ, Hortobágyi T, Karssemeijer EGA, van der Zee EA, Scherder EJA, van Heuvelen MJG. Effects of low- and high-intensity physical exercise on physical and cognitive function in older persons with dementia: a randomized controlled trial. *Alzheimer's Research & Therapy*. 2020;12(1):28. DOI: 10.1186/s13195-020-00597-3

19. Ngandu T, Lehtisalo J, Solomon A, Levälahti E, Ahtiluoto S, Antikainen R, Bäckman L, Hänninen T, Jula A, Laatikainen T, Lindström J, Mangialasche F, Paajanen T, Pajala S, Peltonen M, Rauramaa R, Stigsdotter-Neely A, Strandberg T, Tuomilehto J, Soininen H, Kivipelto M. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. *Lancet*. 2015;385(9984):2255–2263. DOI: 10.1016/S0140-6736(15)60461-5

20. Venegas-Sanabria LC, Cavero-Redondo I, Martínez-Vizcaino V, Cano-Gutierrez CA, Álvarez-Bueno C. Effect of multicomponent exercise in cognitive impairment: a systematic review and meta-analysis. *BMC Geriatrics*. 2022;22(1):617. DOI: 10.1186/s12877-022-03302-1

21. Galle SA, Deijen JB, Milders MV, De Greef MHG, Scherder EJA, van Duijn CM, Drent ML. The effects of a moderate physical activity intervention on physical fitness and cognition in healthy elderly with low levels of physical activity: a randomized controlled trial. *Alzheimer's Research & Therapy*. 2023;15(1):12. DOI: 10.1186/s13195-022-01123-3