Published in final edited form as:

Climacteric. 2014 December ; 17(0 2): 38–46. doi:10.3109/13697137.2014.929650.

Three Midlife Strategies to Prevent Cognitive Impairment Due to Alzheimer's Disease

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Abstract

The slow, progressive accumulation of pathology characteristic of Alzheimer's disease is the principal determinant of cognitive decline leading to dementia. Risk-reduction strategies during midlife focus on raising the clinical threshold for the appearance of cognitive symptoms and on reducing the extent of Alzheimer pathology. Best available evidence suggests an approach based on three, conceptually distinct strategies. (1) Raise the threshold for cognitive symptoms by improving brain health. To achieve this goal, the tactic is to reduce cerebrovascular risks mediated by hypertension, diabetes, cigarette smoking, and hyperlipidemia. (2) Raise the threshold for cognitive symptoms by enhancing cognitive reserve. Here, tactics focus on mental stimulation associated with occupation, leisure activities and social engagement. (3) Reduce the burden of Alzheimer pathology. The most promising tactic toward this end is regular aerobic exercise. Tactics in support of strategies to reduce cognitive impairment due to Alzheimer pathology are not yet substantiated by robust, consistent clinical trial evidence. There is pressing need for well designed pragmatic trials to provide stronger evidence on preventive strategies for late-life cognitive decline and dementia.

Introduction: Cognitive aging, mild cognitive impairment, and dementia

Dementia, or major neurocognitive disorder, is characterized by a decline in cognition that compromises usual daily activities or the ability to live independently. The prevalence of dementia in 2010 was estimated as 36 million worldwide, and 115 million cases are projected for the year 2050¹. Alzheimer's disease is the most common cause of dementia and accounts for about two-thirds of cases². Within the US, an estimated 5.4 million people have Alzheimer's disease³, and 96% are aged 65 years or older. Common symptoms include the insidious onset of late-life impairments in memory and executive functions, followed by more pervasive cognitive deficits.

Alzheimer's disease is distinct from normal, or usual, cognitive aging². Physiological and pathological changes that contribute to cognitive aging are beginning to be identified^{4–6}, but specific mechanisms are still largely unknown. These changes are conceptually distinct from the pathologies of Alzheimer's disease and other dementing disorders. Much of late life cognitive decline is not due these specific dementia pathologies⁷, and in their absence

cognitive aging would not be expected to eventuate in dementia during a normal lifespan (Table 1).

Mild cognitive impairment is used to describe cognitive decline greater than expected for age and education level that does not interfere notably with activities of daily life⁸. Mild cognitive impairment is regarded as prodromal stage for dementia caused by the pathology of Alzheimer's disease or some other cause of dementia. Indeed, new research criteria recognize forms of Alzheimer's disease without dementia⁹, such as mild cognitive impairment due to Alzheimer's disease. Admittedly, the clinical distinction between cognitive aging (without dementia pathology) and mild cognitive impairment (with dementia pathology) is often difficult. In late old age, changes of Alzheimer's disease are not uncommon at autopsy, even in the absence of dementia¹⁰.

Midlife, menopause, and cognitive risk

Midlife is the portion of a woman's life that begins with the menopause transition and continues until age 65 years, the somewhat arbitrary threshold for older adult life¹¹. Menopause is a normal physiological process caused by the age-associated depletion of the primordial ovarian follicles. The ovary as a consequence no longer produces estrogens or progesterone. Mean levels of serum 17 β -estradiol begin to decline about two years before the final menstrual period and reach a permanent nadir about two years after the final menstrual period¹². The median age of natural menopause is 51 years, and the menopause transition transpires over a period of about four years¹³.

During the natural menopause transition and early postmenopause, forgetfulness is common and can evoke disquieting concerns of mental decline. Cognitive symptoms during midlife are associated with depression, anxiety, and feelings of stress^{14,15}. Aspects of attention may be affected¹⁶, but the natural menopause does not appear to lead to poorer memory¹¹. Subtle cognitive decline begins well before the menopause transition and continues through midlife and into old age, probably reflecting age-associated reductions in the number of brain synapses¹⁷⁻¹⁹. Some cognitive symptoms during midlife presumably reflect awareness of ongoing changes of cognitive aging, especially in the setting of low mood, anxiety, or stress. Premature menopause is less well studied²⁰, and surgical menopause at a relatively young age is linked to heightened risk of cognitive impairment or dementia later in life^{21,22}.

After menopause, serum concentrations of ovarian steroids are not strongly related to most aspects of cognitive performance. Levels of estradiol are positively associated with naming (semantic memory; often assessed by asking for the names of pictured objects)^{23,24} but not with memory or executive functions^{24,25}, cognitive domains more often linked to prodromal Alzheimer's disease.^{26,27} The influence of progesterone is less well studied, but in one study serum concentrations in younger postmenopausal women were associated with better verbal memory²⁴. Estrogen-containing hormone therapy when used by healthy postmenopausal women does not substantially affect memory or executive functions^{25,28}. Effects of hormone therapy on Alzheimer's disease risk are controversial and are addressed below.

Pathologies of dementia

Alzheimer's disease is characterized by neuritic plaques and neurofibrillary tangles within vulnerable regions of the brain²⁹. Both are composed largely of aberrant, insoluble, misfolded proteins. Aggregates of β -amyloid fibrils accumulate as plaques in the extracellular space. Neuritic plaques are associated with activated microglia, reactive astrocytes, complement deposition, and other signs of an innate immune response, as well as with abnormally distended neurites (nerve processes). Neurofibrillary tangles occur within the cell bodies of affected neurons. They are composed of tau proteins that have been excessively phosphorylated. In Alzheimer's disease, aggregates of hyperphosphorylated tau are identified in a few brain regions decades before the onset of dementia symptoms³⁰. Amyloid accumulation also begins well in advance of cognitive impairment³¹. Fibrillar β -amyloid within plaque cores is biochemically inert. Smaller, soluble assemblages of amyloid and tau (β -amyloid oligomers and tau paired helical filaments) may be particularly detrimental to neuronal function, as compared to the more salient amyloid plaques and neurofibrillary tangles. Plaques and tangles are not necessarily the proximate cause of neuronal dysfunction, but they reflect the fundamental processes that accelerate synapse loss and eventually lead to neuronal death. In Alzheimer's disease, cognitive impairment is more strongly related to excessive synapse loss than to plaque and tangle counts³².

Most other causes of dementia have their own specific pathologies. Vascular dementia is the second most common cause of dementia. It takes several forms³³ but is usually due to discrete ischemic stroke (infarction) following occlusion of large or small arteries. These can be visualized with structural brain imaging (computed X-ray tomography scan or magnetic resonance imaging scan), but microinfarcts³⁴ may not be detected during life. Atherosclerosis of intracranial arteries, but not atherosclerosis in other vessels, may contribute to dementia in the absence of frank infarction³⁵.

Abnormal protein aggregates are characteristic of several forms of dementia in addition to Alzheimer's disease. These including Parkinson's dementia and dementia with Lewy bodies (α -synuclein), frontotemporal dementia (TAR DNA-binding protein 43, tau, or RNA-binding protein FUS), corticobasal degeneration, progressive supranuclear palsy and dementia pugilistica (tau), and Huntington's disease (huntingtin).

Three preventive strategies

Most dementia is due to Alzheimer pathology in isolation or in combination with other pathologies — such as cerebral infarction or cortical Lewy bodies — that themselves can cause dementia³⁶. A patient can develop dementia when the plaque and tangle burden is relatively modest, if another neuropathology is present at the same time³⁶. A healthy brain that is otherwise free from other pathology can tolerate a moderate plaque and tangle pathological burden before a clinical threshold for dementia is reached^{10,37}. Thus, the clinical expression of Alzheimer's disease occurs when the pathological burden and consequent neural damage exceeds a critical threshold beyond which normal cognitive function is not sustained.

These findings have enormous implications for Alzheimer's disease prevention. Key points are (1) that mild cognitive impairment and dementia due to Alzheimer's disease occur only after a clinical threshold is breached, and (2) that the clinical threshold is lower when additional dementia pathologies are present.

Preventive strategies thus focus on raising the threshold at which cognitive symptoms emerge and on reducing the burden of Alzheimer pathology (Table 2). Threshold elevation is accomplished through the maintenance of brain health and the enhancement of brain reserve. Reducing Alzheimer pathology is problematic. Data are limited, but aerobic physical activity holds particular promise as a potentially effective tactic in this regard.

Strategy 1: raising the threshold by maintaining brain health

When other brain pathologies are present, Alzheimer pathology is more likely to be manifest as cognitive impairment or dementia. Unfortunately, fundamental causes of the neurodegenerative dementias remain largely obscure, and disease-modifying therapies are not available for most of these progressive disorders.

Vascular disease, in contrast, is an attractive target for preventive interventions. The pathologies of cardiovascular disease and Alzheimer's disease are often found together^{33,36}, and the two disorders share common risk factors³⁸. These include hypertension, diabetes, hyperlipidemia, midlife obesity, metabolic syndrome, and cigarette smoking. Although vascular risk factors might theoretically be causally related to β -amyloid and hyperphosphorylated tau, atherosclerosis and vascular lesions are not significantly associated with Alzheimer pathology^{39,40}. The more likely association is with macroscopic or microscopic ischemic injury to the brain, which lowers the threshold for cognitive impairment. Successful implementation of strategies to ameliorate stroke risk and intracranial atherosclerosis would be expected to reduce not only the incidence of vascular dementia but also that of dementia triggered by accumulating Alzheimer pathology. The American Heart Association and American Stroke Association provide evidence-based guidelines for stroke prevention in women⁴¹.

Strategy 2: raising the threshold by enhancing brain reserve

The most thoroughly studied approach to bolstering brain reserve in a healthy brain is through enhancement of cognitive reserve through various types of mental activity. Cognitive reserve implies greater capacity, efficiency or redundancy in terms of brain areas and neural pathways used when a cognitive task is performed⁴². There is fairly consistent evidence that people of greater intelligence, higher educational achievement,⁴³ and cognitively demanding occupations⁴⁴ maintain better cognitive function and are at lower risk for Alzheimer's disease. Mentally stimulating leisure activities^{45,46} and social engagement⁴⁷ might also reduce risk, presumably in part through mechanisms similar to those that promote cognitive reserve. Such activities do not appear to have a direct effect on the pathological burden of Alzheimer's disease⁴⁸; rather they appear to act by enhancing brain reserve.

Evidence for threshold augmentation is derived largely from observational research and not from clinical trials in humans. A concern is that more intelligent people are more likely to be

better educated, pursue more challenging careers, engage in more stimulating leisure pursuits, be more socially connected, and maintain lifestyle practices that reduce vascular risk. It can therefore be difficult to establish a causal relation between any particular factor and the risk of cognitive decline. Despite this caveat, clinical trial data in support of the cognitive reserve hypothesis are beginning to emerge. One randomized trial of community volunteers aged 65 and older compared three forms of cognitive training (verbal memory, problem solving, and visual processing speed) to a control condition⁴⁹. Ten training sessions, with or without booster training 11 and 35 months later, improved performance on the specific targeted cognitive ability (but not other cognitive skills), which was maintained over a two year period. A decade later, those who received cognitive training self-reported better daily functioning, compared to untrained participants⁵⁰. Effects on targeted skills were evident as well for problem solving and processing speed but were not maintained for memory. These findings suggest that cognitive enhancement can have durable effects, although perhaps limited to the specific cognitive processes engaged by the intervention. This study did not find persistent benefit from memory training⁵⁰, however, and effectiveness of memory-specific interventions may be more limited⁵¹.

Strategy 3: reducing the burden of Alzheimer pathology through aerobic exercise

A robust literature links aerobic exercise to cognitive performance and reductions in Alzheimer's disease risk^{52,53}. A meta-analysis based on nine cohort studies associated higher levels of physical activity with a 28% reduction in risk (the 95% confidence interval was 2% to 47%)⁵³. In a young adult cohort, cardiorespiratory fitness was associated with better cognitive function 25 years later⁵⁴. Exercise might affect Alzheimer pathology directly. In a study of transgenic mice that develop Alzheimer-like pathology, long-term treadmill exercise reduced the number of amyloid plaques as well as levels of soluble β -amyloid in the hippocampus, compared to control transgenic animals⁵⁵. Although these mice do not develop neurofibrillary tangles, exercised animals showed lower levels of hyperphosphorylated tau protein, as well. Other research supports the view that exercise training reduces brain levels of β -amyloid in transgenic animals and improves learning deficits⁵⁶.

Human data offer further evidence for an exercise effect on Alzheimer pathology. In an observational study of cognitively normal middle-age and older adults, participants were classified based on levels of self-reported physical exercise during the preceding decade and on Alzheimer's disease biomarkers. The more sedentary participants had greater β -amyloid loads in the brain, as imaged with positron emission tomography, and lower levels of β -amyloid in the cerebrospinal fluid (lower spinal fluid levels are a biomarker of Alzheimer's disease)⁵⁷. In subgroups defined by apolipoprotein E genotype, these associations were significant for those carrying the high risk $\epsilon 4$ allele but not for non- $\epsilon 4$ carriers. Findings thus imply that physical exercise might help protect against Alzheimer pathology in this high-risk group. These results were not broken down by gender, but the $\epsilon 4$ allele of the apolipoprotein E gene conveys higher risk for women than for men⁵⁸⁻⁶⁰.

Exercise might also reduce Alzheimer risk indirectly through threshold modification. This may involve effects on inflammation, oxidative stress, and immune modulation⁶¹. In both

animals and humans, aerobic exercise increases levels of brain derived neurotrophic factor and other growth factors^{57,61–64}. Higher serum levels of brain derived neurotrophic factor are linked to a lower risk of developing Alzheimer's disease⁶⁵. These proteins support neuronal survival, enhance synaptic plasticity, promote new blood vessel formation, and lead to the formation of new neurons in the dentate gyrus of the hippocampus. There is indirect evidence that exercise induces neurogenesis in the human dentate gyrus⁶⁶. In a clinical trial involving 120 healthy older adults, aerobic walking over a one year period of time, compared to a non-aerobic control intervention, increased the volume of the hippocampus⁶² measured by magnetic resonance imaging; this temporal lobe region is critically involved in memory encoding and consolidation. Interestingly, brain derived neurotrophic factor might also mediate cognitive reserve linked to mental activity⁶³.

The US Department of Health and Human Services provides useful guidelines on physical activity for older adults⁶⁷ (Table 3).

Estrogen therapy as a tactic to reduce Alzheimer pathology?

A potential role for estrogens in reducing Alzheimer risk remains controversial, because there is clinical trial evidence for the opposite effect; viz., an increased risk of all-cause dementia. In some laboratory models, however, estradiol reduces Alzheimer pathology. After ovariectomy, estradiol reduces β -amyloid deposition in transgenic mice that develop Alzheimer-like pathology⁶⁸. Other estradiol effects on neural plasticity, neurogenesis, oxidative stress and cerebral metabolism could boost brain reserve^{69–71}, thereby reducing Alzheimer risk indirectly.

In an ancillary study of the Women's Health Initiative involving relatively healthy postmenopausal women aged 65 to 79 years, conjugated estrogens combined with a progestin (medroxyprogesterone acetate) compared to placebo doubled the risk of dementia⁷². This risk represented about 2.3 additional cases of dementia per year, per 1000 women in the age group studied. Among women without a uterus, conjugated estrogens without medroxyprogesterone acetate did not affect dementia risk ($p = 0.2$), although risk was significantly increased in the combined analysis of women with and without a uterus⁷³.

Hormone therapy used after surgical menopause²², by younger postmenopausal women (but not older postmenopausal women)⁷⁴, and during midlife (but not during late life)^{75,76} is associated with lower risk. One interpretation is that estrogen effects on Alzheimer risk are modified by age or temporal proximity to menopause⁷⁷. They may be protective for younger postmenopausal women and hazardous for older postmenopausal women. This possibility is sometimes referred to as the critical window, or timing, hypothesis. It is not known whether Women's Health Initiative memory study findings for women aged 65 to 79 years^{72,73} generalize to women in their early 50s — women most likely to consider hormone therapy for moderate to severe vasomotor symptoms during the menopause transition and early postmenopause. It is also unknown whether unrecognized confounding in observational studies of postmenopausal women might have led to invalid inferences on risk reduction in the younger age group. Women who use menopausal hormone therapy tend to be healthier than other women⁷⁸. Failure to adjust for relevant health differences or the inability to adjust

for any unrecognized differences could confound the measure of association between hormone therapy and Alzheimer risk.

For estrogen therapy, observational evidence indicating benefit in younger postmenopausal women must be weighed against clinical trial data showing harm in older postmenopausal women. Given these uncertainties, expert opinion guidelines suggest that hormone therapy should not be used to help prevent Alzheimer's disease^{79,80}. In the US, Food and Drug Administration labeling includes a black box warning, "Estrogens with or without progestins should not be used for prevention of ...dementia," based principally on findings from the Women's Health Initiative.

For cognitive outcomes apart from dementia, evidence on estrogen is more solid but uninspiring. Here, convincing clinical trial data indicate that menopausal hormone therapy does not appreciably boost or impair most cognitive abilities of relatively healthy postmenopausal women^{25,28}. This conclusion does not pertain to women with premature menopause, who are poorly represented in research to date.

Other tactics

A number of therapies, behavioral interventions and lifestyle practices are purported to improve brain health by reducing oxidative stress, modulating the immune response, reducing inflammation, improving mitochondrial efficiency, or enhancing metabolism. These actions could help maintain brain health or influence Alzheimer manifestations through other mechanisms. Anti-inflammatory medications or statins, moderate consumption of alcohol, treatment of depression, adherence to the Mediterranean diet, and good sleep hygiene might plausibly reduce the likelihood of developing Alzheimer's disease.

Both non-steroidal anti-inflammatory drugs⁸¹ and statins⁸² are associated with reduced risk for Alzheimer's disease. However, neither anti-inflammatory medications⁸³ — corticosteroids, aspirin, cyclooxygenase-2 inhibitors, and nonspecific cyclooxygenase inhibitors — nor statins⁸⁴ have shown clinical efficacy in the treatment of Alzheimer's disease. Nor is there yet convincing evidence that statins help prevent Alzheimer's disease⁸⁵.

Two clinical trials failed to confirm a role for nonsteroidal anti-inflammatory drugs in Alzheimer prevention. The first of these involved patients with mild cognitive impairment, who were treated with rofecoxib, a selective cyclooxygenase-2 inhibitor, or placebo. In this study, rofecoxib increased risk of progression to Alzheimer's disease⁸⁶. Another trial focused on cognitively healthy older adults at increased risk for Alzheimer's disease based on family history. The study was halted prematurely, but participants randomized to celecoxib (another cyclooxygenase-2 inhibitor) or naproxen faced an early increase in Alzheimer risk with no overall effect on risk after extended follow-up^{87,88}.

There is no consensus on the impact of alcohol on Alzheimer risk⁸⁹. In a pooled analysis of cohort studies, the relative risk of Alzheimer's disease for light-to-moderate drinkers compared to nondrinkers was about 0.72 (95% confidence interval 0.61 to 0.86)⁹⁰.

However, alcohol consumption is often associated with healthy behaviors such as regular exercise⁹¹, and the relation between alcohol consumption and long-term health outcomes is almost impossible to assess in a traditional clinical trial setting. An alternative approach, referred to as Mendelian randomization, considers different alleles of the gene for aldehyde dehydrogenase 2. Homozygotes for the inactive allele experience flushing, nausea, and other discomforting symptoms after alcohol ingestion, and for this reason they generally consume little alcohol. In a Chinese population of community dwelling men age 50 years and older, the aldehyde dehydrogenase-2 genotype was, as expected, strongly associated with alcohol consumption. However, it was not associated with scores on tests of memory or global cognition⁹². These results suggest that alcohol may not be cognitively protective, at least for men. In the Whitehall II cohort study, moderate or higher levels of alcohol consumption (36 grams daily or more) — again, at least for men — were associated with faster cognitive decline⁹³, whereas cognitive change did not differ between abstainers and men who consumed lower quantities of alcohol. Taken together, these recent results suggest that low to moderate levels of alcohol consumption do not contribute to cognitive decline, but alcohol consumed in moderation may not help maintain cognitive abilities either.

Women are twice as likely as men to develop depression⁹⁴. Vulnerability to depression may be elevated during the menopause transition⁹⁵, but depression risk does not appear to be increased during the late-postmenopause⁹⁶. Depression is strongly associated with Alzheimer's disease risk^{97,98}, but the key question is whether the association is causal. Neurofibrillary tangle formation in serotonergic and noradrenergic brainstem nuclei can occur well before cognitive symptoms of Alzheimer's disease begin to emerge^{30,99}. These neurotransmitter systems are implicated in depression. Speculatively, some instances of adult-onset depression may be triggered by early pathological changes in these brainstem neurons. If so, the causal pathway would lead from Alzheimer's disease to depression, and not the other way around. Inflammation and oxidative stress may predispose both to depression and to Alzheimer's disease, in which case, also, depression —despite their association with Alzheimer's disease — would not be causally related to Alzheimer's disease. Depression, however, is also linked to Alzheimer's disease in other ways. Levels of cortisol are elevated in depression. This stress hormone may reduce brain reserve through deleterious effects on the hippocampus and possibly may contribute to Alzheimer pathology^{100,101}.

The Mediterranean diet is promising as a preventive intervention. This nutritional pattern roughly reflects traditional food consumption in Greece, southern Italy, Portugal, and Spain. The diet is usually described by a relatively large proportions of fish, unsaturated fatty acids (olive oil), legumes, fruits, vegetables, and unprocessed cereal grains; moderate amounts of dairy products (cheese and yogurt), moderate amounts of wine; and relatively low proportions of meat. Observational research indicates that higher adherence to a Mediterranean diet is associated with lower Alzheimer risk¹⁰², and one version of the Mediterranean diet was reported to improve cognition in older adults without dementia¹⁰³.

Studies in animals indicate that spinal fluid circulates more freely during sleep, increasing the rate of clearance of β -amyloid and other cellular waste products¹⁰⁴. Healthy humans also show diurnal fluctuations in spinal fluid levels of soluble β -amyloid¹⁰⁵. Among community-

dwelling older adults, self-reported sleep duration and poor sleep quality are associated with increased amyloid burden¹⁰⁶, and sleep fragmentation is linked to Alzheimer risk¹⁰⁷. It is postulated that sleep disruption increases amyloid levels in the brain, leading over time to amyloid accumulation, cognitive impairment, and dementia¹⁰⁸. It remains to be shown whether enhanced sleep hygiene during midlife and old age might lower the risk of Alzheimer's disease.

Three midlife strategies to combat cognitive decline and dementia: the take home message

The invidious progression of the pathology of Alzheimer's disease is the most potent determinant of cognitive decline leading first to mild cognitive impairment and then to dementia. Current risk-reduction strategies are not well substantiated by experimental data, although some tactics are better supported than others. The strongest evidence points to a tripartite strategy implemented in midlife or earlier. (1) Ameliorating cerebrovascular risk is expected to raise the threshold for cognitive symptoms by improving brain health. (2) Mental stimulation associated with occupation, leisure activities and social engagement is expected to raise the threshold through effects on cognitive reserve. (3) Regular aerobic physical activity is expected to reduce the accumulation of Alzheimer pathology. Roles of other factors — including midlife hormone therapy, anti-inflammatory drugs, statins, light-to-moderate alcohol consumption, treatment of depression, adherence to a Mediterranean diet, and restful sleep — are less well defined. The lack of reasonable certainty regarding these approaches and others highlights the need for well designed efficacy and pragmatic trials intended to reduce the risk of dementia due to Alzheimer's disease⁵³.

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Table 1

Classification of cognitive decline associated with age

Category	Symptoms impair daily activities or independence?	Symptoms due to a dementia pathology?
Cognitive aging	No	No
Mild cognitive impairment *	No	Yes
Dementia	Yes	Yes

* Symptoms exceed those expected on the basis of cognitive aging *per se*.

Table 2

Strategies and tactics to protect against cognitive decline due to Alzheimer's disease

Strategy	Tactic
1. Raise threshold by maintaining brain health	Cigarette cessation and control of blood pressure, lipids, and blood glucose to reduce the burden of vascular disease
2. Raise threshold by enhancing brain reserve	Mentally stimulating occupational and leisure activities; social engagement
3. Reduce burden of Alzheimer pathology	Aerobic exercise

Table 3

Physical activity recommendations for older adults⁶⁷

Type of exercise*	Examples	Weekly exposure	Interval
Moderate intensity, aerobic (3 to 5.9 metabolic equivalents) [†]	Brisk walking (3+ miles/hour); bicycling (<10 miles/hour); social dancing; doubles tennis	150+ min	Spread throughout the week, each episode 10+ minutes
Or, Vigorous intensity, aerobic (6+ metabolic equivalents)	Jogging or running; swimming; bicycling (10+ miles/hour); hiking uphill; jumping rope; singles tennis	75+ min	Spread throughout the week, each episode 10+ minutes
And, Resistance training, all major muscle groups	Resistance bands; free weights or weight machine; calisthenics	Not specified	2+ days weekly

* Intensity and exposure levels are built up gradually, as safely tolerated.

[†] 1 metabolic equivalent represents the approximate rate of energy expended during quite sitting (consumption of 3.5 ml O₂/kg*minute, or equivalently 1 kcal/kg*hour).