Physical Activity Can Reduce Hypertension and the Long-term Benefits May Contribute toward a Lower Risk of Cognitive Decline and Dementia

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Abstract

Epidemiological studies have consistently shown that chronic mid-life hypertension is linked to an increased risk of cognitive decline and dementia, especially vascular dementia and Alzheimer’s disease. However, clinical trials of pharmacological or exercise-based anti-hypertensive treatments have not always noted reductions in cognitive decline in treated patients. The many pharmacological modes of treatments available, the short-term nature of many studies, and the range in participant ages are some of the reasons clinical trials may not have consistently shown an influence on cognition. Furthermore, hypertension studies have led to the understanding that arterial stiffness is a better indicator of cognition than blood pressure (BP), possibly reflecting inadequacies in BP measurement methods. Exercise interventions have been successful in reducing hypertension, and recent studies have highlighted improvements in certain aspects of cognition. In addition, both aerobic and resistance training exercises are proving to be beneficial. With the aim of reducing the risk of cognitive decline and dementia, multi-domain lifestyle changes encompassing regular exercise, dietary improvements, and cognitive training are being investigated in long-term clinical trials, with encouraging results. In this review, we discuss hypertension, links between hypertension and cognitive decline, as well as clinical trials of hypertension which have investigated exercise and pharmacological treatments and their potential effects on cognition. We also highlight recent multi-domain interventions aimed at reducing the risk of cognitive decline.

Key words: Blood pressure, brain, cognition, Dementia, exercise, lifestyle, mild cognitive impairment, oxidative stress

Introduction

There is currently no cure for Alzheimer’s disease (AD) or most other forms of age-related dementia, despite several decades of research. Therefore, especially in the case of AD, the focus has moved to modifiable risk factors. Hypertension, during mid-life has been associated with an increased risk of later cognitive decline and dementia, mainly vascular dementia and now also AD.¹¹ This review discusses how hypertension is measured, current pharmacological treatments, exercise as a treatment, and the potential of such treatments in reducing dementia risk. Furthermore, the advantages of multidomain, lifestyle-based preventative measures to reduce dementia risk are highlighted.

What is Hypertension?

Until recently, hypertension was defined as a chronic blood pressure (BP) equal to or greater than 140/90 mm Hg. High BP can lead to serious health problems such as stroke, kidney disease, heart attack, or heart failure.¹¹ However, the guidelines concerning treatment options, which depend on associated risk factors, age, and the presence of comorbid conditions, have made this definition inadequate.¹¹ Most analyses concerning hypertension and treatment options investigate the risk of major cardiovascular events or death in the next 5 years; yet for many, there are clearly risks of being in what was considered the high normal range (130/85–139/89 mm Hg), as most people who

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have heart attacks or strokes do not quite meet this original definition of hypertension. In 2018, the American College of Cardiology and the American Heart Association Task Force on Clinical Practice Guidelines redefined hypertension to a lower BP threshold, of 130/80 mm Hg.\(^4\)

In addition to the cardiac risks and potential of kidney damage, hypertension has been known for many years to be linked to cognitive decline, and this added risk provides yet another reason for people to maintain their BP in the normal range, either by pharmacological or non-pharmacological means.\(^5,6\) Furthermore, as described below, the strongest links to age-related cognitive decline (manifesting from the sixth to ninth decade) have been to hypertension in middle-age (in the fourth to fifth decade),\(^7,8\) thus well outside the 5-year time frame of most studies, partly explaining why this association has been hard to establish.

**Measuring BP**

The standard method used to measure BP is on the brachial artery.\(^10\) Recent research concerning potential physiological nuances of the multiple components of BP, such as systolic BP (SBP), diastolic BP (DBP), pulse pressure (PP), mean BP, and central BP have led to doubts about the accuracy and relevance of brachial artery BP. This is of concern as most clinical trials of BP-reducing drugs have used the brachial artery as their means of determining drug effectiveness. Using the brachial artery does not reliably represent central aortic pressure, which is the pressure against which the heart pumps blood.\(^11\) Although the DBP decrease has been shown to be minimal from central to peripheral vessels (<2 mm Hg), the drop in brachial artery BP can be as much as 12 mm Hg and the PP can drop up to 14 mm Hg.\(^12,13\) These differences are important, as cardiovascular mortality can be more strongly related to aortic compared to brachial BP.\(^12,13\) Studies have found that a wide variation in the brachial-aortic SBP difference occurs between patients with similar brachial SBP, finding that 64% of people with normal brachial BP have central SBP at the hypertension class 1 level.\(^14\) Just as importantly, anti-hypertensive drugs can exert different effects on brachial and central pressure.\(^13\) Thus, the use of the brachial artery for monitoring effects of hypertension on central organs may be sub-optimal on many levels. To complicate this further, reviews of long-term BP measurement have concluded that BP variability, from day to day, or week to week, influences cardiovascular events and cardiovascular mortality risk.\(^15\) A recent study has similarly shown that a large BP variation over a period of years is associated with an increased long-term risk of dementia.\(^16\) This adds to the evidence that maintaining a healthy BP from middle-age onward is critical to long-term health.

**Pharmacological Treatments for Hypertension**

There are several classes of anti-hypertension treatments, including angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), calcium channel blockers (CCB), beta-blockers, diuretics, neprilysin inhibitors, and other agents. Due to different modes of action, each class has a different effect on central BP. For example, ACEIs, ARBs, CCBs, and nitrates appear to have greater beneficial effects on central SBP and PP than beta-blockers, despite their similar effects on brachial BP.\(^17\) Therefore, for a similar drop in (brachial) BP, the different anti-hypertension treatments can have different outcomes in clinical trials, for example, concerning cardiovascular mortality. They also have different effects on other aspects of metabolism, in fact the Losartan Intervention for Endpoint Reduction in Hypertension, Anglo-Scandinavian Cardiac Outcomes Trial, and Conduit Artery Function Evaluation trials demonstrated that beta-blockers had adverse effects on metabolism, which increased the risk of diabetes type II, including impaired glycemic control, lower high density lipoprotein-cholesterol, and higher triglycerides.\(^18-20\)

**Exercise as a Treatment for Hypertension**

According to the statistics in the United States, nearly 50% of Americans have high BP, using the redefined hypertension definition, and normotensive people at age 55 have a 90% risk developing hypertension during their lifetime.\(^21,22\) Such statistics, which may be indicative of levels in many western countries, underscore the need to promote preventative measures to reduce such prevalence of what is the most common and costly, yet preventable, risk factor for cardiovascular disease.\(^23\) Although a systematic review in 2008 did not find consistent conclusive evidence of improvements in BP following exercise,\(^24\) more recent studies have added considerable evidence to show such benefits.\(^22\) In 2018, the American College of Cardiology and American Heart Association Task Force on Clinical Practice Guidelines redefined hypertension to a lower BP threshold, of 130 mm Hg for SBP and 80 mm Hg for DBP.\(^4\) The previous Joint National Committee 7 threshold consisted of 140 mm Hg for SBP and 90 mm Hg for DBP. It has been stated in fact that almost all of the new cases of hypertension (using the new definition of 130/80 mm Hg) should be able to reduce their BP without medication, and instead use lifestyle modifications such as exercise.\(^4\) The updated review on the use of physical activity in the prevention and treatment of hypertension concluded that there was strong evidence that physical activity could reduce BP amongst all adults tested (hypertensive, pre-hypertensive, and normotensive). Those subjects with hypertension showed the largest gains (largest drop in BP), followed by those defined as pre-hypertensive.\(^22\) Other studies have since indicated that the quoted drops in BP should translate to significantly reduced levels of cardiovascular disease and stroke.\(^25,26\)

Previously, aerobic and dynamic resistance exercise training had been shown to be beneficial by providing a small but clinically significant reduction in BP, with the greater evidence concerning aerobic exercise. The more recent review reported moderate evidence of similar reductions of hypertension with
either aerobic exercise or dynamic resistance exercise training (or a combination of the two).\(^{[26]}\) It was also shown that other forms of physical activity are beneficial in lowering BP; however, the evidence is currently limited. With such a positive outcome expected, it is unsurprising that exercise is being encouraged and investigated further as a preventative measure for reducing cognitive decline, as hypertension itself, as well as cardiovascular disease and stroke have all been linked to forms of dementia, including AD.\(^{[7,27-29]}\)

**Hypertension and Cognitive Decline**

Many studies and extensive reviews of observational studies have concluded that cognitive decline and dementia are linked to hypertension, particularly mid-life hypertension.\(^{[1,30,31]}\) In the 6th and 7th decade, hypertension has been linked to poorer overall cognitive function as well as decline.\(^{[1,32,33]}\) The level of hypertension also appears to be important. For example, in a clinical trial, keeping BP under tight control at 120/80 mm Hg was found to reduce incidence of dementia, compared to just keeping BP under systolic levels of 140 mm Hg.\(^{[34]}\) The strongest links, however, as mentioned earlier, seem to be in people who have had hypertension for a long time, or who have had the longest period of time between the initial diagnosis of hypertension, and the later development of cognitive problems.\(^{[3,35,36]}\)

Not all studies agree, however, as studies of the very elderly have shown that (untreated) high BP is associated with reductions in cognitive decline.\(^{[37,38]}\) It has been suggested that age-related changes in the vascular system might explain the different response in the very elderly. Since the strongest relationships between hypertension and cognitive decline appear to be related to duration of hypertension, especially if hypertension started in midlife, this suggests long-term vascular damage may be involved.\(^{[3,35,36]}\) If this is the case, a strong relationship between hypertension (newly) diagnosed in the very elderly, and cognitive decline, would be unlikely.

The variety of anti-hypertensive treatments and their modes of action are likely to influence their effectiveness in reducing dementia risk. One retrospective study compared rates of AD diagnosis in over 1.3 million users of six different anti-hypertensive drug treatments, with the users aged 65 years or older. It was found that treatments targeting the renin-angiotensin system (RAS), particularly ARBs, were slightly more protective against onset of AD than non-RAS treatments.\(^{[39]}\)

A review by Hughes and Sink\(^{[40]}\) summarizes the current knowledge concerning the links between cognitive decline and hypertension to a few main points: (1) Longitudinal studies have shown mid-life high BP is linked to increased incidence of cognitive decline and dementia later in life, (2) this association is not as clear from cross-sectional studies of hypertension and cognition in the elderly, (3) randomized controlled trials of anti-hypertensive treatments have not shown clear-cut benefits concerning cognition, (4) studies at midlife have indicated the duration of hypertension and its associated arteriosclerosis (thickening and stiffening of the arteries) are linked to cognitive decline, and (5) greater Abeta (A\(\beta\)) amyloid deposition and cerebrovascular disease, pathologies seen in AD, and dementia, are reported to occur in hypertensive older adults.\(^{[40,41]}\) It has been known for some time in fact, that both A\(\beta\) amyloid deposition (a hallmark feature of AD brains) and the number of neurofibrillary tangles (another hallmark pathology of AD) are greater in patients with high BP,\(^{[42]}\) as well as atherosclerosis.\(^{[40,43]}\) Furthermore, in post-mortem studies of people with normal age-related neuropathology as well as people with non-complicated AD pathology, those who had been on anti-hypertensive medications were found to have less plaques and neurofibrillary tangles than those who had not received treatment for hypertension, though not less than those who had not had hypertension.\(^{[44]}\)

**Hypertension, Cognition, and Pathological Mechanisms**

Hypertension has been shown to affect brain structure – recent advances in neuroimaging methods have led to the findings that high BP, particularly in mid-life, is linked to cerebral atrophy, white matter microstructural damage, and cerebral small vessel disease.\(^{[45,46]}\) This is believed to be the result of endothelial dysfunction and/or vessel wall remodeling.\(^{[5]}\) The higher BP leads to hypertrophic remodeling of the vascular media and smooth muscle cells, leading to reduction in lumen diameter, which in turn leads to increased vascular resistance and vessel wall stiffening. This eventually leads to reduced numbers of downstream capillaries, and in the brain, which needs continuous perfusion; this can lead to hypoperfusion at times when BP is reduced.\(^{[47,48]}\) Lower blood flow (oligemia) can lead to oxidative stress, acidosis, reduced oxygen delivery, and unmet glucose demands, which have all been shown to reduce neuronal function.\(^{[47,49]}\) In addition, a recent review concluded that chronic inflammation (a known risk factor for AD) triggers oxidative-nitrosative stress, which over a long period of time damages fatty acids, proteins, DNA, and mitochondrial function.\(^{[50]}\) Over time, this leads to dysfunctional energy metabolism, endothelial dysfunction, and blood brain barrier disruption, which in turn leads to decreased cerebral perfusion and chronic glucose hypometabolism.\(^{[50]}\) Most of these changes have also been linked to increased production of A\(\beta\) peptides, A\(\beta\) amyloid deposition, activation of the receptor for advanced glycation end (RAGE) products, and increased tau phosphorylation – all pathologies found in AD.\(^{[51-54]}\)

Hypertension is often seen in association with other conditions common from middle age onward such diabetes type II. In people with both conditions, SBP increases linearly with age, whereas DBP declines curvilinearly from as early as 45 years of age, together suggesting the development of increased arterial stiffness. Subjects with both conditions have additive effects on arterial stiffness, and some studies have suggested this is
linked to increased risk of dementia. Reviews of clinical trials, epidemiological data, and other studies support this concept as they have concluded that arterial stiffness is a sensitive predictor of cognitive impairment, in fact it has been found that increased arterial stiffness is more useful in predicting cognitive decline in healthy subjects, than BP itself. In support of a link with AD in particular, a recent study of subjects with mild cognitive impairment (MCI) and dementia revealed associations between higher levels of certain forms of arterial stiffness (as measured by pulse wave velocity) and lower brain volume in areas highly affected in AD, higher brain Aβ amyloid deposition levels as determined by florbetapir-PET scans, and higher white matter hyperintensity. The associations were strongest in individuals with MCI. Interestingly, it has also been shown that education attainment appears to moderate the effects of central artery ageing (including higher aortic stiffness and central BP) on cognitive performance in middle-aged and older adults. This is similar to higher education and occupation levels being linked to cognitive reserve, protecting against development of dementia.

Studies have also investigated the relationship between hypertension and sleep disturbances. Sleep apnea and sleep deficiency are known as symptoms of several neurodegenerative diseases, including AD, yet a causative role is emerging, and sleep impairments are now considered as risk factors for dementia. For example, recent studies have found higher levels of biomarkers (such as homocysteine, clusterin, acute-phase proteins, Aβ, and inflammatory cytokines) of both AD and vascular dementia in people with obstructive sleep apnea. In one recent study of an older population considered at risk of dementia, reduced cortical thickness was found to be linked to oxygen desaturation; though conversely, increased hippocampal and amygdala volumes were associated with sleep disturbances, with the authors concluding that further sleep studies in such dementia high risk groups are required. Inadequate sleep has also been associated with oxidative stress and homocysteine levels, both of which are risk factors for cognitive decline and AD. Such findings are relevant here as sleep apnea is strongly associated with hypertension, and further studies into the pathophysiological mechanisms linking hypertension, sleep disturbances, and dementia are needed. Sleep apnea is also readily treatable, providing an avenue to delay dementia onset.

Hypertension Treatments and Cognitive Decline

As hypertension has shown significant links with later cognitive decline, it would be expected that treatments to control BP would reduce incidence of dementia, however, as mentioned above, studies of hypertension treatments have not shown clear-cut conclusions concerning this potential treatment effect. One reason often mentioned that may explain this apparent discrepancy is that cognitive measures have almost always been a secondary measure, not a primary outcome of a trial, and studies of hypertension treatments are rarely of the longitudinal type required to determine any effect on risk of cognitive decline or dementia, many years later. The differences between the effects of the classes of antihypertensive treatments also make comparisons of such treatments difficult. Furthermore, treatments for hypertension are now rarely prescribed alone; for example, lipid-lowering statins are often given together with antihypertensive treatments, which further limits the interpretation of the beneficial effects of anti-hypertensives in preventing or delaying cognitive decline.

Nevertheless, there is considerable evidence that hypertension is linked to later cognitive damage, as recent systematic reviews of both longitudinal and cross-sectional studies show that antihypertensive drugs, particularly CCB and RAS blockers, may be beneficial in preventing cognitive decline and dementia. However, these studies conclude that there is still a need for more clinical trials where the primary aim is to discover whether anti-hypertensive treatments can reduce the risk of cognitive decline and dementia.

Exercise and Dementia

A Cochrane systematic review in 2008 concluded that aerobic exercise improved aspects of cognitive function in healthy older adults, particularly in the areas of cognitive speed, delayed memory functions, auditory and visual attention, as well as motor function. Cardiovascular fitness also improved with the exercise, and although it would seem likely this was responsible for the improved cognition, there was no clear evidence that this was the case, and as such, it was considered that any exercise might achieve the same changes. The variety of exercise interventions, the types of neurological disorders being tested, the different cognitive tests carried out, and the relatively short time span of most of these studies have all limited the progress in this research to some extent. A more recent Cochrane review of 12 clinical trials (8–26 weeks long) also found little evidence of cognitive benefit in healthy older adults over 55, even if cardiorespiratory fitness improved. Again, the range of study formats may have limited the chance of significant overall findings and in most (if not all) cases, cognitive changes were secondary outcome measures.

In non-hypertensive populations, some studies and meta-analyses have indicated that acute exercise improves executive function, for example speed of processing, and may also improve memory. More recently, moderate to vigorous exercise was found to produce significant benefits to executive function and memory, and acute aerobic exercise was found to improve certain cognitive functions in both hypertensive and non-hypertensive middle-aged adults. Another recent study has shown that resistance exercise in subjects with MCI can protect AD-vulnerable regions of the hippocampus from degeneration. In the study of acute aerobic exercise above, it was noted that many of the hypertensive subjects were on antihypertension medications, which are likely to have attenuated differences between the groups, with varying degrees of
influence, due to the different types of anti-hypertensive drugs being taken.

Hypertension is common from middle age onward, and aerobic exercise is highly recommended as a method to reduce BP. As mentioned earlier, there is mounting evidence of strong links between long-term high BP and associated artery damage and stiffening, and the development of dementia later in life, yet there is a paucity of data demonstrating a direct effect of exercise on cognitive function and/or decline later in life, in subjects with hypertension. The length of clinical trials needed to provide conclusive evidence may be prohibitively long. Nevertheless, the considerable knowledge of links between hypertension and later cognitive decline has led healthcare professionals to promote aerobic exercise to reduce BP, with the aim of maintaining cognitive health. A recent international consortium across 15 countries in 5 continents, the Cohort Studies of Memory in an International Consortium collaboration cohort study, found that vigorous physical activity was associated with better cognitive performance, along with higher levels of education. The same study highlighted how other individual modifiable risk factors can influence study results, as declines in at least one cognitive outcome were shown to be associated with current smoking status, diabetes, and history of stroke.

**Multi-factorial Lifestyle Changes**

We have discussed evidence of positive cognitive outcomes following aerobic exercises and resistance training in aged cohorts, and it is likely that these benefits result at least partly from a reduction in hypertension. Healthy ageing, longevity, and a reduced risk of dementia have also been linked to diet – another modifiable lifestyle component. The traditional Mediterranean diet (MeDi) and Okinawan diet have both been associated with longevity. More recently, aspects of the MeDi and the Dietary Approaches to Stop Hypertension (DASH) diet have been combined to form the MIND diet, with the specific aim to promote brain health. The MeDi, Okinawan diet, DASH, and MIND diets all emphasize the intake of a variety of fruits and vegetables, fish, whole grains, and healthy fats, while having a low intake of saturated fat, processed foods, added sugar, and little or no red meat or processed meats. Epidemiological studies and more recent clinical studies have provided evidence that the MeDi and MIND diets can reduce aspects of cognitive decline.

Until quite recently, most preventive interventions have been tested in small groups, with studies focusing on only one lifestyle factor. Many of these studies have yielded negative or modest results. The etiology of AD dementia is considered to be multifactorial and multidomain interventions that simultaneously target several risk factors and mechanisms might be the strategy for optimal preventive effects, as discussed in a recent review. With the Lancet Commission recently indicating that up to one third of AD and related dementias may be delayed or prevented with reductions in modifiable risk factors, the optimization of lifestyle modifications to reduce such risk factors is urgently needed.

In the last 10 years, several ambitious multidomain lifestyle intervention studies to prevent cognitive decline have yielded encouraging results. Some studies combined regular exercise and healthier diets, for example, the Washington Heights-Inwood and Columbia Aging Project and Exercise and Nutritional Interventions for Cognitive and Cardiovascular Health Enhancement (ENLIGHTEN) trial, with the combined lifestyle changes showing greater benefits than the individual components. ENLIGHTEN investigated the benefits of aerobic exercise, the DASH diet, or a combination of both, in a cohort of sedentary people aged 55 or over, with vascular cognitive impairment though no dementia. Interestingly, the DASH diet groups in the study, and not the exercise-only group, showed reduced dependence on anti-hypertensive treatments as a result of the intervention. Conversely, improved aerobic fitness and lower sodium intake were associated with improved executive functioning in this study. Other studies have investigated physical exercise in combination with brain training exercises. For example, a study using a cohort of healthy older adults which tested physical activity (a combined walking and resistance training program), a computerized brain training program (through Posit Science) and a combination of both, discovered that the combination improved cognition and cerebral glucose metabolism. A more recent pilot clinical trial which tested an interactive physical and cognitive exercise program (iPACESTMv2.0) reported significant improvements in executive function and that the improvements were associated with changes in levels of the salivary metabolic biomarkers cortisol and insulin-like growth factor-1.

The multi-domain Alzheimer preventative trial (known as MAPT) investigated the effect of physical activity counseling (Advice to engage in 150 min of moderately intensive physical activity per week), nutrition counseling, cognitive training, and preventative consultations in a cohort of adults aged 70 or over, with subjective memory complaints. Participants also received either an omega-3-polyunsaturated fatty acid supplement or placebo. Only those participants in the intervention group who were also taking the supplements demonstrated significant improvements, in the Mini-Mental State Examination (cognitive impairment questionnaire) scores. The ENCORE (Exercise and Nutritional Interventions for Cardiovascular Health) study investigated the effect of aerobic exercise, following the DASH diet and the combination of the two on BP and metabolic outcomes in an overweight middle-aged cohort. The DASH diet resulted in lower BP, and the addition of exercise and weight loss resulted in even greater BP reductions. The combined treatment also improved the secondary outcome measures of executive functioning, learning, and memory.

The ambitious Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability trial combined regular aerobic exercise, aspects of the MeDi and DASH diets,
a computerized brain training program, and regular health monitoring.\cite{103,104} In their cohort of adults aged 60–77, with cardiovascular risk factors and some evidence of neurocognitive weakness based on the CERAD test battery, this study provided evidence of neurocognition improvements resulting from the 2-year intervention. Cardiorespiratory fitness was found to associate most strongly with the observed neurocognitive improvements in executive function and processing speed (but not memory).\cite{105} This study has initiated a world-wide FINGERS collaborative network of trials, to replicate the study in many countries with the aim of validating the results in different populations and cultures.\cite{106} Studies are already underway or being planned in the USA (US-POINTER), Australia (AU-ARROW), Singapore (known as SINGER), China (MIND-CHINA), and other countries (for further information see http://wwfingers.com).

The aforementioned multimodal intervention studies, mostly ongoing or completed in the last 10 years, have demonstrated that changes to multiple aspects of lifestyle are providing health improvements in various domains, delivering benefits to the cardiovascular system, metabolism, and cognitive health. The promotion of such lifestyle changes, particularly to middle-aged and older adults, would be a valuable preventative strategy to both improve the quality of life of ageing populations and to reduce the burden on public health departments, hospitals and carers.

**Conclusions**

Hypertension is a major risk factor for many chronic diseases and serious health events. It affects more than 40% of adults worldwide and is associated with stroke, myocardial infarction, heart failure, and other cardiovascular diseases. It has also been shown to cause functional and structural damage to the brain, which increases the risk of cognitive impairment and dementia. Vascular structural changes, endothelial dysfunction, and sympathetic overstimulation have been described as the major contributing factors to the pathophysiology of hypertension.\cite{106,107} Exercise has been shown to be an effective component of nonpharmacological interventions for BP control. The type and frequency of exercise that may be needed to be effective in BP management are currently being investigated, both to understand the physiology behind the improvements, as well as to find the most effective individual exercise “prescriptions.” More recently, clinical trials of multidomain lifestyle interventions that include for example exercise, diet modification, brain training exercises, medical counseling, and encouragement of social engagement, are showing considerable promise, both in the preservation of certain cognitive function domains, as well as in the improvement of cardiovascular, and metabolic risk factors. The benefits of such trials will be far-reaching, by providing a pathway for improving the quality of life for the ageing population as well as reducing public health costs.

**References**


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