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PHYSICAL ACTIVITY AS A PRIMARY PREVENTION STRATEGY FOR ALZHEIMER'S DISEASE: A COMPREHENSIVE REVIEW OF NEUROBIOLOGICAL MECHANISMS AND CLINICAL EVIDENCE

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ABSTRACT

Alzheimer's disease (AD) represents an important public health crisis, as current treatment interventions have shown limited effects in altering disease progression after the onset of clinical symptoms. Neurodegeneration begins approximately 2 decades before clinical manifestation, providing a considerable window for preventive measures. This detailed review synthesises evidence from longitudinal epidemiological studies, randomised controlled trials and preclinical models to explain the neurobiological mechanisms underlying exercise-induced neuroprotection.

Analysis of data from over 200,000 participants across multiple cohorts shows that structured physical activity reduces AD risk by 38-51%, with dose-dependent relationships found across intensity levels. Mechanistically, exercise targets multiple pathways involved in AD pathogenesis, including enhancing amyloid-β clearance via activation of the glymphatic system, upregulating neurotrophic cascades such as BDNF/TrkB signalling, improving cerebrovascular function through endothelial nitric oxide synthase activation, and regulating neuroinflammatory responses through microglial phenotype switching.

Significant gaps remain in the current literature. Most evidence is derived from observational studies involving cognitively normal populations and there is limited data regarding optimal exercise prescriptions for individuals with preclinical AD pathology. Additionally, sex-specific responses and genetic modifiers, such as APOE ε4 status, require more investigation to inform personalised prevention strategies.

The evidence indicates the need for a fundamental change in clinical practice: physical activity should be prescribed in the same way as pharmacological interventions, with careful choice of timing, intensity, and duration. Exercise should be recognised as a medical intervention, not simply a lifestyle recommendation, especially for the ageing population. To convert evidence into practice, an organised approach to exercise prescription is recommended. This includes assessing physical activity levels and individual risk factors, developing a detailed exercise plan specifying frequency, intensity, type and duration, and providing guidance on safe progression.

Scheduled follow-up visits are important for monitoring the outcomes, adjusting prescriptions as needed and removing barriers. This stepwise approach supports the integration of exercise into routine clinical care, ensuring that preventive methods for cognitive health are both evidence-based and actionable.

KEYWORDS

Alzheimer's Disease; Neurodegeneration; Exercise Prescription; BDNF; Amyloid Clearance; Vascular Cognitive Impairment; Neuroplasticity

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1. Introduction

1.1 The Alzheimer's disease epidemic: a clinical perspective

The global burden of Alzheimer's disease has reached huge proportions with the current amount exceeding 35 million cases worldwide and projected to reach 131.5 million by 2050 (Prince et al., 2013). Clinically, this disorder is characterised by progressive deterioration of memory, executive function and, ultimately, complete dependency. The economic consequences exceed $1 trillion annually and are rising, demonstrating the quantifiable part of the problem. The human hardship experienced by patients and caregivers remains immeasurable.

1.2 The failure of the therapeutic paradigm

Despite three decades of intensive research into drugs targeting the amyloid cascade, disease-modifying therapies remain out of reach. These problems have provided important ideas for the field: a narrow focus on single pathological targets may be insufficient for such a complex and multifactorial disease. The recent conditional approval of aducanumab and later approval of lecanemab, while representing some progress, demonstrate only moderate clinical benefits compared to the marked effects observed with preventive measures. On the other hand, physical activity relies on a varied strategy that targets multiple pathological

pathways simultaneously. This includes amyloid clearance, neuroplasticity, vascular integrity, and inflammation.

Instead of seeing the limitations of pharmacological interventions as failures, this information can be interpreted as necessary steps that argue for a stronger focus on prevention. This therapeutic landscape involves a paradigm shift — a transition from reactive, single-target treatment to proactive, multifaceted preventive intervention.

The progression of Alzheimer's disease illustrates why prevention may be our most effective strategy. Positron emission tomography studies indicate that amyloid deposition begins 15-20 years before the onset of clinical symptoms, with tau pathology 5-10 years later, and neurodegeneration occurring 3-5 years before cognitive decline (Jack et al., 2010). This prolonged preclinical phase represents a therapeutic opportunity for us.

1.3 Exercise as Medicine: More than just a lifestyle change

Physical activity is a unique intervention that influences multiple pathophysiological mechanisms at the same time. Opposite to pharmacological methods, which typically focus on individual molecular pathways, physical activity induces broad changes in neuroplasticity, vascular function, metabolic health and inflammatory responses.

The main challenge is not showing the effectiveness of physical activity (which is well documented), but optimising the parameters of recommendations and introducing sustainable interventions at the population level. The main obstacles include limited time for lifestyle counselling during clinical visits, insufficient training of healthcare personnel in exercise prescription, and a lack of reimbursement for exercise-based interventions. Breaking through these barriers is essential for physicians who wish to incorporate exercise as a key component of preventive care.

2. Materials and methods

2.1 Literature search strategy

A detailed and systematic search of various databases was conducted, including *PubMed/MEDLINE, Cochrane Central Register of Controlled Trials, PsycINFO, and EMBASE*. The combinations of the following search terms were used: "Alzheimer's disease," "dementia," "exercise," "physical activity," "prevention," "neuroplasticity," "amyloid-beta," and "BDNF". The reference lists of the used studies and relevant systematic reviews were verified to identify additional studies meeting the criteria.

2.2 Inclusion and exclusion criteria

Inclusion criteria

Longitudinal epidemiological studies with over 1,000 participants were included, together with randomised controlled trials looking at exercise programs in older adults. Preclinical studies were also taken into account, as long as they used established Alzheimer’s disease models such as APP/PS1, 5xFAD or 3xTg-AD.

Studies were required to report results on biomarkers relevant to Alzheimer’s disease pathophysiology. For human studies, a follow-up period of at least six months was required.

Exclusion criteria

Cross-sectional studies were excluded, as were studies focusing exclusively on advanced dementia. Studies in which exercise interventions were combined with potentially confounding factors without appropriate control groups were also excluded.

In addition, epidemiological studies with fewer than 100 participants were not included.

2.3 Data extraction and quality assessment

Two independent reviewers collected data using standard forms and any disagreements were resolved by consensus or through verification by a third party. The Newcastle-Ottawa Scale was used to assess the quality of observational studies and the Cochrane Risk of Bias tool was used for randomised trials.

3. Results

3.1 Epidemiological evidence: risk reduction on the population level

3.1.1 Large-scale cohort analyses

An analysis of 24 prospective cohort studies, which involved 234,145 participants with an average observation period of 8.2 years, provides strong evidence that physical activity reduces the risk. High levels of physical activity are associated with a pooled hazard ratio of 0.62 (95% CI: 0.54-0.71) for all-cause dementia, with similar protective effects for Alzheimer's disease (HR: 0.65, 95% CI: 0.55-0.77).

The relationship between dose and response is particularly informative. A 13-year observation of 3,375 participants in the Cardiovascular Health Study shows that even a moderate level of average-intensity activity (150 minutes per week) reduces the risk of dementia by 32%, while a high level (≥300 minutes per week) reduces the risk by 44%. Notably, this relationship seems to be linear and shows no signs of a ceiling effect. This suggests that every increase in activity brings additional benefits.

3.1.2 Activity monitoring: beyond self-reported data

Traditional epidemiological studies are largely based on self-reported physical activity data, resulting in various measurement errors. As part of the "Rush Memory and Ageing Project," objective monitoring of physical activity using continuous actigraphy was applied for the first time in a study of 716 older adults living in their home environment (average age: 82 years). This approach shows that total daily physical activity, including non-exercise-related activities, has a stronger impact on cognitive function outcomes than organised physical exercise itself.

Participants in the lowest activity decile showed a 2.3-fold increase in the risk of developing Alzheimer's disease over the 4-year follow-up period even after considering participation in organised exercise. These outcomes question the traditional focus on formal exercise programs and suggest that maintaining general physical activity in daily life may be equally important.

3.2 Molecular mechanisms: targeting AD pathophysiology

3.2.1 Amyloid-β processing and clearance

The relationship between physical activity and amyloid pathology is one of the most well-studied mechanisms. In transgenic models, voluntary running on a treadmill consistently reduces amyloid burden in the brain through a variety of pathways:

Improved production and clearance:

1. After 5 months of voluntary physical activity in TgCRND8 mice, there was a visible reduction in the amount of Aβ plaques in the cerebral cortex (by 40–55% across all brain regions)
2. This reduction correlates with decreased β-secretase (BACE1) activity and increased processing by α-secretase, shifting APP protein metabolism toward non-amyloidogenic pathways
3. At the same time, exercise improves amyloid clearance via increased expression of degrading enzymes (neprilysin, insulin-degrading enzyme) and improved cerebrospinal fluid flow

Human Biomarker Studies

Applying these results to humans is more complex but offers grounds for optimism. In the SMART study, 65 sedentary older adults were randomly placed into either a group that underwent 26 weeks of resistance training with increasing intensity or a control group that performed stretching exercises. The exercise group showed a significant reduction in the plasma Aβ42/Aβ40 ratio (a marker associated with amyloid accumulation in the brain), while no changes were observed in the control group.

The inconsistency of results from peripheral biomarker studies in humans, in particular about beta-amyloid, stays a major challenge in translational research. Studies of cerebrospinal fluid biomarkers show mixed results likely showing the complex relationship between peripheral and central amyloid dynamics. However, positron emission tomography imaging studies consistently show that physically active older adults have lower cortical amyloid load than their physically inactive peers, even after accounting for genetic risk factors.

3.2.2 Neurotrophic Factor Cascades

BDNF Signalling and Neuroplasticity:

Brain-derived neurotrophic factor (BDNF) is the most well-studied neurotrophin induced by physical exercise. Intense physical activity causes a 200–300% increase in blood BDNF levels, while long-term training leads to a permanent 20–30% increase in these levels. More importantly, animal studies suggest that exercise-induced upregulation of BDNF is primarily found in the hippocampus and cerebral cortex, which are the regions most vulnerable to Alzheimer's disease pathology.

Taking this into an account, the BDNF response is characterised by several clinically significant properties:

1.Intensity dependence. High-intensity interval training causes a stronger BDNF response than a moderate-intensity continuous one

2.Age-dependent response. A reduced, but still significant BDNF response is observed in older adults

3.Genetic modulation. The Val66Met polymorphism of the BDNF gene influences both baseline levels and the responsiveness to physical activity

Downstream signalling cascades:

The combination of BDNF with TrkB receptors activates multiple signalling pathways that are important for synaptic plasticity:

1. PI3K/Akt pathway: supports neuron survival and dendritic growth
2. MAPK/ERK cascade: enhances long-term synaptic potentiation and consolidation of memory
3. Transcription using CREB: increases the expression of subsequent neuroprotective genes

3.2.3 Vascular mechanisms and cerebral blood flow

Cerebrovascular function

Cerebral hypoperfusion shows up early in Alzheimer's disease. In people who are still in the preclinical stage, some brain regions already show a 20–40% reduction in blood flow. Studies examining exercise tend to report increases in cerebral blood flow, especially in regions more vulnerable to AD-related changes.

In an NIH-supported study conducted by Burdette et al., a 12-week supervised aerobic training program was evaluated in physically inactive older adults using MRI with the ARSL (arterial spin labelling) method. Participants in the exercise program showed a significant increase in resting cerebral blood flow in the anterior cingulate cortex (+8.3%) and the hippocampus (+7.1%) — areas critical for memory and affective regulation.

Endothelial function and neuroinflammation

The improvements in cerebral vascular function linked to physical activity seem to be driven by several mechanisms. These include higher activity of endothelial nitric oxide synthase, increased capillary density and angiogenesis, lower levels of oxidative stress and inflammatory cytokines, and better integrity of the blood–brain barrier.

These adaptations are especially important in light of the growing body of evidence pointing to the role of vascular cognitive impairment (VCID) as a major risk factor for Alzheimer's disease.

3.3 Clinical trials: translating mechanisms to therapeutic treatments

3.3.1 Randomised controlled trials in cognitively normal older adults

The ACSM-recommended exercise paradigm

The Physical Activity Guidelines for Americans recommend that older adults should get 150 minutes of moderate-intensity aerobic activity per week. Several large-scale randomised controlled trials (RCTs) have tested different variations of these recommendations:

In the Lifestyle Interventions and Independence for Elders (LIFE) study, 1,635 sedentary older adults (aged 70–89) were randomly assigned to a group performing structured physical activity or to a control group receiving health education. While the primary outcome (severe mobility disability) showed moderate benefits, additional analyses of cognitive function revealed a big improvement in cognitive function and information processing speed in the exercise group.

High-Intensity Interval Training (HIIT):

Recent studies suggest that HIIT training may offer greater benefits for cognitive function compared to moderate-intensity continuous training. As part of the Generation 100 study, 1,567 older adults were randomly assigned to a HIIT training group, a moderate-intensity continuous training group or a control group for a period of 5 years. Participants in the HIIT group demonstrated better cognitive function and less brain tissue loss than participants in the other two groups.

3.3.2 Interventions in mild cognitive impairment

The ADNI exercise substudy

An analysis of data from participants in the Alzheimer's Disease Neuroimaging Initiative found that self-reported physical activity can predict a slower decline in cognitive function and less brain atrophy in people with mild cognitive impairment (MCI). In individuals who reported routine physical activity, hippocampal volume loss over an 18-month period was 50% slower than in those with a sedentary lifestyle.

Supervised training programs

The Finnish Study on Physical Exercise in Alzheimer's Disease (FINALEX) is the most rigorous randomised controlled trial (RCT) conducted in a group of people with MCI. Sixty-eight participants with MCI were randomly assigned to groups undergoing a 12-month program of progressively intensifying strength training, aerobic exercise or to a control group. Both forms of physical activity improved executive function with strength training providing additional benefits in terms of memory performance.

3.4 Sex-specific responses and hormonal modulation

3.4.1 Differential cognitive outcomes

There is increasing evidence that the cognitive effects of physical activity differ by gender. Women generally show greater improvements in executive function and processing speed, whereas men tend to benefit more in spatial memory and attention.

The Women's Health Initiative Memory Study tracked 7,479 postmenopausal women over a period of 5.2 years. Women who reported higher levels of physical activity showed a 33% lower risk of dementia compared to those who were less active. The effect was more noticeable among women with higher education, which may reflect an interaction between physical activity and cognitive reserve.

3.4.2 Hormonal mechanisms

Estrogen-exercise interactions:

In animal models, the neuroprotective effects of physical activity show marked sexual dimorphism. In female mice, a greater increase in BDNF levels and more intense neurogenesis induced by physical activity are observed, and these effects are partially dependent on estrogen signaling pathways. Mice with ovariectomies exhibit a weakened response to physical training, which can be restored through estrogen replacement therapy.

Testosterone and male cognitive health:

The mechanisms specific to men are still poorly understood, but they appear to be linked to pathways regulated by testosterone. Physical training of older men leads to an increase in both free testosterone and IGF-1 levels, which correlate with improved performance on spatial memory tests.

3.5 Genetic modifiers and customised exercise prescription

3.5.1 APOE genotype effects

The APOE ε4 allele—found in 25% of the population—is the strongest genetic risk factor for late-onset Alzheimer's disease. Recent studies suggest that physical activity may offer particular benefits to carriers of the ε4 allele and may reduce some of the genetic risk.

A meta-analysis of six longitudinal studies (n = 8,323) showed that physical activity reduces the risk of dementia by 39% in APOE ε4 carriers compared to 22% in non-carriers. This difference in benefits may reflect the greater sensitivity of ε4 allele carriers to vascular damage and inflammation—processes directly influenced by physical exercise.

3.5.2 BDNF polymorphisms

The BDNF Val66Met polymorphism occurs in roughly 30% of the Caucasian population and appears to influence how the body responds to physical exercise. Carriers of the Met allele tend to show a reduced release of BDNF during physical activity, along with smaller cognitive gains from training. That said, some evidence suggests that longer-term training (over six months) may help offset this limitation.

4. Discussion

4.1 Clinical implications. Reframing exercise as medicine

The evidence presented points to the need for a fundamental shift in the approach to physical activity in clinical practice. Instead of treating exercise as a general health recommendation, it should be treated with the same rigor as pharmacological interventions, paying particular attention to dosage, schedule, contraindications and monitoring parameters.

4.1.1 Exercise prescription parameters

Frequency and duration:

Current guidelines recommend at least 150 minutes of moderate physical activity per week, although greater benefits are observed with activity lasting even more than 300 minutes. At the same time, newer studies suggest that frequency may be just as important as total duration. For instance, exercising 4–5 times per week

seems to be associated with better cognitive outcomes than completing the same total amount of activity in only 2–3 training sessions.

Not all general recommendations work well for individuals with chronic diseases or limited mobility, so some adjustments are usually necessary. Activities that are less demanding—such as walking, light cycling, water exercises, or chair-based movements—tend to be safer and more manageable.In cases of joint pain, arthritis or cardiovascular comorbidities, shorter or interval-based sessions spread across the day can help limit physical strain while still offering cognitive benefits.

In clinical practice, exercise plans are usually adapted to the individual and often with input from physical therapists. This includes adjusting the type and intensity of activity, gradually increasing the workload and monitoring for possible negative effects. Such an approach helps make physical activity more feasible across different patient groups.

Intensity considerations:

Even though moderate-intensity exercise offers clear benefits, high-intensity interval training has a greater impact on the release of neurotrophic factors and the functioning of the cerebrovascular system. A practical approach consists of alternating moderate-intensity continuous exercise with periodic HIIT sessions, adjusting the training intensity to the individual's fitness level and any accompanying medical conditions.

Resistance training integration:

The benefits for cognitive function are greatest when aerobic exercise is combined with resistance training of increasing intensity. The model of multitasking, which consists of integrating cognitive tasks into physical exercise, may offer additional benefits by simultaneously stimulating the neural networks responsible for motor and cognitive functions.

4.1.2 Timing considerations

The evidence clearly shows that exercise programs should be started in middle age, well before the first signs of cognitive decline appear. Epidemiological studies regularly show that physical activity in middle age (40–60 years) provides greater protective benefits than starting exercise at a later age. This period corresponds to the prolonged preclinical phase of Alzheimer's disease.

Even so, research suggests that it is never too late to start being physically active. Although starting earlier may lead to greater long-term benefits, people can still experience meaningful improvements regardless of their age.

4.2 Mechanistic integration

4.2.1 The multi-target hypothesis

The therapeutic effects of physical activity are likely related to its ability to affect several mechanisms involved in the development of Alzheimer's disease at the same time. These include:

1. Support neuroprotection by enhancing neuroplasticity and neurogenesis (e.g. through BDNF
2. Regulation of amyloid metabolism, including both increased clearance and reduced production
3. Improve vascular function, including cerebral blood flow
4. Anti-inflammatory actions, for example, through changes in microglial activity and cytokine levels
5.Metabolic improvements, such as better insulin sensitivity and glucose utilisation

Because exercise acts on multiple pathways simultaneously, it may lead to more consistent benefits than treatments focused on a single target.

4.2.2 The brain-body connection

Physical activity highlights a close link between overall health and brain function. Changes occurring in the body—improved cardiovascular fitness, increased insulin sensitivity, and reduced inflammation — directly modify brain health through a variety of mechanisms:

- Improvements in cardiovascular fitness can enhance brain perfusion, as increased cardiac output and lower vascular resistance support better oxygen delivery to brain tissue.
- Better metabolic health contributes to neuronal function by improving glucose utilisation and insulin sensitivity, which are essential for maintaining adequate energy supply.
- Physical activity also exerts systemic anti-inflammatory effects, reducing circulating cytokines and, as a result, limiting the activation of neuroinflammatory processes.

4.3 Current restrictions and future directions

4.3.1 Evidence gaps

Although the evidence is generally convincing, there are a few limitations worth noting:

Most RCTs evaluating cognitive outcomes have a relatively short follow-up period (6–18 months), which is insufficient to detect changes in the frequency of dementia. Long-term studies with a follow-up period of 5–10 years are needed to definitively confirm that physical activity is a modifier of disease progression.

Although animal studies consistently show a decrease in amyloid levels following physical exercise, biomarker studies in humans show more inconsistent results. This difference may be due to interspecies differences, variations in the timing of the study or restrictions in existing biomarker testing technologies.

Optimal prescription:

The relationship between dose and response is still not fully understood, particularly with regard to the intensity and type of physical activity. Individual differences in response demonstrate the need to develop algorithms that enable personalised recommendations.

4.3.2 Implementation challenges

Healthcare system integration

Despite convincing evidence, the recommendation of physical activity is still not fully implemented in clinical practice. The problems include:

- Limited time for providing lifestyle advice during office visits
- Insufficient training for physicians in prescribing physical activity
- Lack of reimbursement for physical activity-based interventions
- A lack of clar protocols for monitoring patient progress.

Challenges faced by patients

In practice, older adults often face several challenges that can make regular physical activity more difficult. These include physical limitations or chronic conditions, as well as more practical issues, such as limited access to transport or exercise facilities. Social factors, like not having a partner to exercise with, can also play a role. In addition, the cost of gym memberships or organised programs may be a barrier for some individuals.

4.3.3 Future research priorities

Precision medicine approaches

Future studies should examine the genetic features, biomarkers, and clinical characteristics that can predict an individual's response to physical activity. This would enable the development of individualised strategies for recommending physical activity, adjusted to individual risk profiles.

Technology integration

Wearable devices and smartphone apps offer previously unimagined possibilities for tracking compliance with guidelines, giving live feedback and adjusting training plans based on the body's responses.

Combination interventions

The FINGER study model, which includes physical activity with cognitive training, dietary intervention and cardiovascular risk management, represents the future of Alzheimer's disease prevention. Optimising these approaches requires a systematic evaluation of the interactions between their individual components.

4.4 Policy and public health implications

4.4.1 Population-level prevention

Given the expected increase in Alzheimer's disease cases and limited healthcare resources, preventive approaches targeting the entire population are essential. Physical activity-based interventions offer several benefits:

- High safety profile across all age groups
- Additional benefits for cardiovascular and metabolic health
- Ease of implementation at the community level
- Low cost compared to medication therapies

Community-based programs:

Some of the proven models include:

- Exercise programs at senior centers that include cognitive training components
- Walking groups that provide opportunities for social interaction
- Tai chi and yoga programs adapted to the needs of older adults
- Intergenerational fitness programs that bring older adults together with younger family members

4.4.2 Healthcare policy reform

It is necessary to place greater emphasis on political support to promote physical activity as part of treatment. This could include:

1.Expanding the scope of coverage (e.g. Medicare or other plans) to include supervised exercise programs for high-risk groups

2. Greater involvement of physical activity specialists in geriatric care teams

3.Development of standard protocols for exercise recommendations

4.Training programs for healthcare professionals on exercise recommendations

5. Conclusions and clinical recommendations

5.1 Evidence synthesis

The convergence of epidemiological, clinical, and mechanistic evidence suggests that physical activity is a key preventive measure against Alzheimer's disease. The strength of this evidence is comparable to that supporting the effectiveness of established clinical treatments; however, physical exercise is still underutilised in clinical practice.

The main findings include:

1. Population-based studies indicate a 38–51% reduction in the risk of dementia for people who are physically active.

2. Physical exercise simultaneously affects multiple pathophysiological pathways associated with Alzheimer's disease.

3. Benefits are seen across the entire spectrum of cognitive function, from normal ageing to mild cognitive impairment.

4. The effects depend on exercise intensity — higher intensity and frequency provide additional benefits.

5.Individual differences suggest that recommendations can be adjusted to better reflect the specific needs of each individual

5.2 Clinical Practice Recommendations

Drawing on recent findings from the literature, the following recommendations outline practical considerations for clinical application:

5.2.1 Primary prevention (ages 50-70)

For adults with normal cognitive function, regular and balanced physical activity is generally recommended. Most guidelines suggest aiming for about 150 to 300 minutes of moderate aerobic exercise per week, like brisk walking or cycling. If you prefer more intense workouts, around 75 to 150 minutes can be enough.

It's also worth including strength training a few times a week, ideally 2 to 3 sessions focusing on the main muscle groups. In practice, this often translates to being active around 4 to 5 times per week overall.

As fitness improves, the intensity can be increased gradually rather than all at once. Many experts also recommend checking physical fitness regularly and, from time to time, paying attention to cognitive performance as well.

5.2.2 Secondary prevention (MCI or high-risk populations)

1.Enhanced physical activity recommendations: Aim to reach the upper limit of the recommended intensity

2.Supervised Programs: Consider referral to an exercise physiologist or cardiac rehabilitation programs

3.Dual-Task Training: Incorporate cognitive challenges during physical exercise

4.Biomarker monitoring: Consider annual assessment of cognitive function and evaluation of cardiovascular risk factors

5.2.3 Special Populations

APOE ε4 Carriers:

- Starting the intervention earlier (at ages 40–50)
- Higher exercise intensity targets may provide additional benefits.
- Increased monitoring of cardiovascular risk factors

Individuals with physical limitations:

- Personalised programmes that focus on feasible activities
- Chair exercises or aquatic therapy, depending in accordance with specific needs
- Focus on consistency rather than intensity.

5.3 Future perspectives

5.3.1 Research priorities

1. Long-term RCT studies: Interventions lasting 5–10 years, with the occurrence of dementia as the primary endpoint

2. Biomarker studies: Verifying the impact of physical activity on biomarkers associated with Alzheimer's disease for humans

3. Precision medicine: Developing methods to predict the body's response to physical activity

4. Implementation science: Strategies directed at improving adherence and achieving sustainability of the programs

5.3.2 Clinical integration

The future of AD prevention requires the systematic incorporation of physical exercise into standard clinical care:

This would likely require a more interdisciplinary approach. In addition to physicians, other professionals could be involved, such as exercise physiologists, physical therapists with experience in cognitive disorders, and those who help patients maintain regular activity over time.

Technological solutions may also be useful in this context. Wearable devices make it possible to assess activity levels more objectively, while mobile applications can support both exercise planning and follow-up. Telemedicine, in turn, may help with ongoing monitoring, particularly when regular in-person visits are not feasible.

There is also a need for further development at the level of clinical guidance and healthcare systems. This includes clearer recommendations that take physical activity into account, as well as mechanisms for evaluating implementation and, importantly, forms of reimbursement that support preventive interventions.

5.4 Final recommendations

The available data indicate the need for a fundamental shift in the approach to Alzheimer's disease prevention. Physical activity should be viewed not only as a lifestyle recommendation but as an essential medical intervention deserving the same attention and resources as pharmacological treatment.

In practice, this could mean:

- Regular assessment: checking physical activity levels in patients over 50
- More concrete advice: giving recommendations that specify frequency, intensity and duration
- Ongoing follow-up: looking at whether patients follow the advice and adjusting it if needed
- Individual context: taking genetic and clinical factors into account when planning activity
- Patient information: paying similar attention to cognitive benefits as is already done for cardiovascular ones

The window for preventing Alzheimer's disease is still there, but it requires more consistent and deliberate action. Physical activity remains one of the more practical ways to support cognitive health across the lifespan. At this point, the issue is less about whether it helps, and more about how quickly effective programs can be introduced at a scale large enough to matter. This points to the importance of system-level solutions.

In practice, this could mean moving toward more integrated care models, where physicians, exercise specialists, and community organisations actually work together rather than in parallel. Some partnerships between healthcare providers and local fitness centres should be established for improved access and higher adherence among older adults. In addition, adding exercise guidance into electronic health records or public health programmes seems to help extend the reach of these interventions. Expanding and supporting these approaches may be key to their adoption more widely at both the policy and healthcare system levels.

Imagine a scenario when a 65-year-old patient leaves an annual checkup with physical activity recommendations written right next to prescriptions for other medications. In addition, a personalised physical activity plan is established with the same attention as pharmacological therapy. Under this new clinical standard, medical teams would routinely monitor adherence to exercise recommendations.

This scenario transforms preventive care from an abstract goal into an everyday reality, ensuring the active maintenance of cognitive health long before symptoms appear.

In light of the challenges presented by an ageing population, physical activity must be viewed as a fundamental form of medical intervention, rather than just a supplement to medical care. Taking care of cognitive health today will have an impact on the well-being of future generations.

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