THESIS BEHAVIOURAL- AND NEUROSCIENCES

Run for your life:

Prevent a public health burden

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Introduction

Until 1997 case-control studies showed a low prevalence of diabetes in Alzheimer's disease patients. [1-4] In 1997, however, a prospective cohort study with a population-based design, was published: the Rotterdam study.

The Rotterdam study investigated whether Diabetes Mellitus type 2 (T2DM) increases the risk of dementia and Alzheimer's disease (AD). They found an increased risk of developing AD among Diabetes Mellitus (DM)-patients, especially those treated with insulin. [5]

The same year a historical cohort study was published and the results showed, just like the Rotterdam study, a contradiction with the previous studies. This study focused on the relative risk of dementia and AD in persons with adult onset DM (AODM). The results show a significantly increased risk for dementia, for both men and women, when the person was diagnosed with AODM. The risk of AD was also increased for both men and women, but only significantly elevated in male subjects. [6] These results correspond with previous studies that showed an association between AODM and AD and are consistent with cross-sectional studies showing that persons with diabetes score lower on some tests of cognitive function compared to persons without diabetes. Next to that, persons with Alzheimer's disease exhibit impaired glucose regulation compared with normal subjects. [6]

World wide aging

The results from the Rotterdam study had a great impact, because the possibility of an increased risk in developing Alzheimer's disease would have great implications for the society. [7] Aging is a worldwide phenomenon and according to the UN Aging Program and the US Centres for Disease Control and Prevention it is expected that the number of elderly (65+) will increase from 420 million in the year 2000, to almost 1 billion in the year 2030. This would mean that the percentage of elderly will increase from 7 to 12 percent of the total world population. [8, 9]

Prevalence

The prevalence of Alzheimer's disease is strongly associated with an increasing age, which means that AD can be expected to become a great burden for health care in all countries. [10] As the world population ages, the number of older adults living with Alzheimer disease (AD) is estimated to increase from the current 26.6 million to 106.2 million by 2050. This would mean, 1 in 85 persons worldwide would be living with the disease. [11]

In the Netherlands, the CBS estimated the number of AD-patients in the year 2000 at 170.000 and they expected this to increase to a 207.000 patients in the year 2010 (as can be derived from figure 1 displayed below). The following years the number of AD-patients is expected to expand to 412.000. This would mean that in 2000 there was 1 patient in 93 Dutch citizens and in 2050 there will be 1 patient in 44 Dutch citizens. [12]

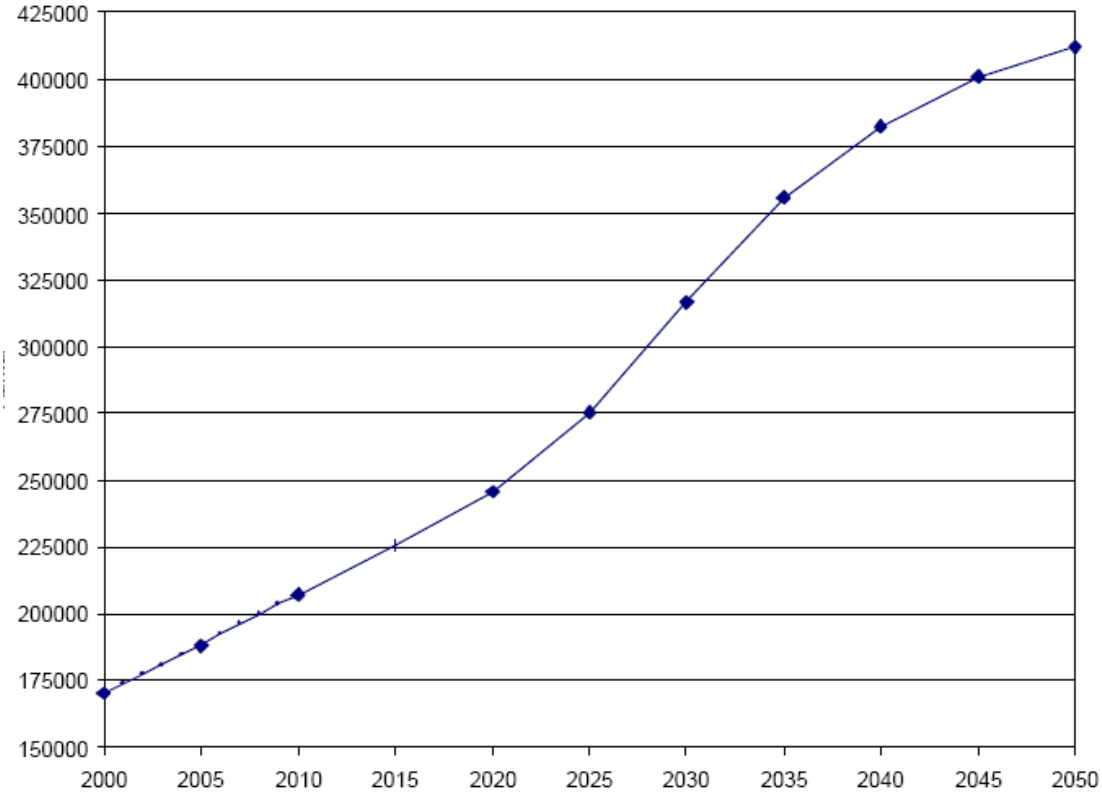

Figure 1: the expected number of AD-patients in the Netherlands.

The number of people with diabetes is increasing due to population growth, aging, urbanization and increasing prevalence of obesity and physical inactivity. It is expected that the number of people with diabetes will rise from 171 million in the year 2000 to 366 million in the year 2030. The most important factor in this elevation appears to be the increase in the proportion of people above 65 years of age across the world. [13]

Especially because of the aging phenomenon and the expected rise in prevalence of both Alzheimer's disease and Diabetes Mellitus, it is important to understand the pathologies and to find a way to fence off or prevent increased health burden. The aim of this thesis is to describe the pathologies of AD and T2DM, explicate one possible link between those two and discuss a possible way of prevention.

Alzheimer's disease

Discovery and history

In 1901 a German psychiatrist, Alois Alzheimer, admitted a 51-year old lady to the hospital in Frankfurt. She had hallucinations, delusions, focal symptoms and progressive memory loss. The lady in question, Auguste D., kept repeating that she had lost herself. After the death of the woman, Alzheimer performed a pathological-anatomical investigation on her brain. With a silver staining he identified neuritic plaques, reported earlier by Blocq and Marinesco in an elderly patient with epilepsy, and neurofibrillary tangles. He was the first to describe these tangles and together with the clinical description, his post-mortem findings formed the first definition of Alzheimer's disease. Emil Kraepelin, in whose laboratory the research was performed, named the pathology after Alois Alzheimer. [14, 15]

Introduction

Alzheimer's disease (AD) is an incurable progressive neurodegenerative disease with a multifactoral cause, but older age is the strongest risk factor. Both familial and sporadic forms of AD occur. [16, 17]

Much research has been done to the age-related biological processes that could implicate the pathogenesis of this disease. The association of increasing age and AD could partially reflect the cumulative effect of various risk factors and protective factors over lifespan. [18]

Pathology

Even though the pathogenesis of AD differs in every individual, there are many common symptoms. The most commonly recognized symptom is memory loss. As the disease progresses, the symptoms might include for example delusions, nonspecific agitation, and diurnal rhythm disturbances. [19]
Deterioration in language abilities, decline in visuospatial skills and disturbances of executive function including abstraction and judgement are symptoms that can also occur [20] The mechanisms before and during the onset of the disease are not well understood, but studies indicate that extracellular amyloid-β plaques and intracellular neurofibrillary tangles of tau-protein in the brain tissue play a major role in this pathology. [21]

Microglia get stimulated by these plaques and send out inflammatory signals. Inflammation in AD is thought to be a secondary response which results from impaired processing and precipitation of amyloid-β. This inflammatory response will ensure and maybe even cause additional neuronal loss. [22]

Besides these cognitive changes, AD can also affect physical function. The mobility, ambulation and home management skills decline more rapidly over the course of one year compared to control with similar age and physical health. The risk of injuries is also increased among AD-patients [23] and when a person with dementia or AD is injured after a major fall, the prognosis for full functional recovery is extremely poor. [24]

Diabetes Mellitus type 2

Discovery and history

Diabetes Mellitus literally means 'sweat deluge' as a reference to the sweet taste of urine. In 1889 Joseph von Mering and Oskar Minkowski discovered that the pancreas plays an important role in the pathology of DM, when they observed that dogs without pancreases showed symptoms of DM and shortly afterwards died. [25] Sir Schlafer insinuated in 1910 that diabetes-patients were deficient in one single chemical, normally produced by the pancreas. Referring to the islets of Langerhans, he suggested to call the chemical 'insulin'. Ten years later, Sir Frederick Grant Banting and Charles Herbert Best showed that they could reverse induced diabetes in dogs by feeding them an extract of pancreatic islets of Langerhans cells of healthy dogs. [26] These men continued their research and eventually purified the hormone insulin from bovine pancreases. This led to an effective way of treatment, insulin injections, and Banting and Best received the Nobel Prize in Physiology or Medicine in the year 1923. It was not until 1980 that a biotech company in the U.S. developed insulin and that the hormone could be produced in large quantities.

Introduction

Diabetes Mellitus (DM) is a heterogeneous metabolic disorder, which needs constant medical attention to control the development. DM is characterized by hyperglycemia resulting from inadequate insulin secretion and/or a deficit in target cell responsiveness.

Two different types of DM exist, which can be characterized by different pathologies.

Pathology

Type 1 Diabetes Mellitus (T1DM) is an auto-immune disorder and is marked by a progressive inability of the pancreas to secrete insulin due to destruction of the beta-cells. The onset is quite abrupt and commonly occurs in children. [27] This type of DM accounts for 10 percent of all the DM-cases. [28]

Type 2 Diabetes Mellitus (T2DM) is characterized by a peripheral insulin-resistance and an insulin-secretion defect. All overweight individuals have an insulin-resistance, but only those who are incapable of increasing the insulin-production by beta-cells, will develop T2DM. This type of diabetes used to be called 'adult onset diabetes mellitus' (AODM) and commonly occurred among individuals older than 40 years. However, with the epidemic of obesity and the inactivity in children, T2DM is diagnosed in young children more often.

Multiple studies show that the complications of diabetes extend into the central nervous system (CNS) [29] and there are deficits in insulin receptor signalling and impairments in the HPA-axis function. It is theorized that insulin deficiency contributes to neurological and psychiatric complications in diabetes. [30, 31] Insulin receptor knock out in mice showed symptoms that correspond to T2DM and/or polycystic ovary syndrome (PCOS). Both these syndromes show hyperinsulinism, but the function and transport of insulin in the CNS in these two syndromes is decreased by obesity. [29]

In T2DM the islets of Langerhans are hallmarked by β-cell loss [32, 33] and islet amyloid derived from islet amyloid polypeptide (IAPP). [32, 34, 35] IAPP is co-expressed and secreted together with insulin by β-cells. Like amyloid-β peptide, IAPP spontaneously forms into amyloid aggregates. [36]

Insulin as a link between AD and T2DM

After the discovery that AD-patients more often have a diabetes history, many researchers focussed on the link between AD and T2DM. To clarify the association between the two pathologies, one suggested link will be discussed: the role insulin plays in AD and DM.

Homeostasis of glucose concentrations is established via glucose sensors in the beta-cells of the pancreas. These sensors detect blood glucose elevations, which will lead to the secretion of insulin by the beta-cells. Circulating insulin concentrations will increase, suppress the hepatic glucose output and stimulate the skeletal muscle and adipose tissue to take up glucose. [37]

Insulin and the CNS

The brain was considered to be insulin-independent, but clinical and basic research showed the opposite: despite the evidence that insulin is not produced in the brain itself, [38, 39] insulin receptors (IRs) and mRNA expression have been found to be distributed in the rat brain. [40, 41] These IRs are expressed by astrocytes, neurons, [42] peripheral sensory and autonomic ganglia [43] and insulin increases the glucose uptake by astrocytes. [44] Clinical research showed that patients suffering from Alzheimer's and Parkinson's diseases exhibit reduced expression of IRs in the brain. [45] This suggests that insulin and its receptor plays a role in the pathologies of AD and Parkinson's disease.

Aging

The regulation of the neuronal glucose metabolism diminishes during aging, due to a reduction of the neuronal insulin signal transduction. The insulin concentration, number of IRs and their activity have been shown to decrease beyond the age of 60 years. [46] The insulin concentration in dialysate of the hypothalamus of aged rats was half the levels of young animals after glucose stimulation. [47] The increase in the concentration of circulating cortisol, which is age-associated, and the maintained elevation of cortisol after stress may participate in the diminution of insulin receptor function [48, 49] Compared to adulthood, the elevation of cortisol also in the brain is mirrored by its drastic increase in cerebrospinal fluid. [50] The concentration of noradrenalin in the brain also increases with aging [51-53] what may contribute to the decreased activity of the neuronal insulin receptor. The neuronal insulin signal transduction cascade undergoes changes with brain aging, all resulting in a decreased receptor function. [54]

In aging, both synthesis and release of acetylcholine were demonstrated to be reduced [55, 56] which results in an imbalance between noradrenergic and acetylcholinergic innervation of microvasculature. This imbalance may contribute to the morphologic abnormalities in microvasculature during aging and in particular in sporadic AD [57] and

could explain how this morphology affects the clinical course of sporadic AD and dementia due to the contribution of cerebrovascular abnormalities in patients 80 years and older [58]

Pathologies

To understand the relations between T2DM and AD, it is important to understand the role insulin plays in the regulation of our metabolism. Insulin reduces food intake and bodyweight when it acts on the brain and it is thought to be an important adiposity signal. [59] Obesity in humans seems to be associated with a lack of insulin in the CNS, even though the serum insulin levels are elevated. [60] Research showed a decreased cerebrospinal fluid(CSF)/ plasma ratio with increasing body weight, which can indicate that human obesity is characterized by a relative CNS insulin defect. [60] This association was also found in animal studies. Obese rodents have relatively decreased CSF insulin levels compared to plasma levels. [38]

The sensitivity of the insulin receptor at the BBB could be decreased in obesity, despite the elevated circulating insulin levels. [61] This would explain the decreased CSF/plasma ratio of insulin. The reduced insulin levels in the brain then favour weight gain and the peripheral insulin resistance will increase. This resistance will decrease insulin uptake into the CNS and the cycle will start over again. [29]

Neurodegenerative processes are influenced by brain insulin [62] and human AD patients have lower CSF-insulin and higher plasma insulin compared to healthy individuals. This yields in a decreased CSF/plasma ratio, which is also found in obese people. Despite the lack of knowledge about the mechanism, it has been shown that insulin affects several brain functions, including cognition and memory [63] and that the insulin and insulin receptor signal transduction play a role, via biochemical stimuli, in memory formation and memory function. [54] Treatment with insulin of individuals with Alzheimer's disease has shown improvement in memory and cognitive performance. [64]

DM is associated with damage to the CNS and cognitive deficits. [65, 66] In both T1DM and T2DM impairment of learning and memory has been documented, which can vary in severity and involve mainly verbal memory and complex information processing. [67, 68]
Research with an experimental model showed that obesity aggravates neurodegeneration. [69] The increased prevalence of dementia among T2DM-patients might be explained by the elevation in serum insulin levels, which has been associated with impaired cognitive function. [70]

Amyloid protein

Amyloid protein deposits, consisting of islet amyloid polypeptide (IAPP) are commonly observed in pancreatic islets of diabetic patients [71] Treatment with insulin or metformin decreases IAPP concentrations in DM patients, while treatment with sulfonylureas, the most commonly used antidiabetic drugs, increases IAPP concentrations. [72]

Amyloid proteins, particularly amyloid- β (AB), are also key players of the molecular components of plaques in AD. AB is a small protein, derived from cleavage of a larger peptide, amyloid precursor protein (APP). [73]
While IAPP has a structural similarity of 90% with APP it is reasonable to assume that AD predisposes for insulin resistance and T2DM. [74, 75]
Several studies indicate that insulin regulates the metabolism of (AB) and tau proteins. [76-78] It is suggested that desensitization of the neuronal insulin receptors and signalling events in AD, will lead to a decrease in acetylcholine and a corresponding decrease in cerebral blood flow. These changes will cause the development of chronic, progressive deficits in brain oxidative metabolism. [54]

Prevention public health burden

There are multiple resemblances between the pathologies of AD and DM. The prevalence of both pathologies increases with age. In both pathologies there is a deposition of amyloid-protein. In T2DM the islets of Langerhans are characterized by beta-cell loss and islet amyloid derived from IAPP, which is co-secreted with insulin by the beta-cells. In AD the brain dysfunction is characterized by loss of cortical neurons and deposition of amyloid beta, derived from ABPP. The insulin signalling pathway interferes with the mechanisms of the amyloid-deposition in both pathologies.

Since AD as well as DM is expected to become a world wide health problem, prevention is a major goal of the current era. It is important to reduce the prevalence of these pathologies and find a treatment or lifestyle change that reduces the risk for developing AD and DM.

In this chapter a selection of research results will be presented and the relevance for society will be explicated.

Exercise and weight loss in DM

Many studies investigated the effect of lifestyle change on developing T2DM. One of the first clinical trials was executed with a Chinese population and followed almost 600 males and females who were randomly put on a diet, exercise program, or both. The diet-group had to increase the vegetable intake en decrease intake of alcohol and sugars; the activity group had to increase their activity by 20 minutes moderate exercising a day. After six years, all three groups were similarly effective in reducing T2DM, with a 31-46% risk reduction, compared to a non-treated control group. Still most participants progressed to diabetes during long-term follow up, but the prevalence among the individuals who were put on a diet or exercise program, was still lower than in the placebo group, respectively 80% compared to 93%. [79]
In a Finnish Diabetes Prevention Study 522 overweight individuals were randomly divided in 2 groups, a control group or a group of individuals who would get an intensive lifestyle modification, including diet program, a weight-loss goal of 5 % of total body weight and at least 30 minutes aerobic of resistance training a day. At the 3 year follow-up the group with lifestyle changes reduced their risk by 58% compared to the control

group. Three years after the active intervention, this group maintained a relative reduction for developing T2DM, respectively 36%. [80]
This suggests that the benefits could be maintained outside of a structured clinical setting. With this study the clinically significant impact of intensive lifestyle modification on reduction of diabetes was demonstrated. [81]

As mentioned above, studies showed that modification of lifestyle is an effective tool for preventing or delay T2DM. They demonstrate that physical activity with moderate intensity can decrease the risk to develop T2DM. Regular vigorous exercise also reduces the incidence of T2DM. This benefit was most pronounced in obese people and the results were independent of BMI. [82] In addition, a recent study shows that exercise for at least 2,5 hours a week also reduces diabetes risk, even if there is no weight loss involved. [81]

Even though physical activity without weight loss reduces the diabetes risk, weight loss is a predominant predictor of a reduced diabetes incidence; for each kilogram of weight lost developing diabetes was reduced with a 16%. The greatest risk reduction was found in participants older than 60 years, which is reasonable because this group achieved the biggest weight loss and had the greatest increase in physical activity in comparison to younger participants. [81]

So physical exercise appears to be a promising approach to primary prevent T2DM. Further research is needed to investigate the intensity, duration, and frequency of activity that will be most beneficial and most effective in reducing the incidence of T2DM. [82]

Exercise and weight loss in AD

Since many diseases, like T2DM, could benefit from lifestyle changes and interventions, studies have investigated the effect that modifications have on the onset and development of cognitive decline, dementia and AD.
If regular physical exercise was shown to be effective in reducing the risk or delaying the onset of dementing illnesses, it would be another compelling reason to promote physical exercise. [83]

Observational studies have found that physically active people are less likely to experience cognitive decline, in comparison to sedentary people. A higher level of physical activity over 2 years was associated with an improved cognitive score [84] and men who walk at least two miles a day, are 1,8 times less likely to develop dementia than sedentary men over a follow-up period of six years. [85]
Subsequent prospective studies also showed that there is a reduced incidence rate (32% reduction) of dementia among people who exercise 3 or more times a week [83] and that the association between physical activity and cognition is also evident when the activity is confined to later life. [86]

Due to a lack of evidence from randomized trials, the Fitness for the Aging Brain Study (FABS) was carried out in 2008 to investigate whether home-based physical activity for 24 weeks reduces the rate of cognitive decline among older adults with increased risk for dementia. [87] The participants were encouraged to exercise with

moderate intensity for at least 150 minutes per week, divided into 3 exercise sessions of 50 minutes. When the participants already achieved the 150 minutes with their baseline activity, they were encouraged to increase their activity with 1 session of 50 minutes. Cognitive changes were measured with *Alzheimer Disease Assessment Scale–Cognitive Subscale* (ADAS-Cog) where a person can sore 0 – 70, with higher scores indicating greater severity of cognitive impairment. After the intervention, the intervention group had an improvement of 0.69 point on the ADAS-Cog score, compared to the control group. This is a small improvement, but it could be important considering the relatively little increase the participants had in their activity pattern. The benefits of this activity were apparent after six months and they persisted for at least 12 months after de intervention. [87] Still it is disputable if the persons who will need an intervention are able to increase there activity with even a 150 minutes per week. Especially because the major part of the AD-patients or people with cognitive decline are physically restricted.

In 2001 the Canadian Study of Health and Aging [88] showed results that could be combined with the study of Lautenschlager et al. Laurin and colleagues found a significant protective effect of regular physical activity on the risk of cognitive impairment and dementia, especially of the AD-type. Important is that the association is a significant dose-response relationship, were the risk of developing a cognitive impairment or dementia decreases when the level of physical activity increases.

Besides cognitive improvement, physical exercise also has advantages of health benefits that are not confined to cognitive function alone. Findings suggest that exercise improves depression, quality of life, number of falls, cardiovascular function and disability. [87]
Considering these improvements, physical activity has advantages in comparison to the use of medicines, which act on mechanisms or causes of pathologies and do not improve the overall physical state. Moreover, many medicines also have side effects, which do not occur when increasing the amount of physical exercise.

Discussion

With the world wide aging phenomenon, T2DM and AD will contribute to a public health burden. In 2003, the costs for DM care were 2% of the total health care costs from the Netherlands and the average costs per patient were €1900,-. The National Institute for Public Health and the environment (RIVM) expects a total of at least 1.3 million diabetes-patients in 2025 [89] and a rise of 1,3% in diabetes costs a year [90].
On top of this rise of DM-cases, it is expected that there will be 1 AD-patient at 44 Dutch citizens in the year 2050. [12] If the onset of AD could be delayed by one year, 9.2 million fewer cases of AD would occur worldwide. [11]

These data reflect the importance of primary prevention of the pathologies of DM and AD. If governments would be convinced by the evidence that physical activity is effective in reducing the risk of delaying the onset of both, it would be another compelling reason to promote physical exercise and lifestyle changes among their citizens.

An increase of physical activity by 20 minutes a day already reduced the risk for developing T2DM. During the follow-up most participants progressed to diabetes, but the prevalence among the activity-raisers still was decreased by 13%. When overweight individuals were encouraged to lose 5% of their bodyweight and exercise at least 30 minutes a day, they reduced their risk by 58% compared to the control group. After three years they still had a relative risk reduction for developing T2DM, respectively 36%. Physical activity can also reduce the diabetes risk when there is no weight loss involved. Still weight loss is a predominant predictor of a reduced diabetes incidence.

Sedentary people are more likely to experience cognitive decline in comparison to physically active people. This suggests that physical activity benefits an individual in the risk for developing dementia or AD. Individuals who walk at least two miles a day are 1.8 times less likely to develop dementia and a risk reduction of 23% was found in persons exercising 3 or more times a week. With an activity increase of 150 minutes a week, divided in 3 sessions of 50 minutes, a small improvement in cognitive functioning was found. This could complement the findings that there is a dose-response association between the risk of developing a cognitive impairment and physical activity.
Additionally exercise does not only improve cognitive functioning, but also benefits many other physical functions.

All these findings suggest that regular physical activity could represent an important and potent protective factor for AD and DM. The findings of the Rotterdam study and the knowledge that there is an increased risk of developing AD among DM-patients could mean that the relevance of exercising against these two pathologies could even be of bigger importance that one would expect.

The Dutch government set a standard of exercise among adults, 30 minutes of moderate exercise a day for at least 5 days a week. Only 68% of the adults fulfill this standard. Besides a group of citizens that do move, but not meet the standard, there is a group of totally sedentary Dutch. The percentage of inactive Dutch citizens decreased in the period between 2000 and 2007, respectively from 9 to 5%, but increases since 2008. [91]

This thesis explicates the importance of exercising to prevent or decrease the risk for developing T2DM or AD. Governments should deliberate about ways to facilitate meeting the standard of exercise, for example by creating a possibility for people to exercise twice a week at work. The increase of activity will not only give citizens benefits by decreasing the risk for developing T2DM or AD, it will also improve their overall physical functioning. It is of great importance that all people are aware of the major benefits exercising has compared to a sedentary lifestyle, and that scientist focus on investigating the intensity, duration and frequency of exercising that will be most beneficial in reducing T2DM and AD.

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