REVIEW

Dietary habits, lifestyle factors and neurodegenerative diseases

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Abstract

Worldwide stroke is increasing in parallel with modernization, changes in lifestyle, and the growing elderly population. Our review is focused on the link between diet, as part of 'modern lifestyle', and health in the context of genetic predisposition of individuals to 'unhealthy' metabolic pathway activity. It is concluded that lifestyle including high sugar diets, alcohol and tobacco addiction or high fat diets as well as ageing, brain injury, oxidative stress and neuroinflammation, negatively influence the onset, severity and duration of neurodegenerative diseases. Fortunately, there are several healthy dietary components such as polyunsaturated fatty acids and the anti-oxidants curcumin, resveratrol, blueberry polyphenols, sulphoraphane, salvionic acid as well as caloric restriction and physical activity, which may counteract ageing and associated neurodegenerative diseases via increased autophagy or increased neurogenesis in the adult brain.

Key Words: *brain injury; dietary habits; lifestyle; metaflammation; neurodegeneration; oxidative stress; type 2 diabetes mellitus*

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doi: *10.4103/1673-5374.266045*

Received: *December 21, 2018*
Accepted: *June 20, 2019*

Introduction

Worldwide stroke is increasing in parallel with modernization, changes in lifestyle, and the growing elderly population. Individuals with a healthy, low-risk lifestyle (no smoking, daily exercise, moderate alcohol consumption and having a moderate weight during their mid-forties) had a significantly lower risk of neurodegenerative diseases than the high-risk lifestyle group. Therefore, the relatively high incidence of neurodegenerative diseases may be due in part to the negative influence of daily risk factors including (Donnan et al., 2008): stress, lack of physical exercise, unhealthy nutrition, obesity, high cholesterol levels in plasma, smoking, alcoholism or arterial hypertension.

Some intrinsic factors such as ageing, but also brain injury and associated exaggerated neuroinflammation, oxidative stress, as well as lifestyle factors including high sugar diets and high fat diets, alcohol and tobacco addiction, negatively influence neurodegeneration. But there are many components in our diet (polyunsaturated fatty acids, the antioxidants curcumin, resveratrol, blueberry polyphenols, sulphoraphane and salvionic acid) as well as caloric restriction, along with physical exercise that may allow us to live a healthier and longer life (Poulose et al., 2017). Although the progress of neurodegenerative diseases is, to some extent, measurable through anthropometric, lifestyle, and clinical factors, the mechanisms underlying neurodegenerative disease progression are not fully understood. The current review focuses on the link between lifestyle and health in the context of genetic predisposition of individuals to 'unhealthy' metabolic pathway activities by performing a systematic literature search of the last 10 years. Data were from PubMed and Google Scholar.

Mechanisms Linking Lifestyle and Diet-Induced Metabolic Inflammation to Cerebrovascular Diseases

Fuelled by an increasingly sedentary lifestyle along with an unhealthy, "westernised" diet, the type 2 diabetes mellitus (T2DM) epidemic has expanded in parallel with obesity in modern societies.

For decades, a diet rich in saturated fat and cholesterol has been seen as the major dietary factor leading to an increased risk of atherosclerosis and cerebrovascular diseases (Hu and Willett, 2002). Indeed, bad nutritional habits may lead to metabolic disorders including hypertension, metabolic syndrome, cerebrovascular diseases, stroke, insulin resistance and T2DM, all triggered by a systemic, chronic inflammation, also called metabolic inflammation or metaflammation (Olefsky and Glass, 2010). It has been postulated that lipid hormones including sphingolipids and eicosanoids in concert with cytokines and adipokines play an important role in this process by inducing adverse regulatory responses in target cells such as macrophages. However, it has been

estimated that 30% to 70% of T2DM risk can be attributed to genetic background (Poulsen et al., 1999). Therefore, the investigation of gene-environment interactions holds promise in shedding light on the interplay between environmental factors and genetics (Cornelis and Hu, 2012).

Genome-wide associations studies between genetic variants and traits has become an essential approach in identifying disease-causative genes. Genome wide single nucleotide polymorphism (SNP) typing technology applied to large sample sets has provided insights into the pathogenesis of T2DM (http://www.genome.gov/gwastudies/). However, the identification of these loci does not contribute to the clinical prediction of diabetes beyond that of traditional risk factors, such as sedentary lifestyle, obesity, or family history of diabetes. Nevertheless, the recent identification of a genomic SNP pattern providing insights into the mechanisms underlying obesity will enable a deeper understanding of the association between SNPs and lifestyle factors (Locke et al., 2015; Shungin et al., 2015). Furthermore, genome-wide association studies are beginning to unravel the genetic contribution to human metabolic individuality by analysing the clinical associations between SNPs and so-called intermediate phenotypes (Bictash et al., 2010; Illig et al., 2010; Teslovich et al., 2010; Suhre et al., 2011; Kettunen et al., 2012).

Nutrition and Neurodegenerative Diseases

Trace elements: iron

Iron status is involved in the pathophysiology of a series of conditions found in elderly people, both men and women. The correlation between low levels of haemoglobin and high levels of ferritin might be related to an increased disease pathology, even though iron status seems to be the result, not the cause, of these changes. Many studies are highlighting iron homeostasis in mitochondria and the impact of inflammation on iron overload in neurodegenerative diseases. An excess of redox-active iron in the mitochondrial redox-active pool, will result in an overproduction of hydroxyl radicals and an increment in oxidative stress. Then again, lack of iron will impede various processes which utilize iron as a cofactor (Urrutia et al., 2014). Another study published in 2018 by Wawer and his colleagues which investigated if Parkinson's disease (PD) patients with sleep behaviour disorder have different patterns of neurodegeneration when compared to patients without sleep behaviour disorder, suggests that there is a positive association between unified PD rating scale (UPDRS III) score and iron levels and between iron levels and inflammatory markers (Wawer et al., 2018).

Long chain polyunsaturated fatty acids

Regarding the influence of diet and lifestyle variables on PD severity, Mischley and her colleagues conducted a study, which aimed to describe how modifiable lifestyle factors can influence the rate of progression of PD. They included in the study with 1053 participants, who had a diagnosis of idiopathic PD. To assess PD severity, an assessment tool was used for patient-reported outcomes in PD. To quantify dietary intake, a food frequency questionnaire was developed. The lowest PD severity score was associated with plant and fish-based diets. Only coenzyme Q10 and fish oil among nutritional supplements had a statistically significant correlation with PD, reducing rates of PD progression. Regarding nutritional behaviours, patients who prepared their meals by themselves had a protection against PD whereas those who bought their meals from local markets or ate out had lower patient-reported outcomes in PD scores (Mischley et al., 2017).

Oxidative stress, anti-oxidants and neurodegenerative diseases

It is known that oxidative stress plays an important role in the ageing process and neurodegenerative diseases. As it is a powerful antioxidant, the neuroprotective properties of ascorbic acid mitigate neuroinflammation and amyloid-beta peptide deposition by trapping free radicals and suppressing the expression of pro-inflammatory genes. In a recent study, Kim et al. (2015) investigated the effects of high-dose ascorbic acid supplementation (1250 mg/d) in humans. Thus, supplementation of daily food with ascorbic acid for eight weeks, led to a reduction in advanced glycation end products, especially in non-smoking men. The reduction inglycation end products was also associated with an improvement in the levels of plasma high-density lipoprotein and an improvement in low-density lipoprotein composition. Therefore, supplementation with ascorbic acid could exert protective effects against atherosclerosis and related systemic inflammation by reducing conversion of macrophages to foam cells. At a molecular level, this study demonstrated that ascorbic acid negatively regulates post-transcriptional expression of several microRNAs. Thus, ascorbic acid consumption led to a 90% decrease in miR155 levels, suggesting that high doses of ascorbic acid may significantly diminish inflammation by modulating miRNA levels (Kim et al., 2015).

An association between cognitive impairment and antioxidant capacity has been suggested by many studies (Soysal et al., 2017). Even though, in large population studies, the correlation between ascorbic acid intake and neuroprotection in the onset of Alzheimer's disease (AD) has not yet been demonstrated, a synergic association between ascorbic acid and vitamin E supplementation was shown to have a preventive action on AD (Monacelli et al., 2017).

A study conducted in 2016 used a mouse AD model (APPswe/PS1dE9 double transgenic mice) in order to observe the anti-oxidative effects of curcuma at the level of synapse-associated proteins. The treatment was administered for 6 months, the results showing an amelioration of the quantity and ultrastructure of synapses. The expression of PSD95 and Shank1 was decreased in the hippocampus CA1 area of the transgenic mice shown by western blot assay and immunohistochemistry techniques, as compared to the treatment group, which showed an increased expression of the proteins. This finding indicated that curcuma consumption could improve the function and structure of synapses through the regulation of PSD95 and Shank1 proteins (Feng

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et al., 2016). Another study using the same AD mouse model focuses on the mechanism involved in impaired insulin signaling and insulin resistance. The immunohistochemistry techniques and western blot analyses demonstrated that the expression of phosphatidylinositol-3 kinase, serine-threonine kinase and their phosphorylated forms increased, while insulin receptor and insulin receptor substrate-1 were lower in the CA1 area of the hippocampus. The animals received one of 3 doses of curcuma (400, 200 or 100 mg/kg per day) for 6 months, the most effective dose being the medium one among the treatment groups (Wang et al., 2017).

Using the same curcuma doses (400, 200 or 100 mg/kg per day), a more recent study of double transgenic mice investigated both signaling pathways and glucose metabolism regulation in the brain as well as the learning and memory ability. Glucose metabolism was monitored using PET-CT techniques with images that 3 months after the treatment showed a higher average glucose metabolism in the treated group. Immunohistochemistry staining and western blot analyses showed up-regulation of insulin-like growth factor 1, insulin receptor substrate 2, phosphatidylinositol-3 kinase, serine-threonine kinase and their phosphorylated forms but decreased insulin receptor and insulin receptor substrate 1 (Matsuda et al., 2018).

Smoking and neurodegenerative diseases

A recent analysis of the impact of 24 modifiable factors on the incidence of AD suggested an association between AD and education i.e., genetically predicted higher educational attainment was associated with fewer AD cases. Regarding lifestyles and dietary factors, the results for smoking, coffee consumption and 25(OH) vitamin D were significantly associated with AD as follows: higher numbers of cigarettes smoked gave lower odds for AD, higher 25(OH) vitamin D concentrations gave lower odds for AD and higher consumption of coffee gave higher odds for AD (Larsson et al., 2017).

Frontotemporal dementia and alcohol, tobacco and coffee abuse

A multicentre case-control retrospective study analysed alcohol, tobacco and coffee consumption among 151 patients with frontotemporal dementia and their matching controls. There was no association between coffee and tobacco use and frontotemporal dementia, but alcohol intake decreased the risk of frontotemporal dementia, with a significant reduction for current alcohol users. Furthermore, there was an inverse correlation with the years of exposure to alcohol. However, the amount of alcohol consumed was not given in the study (Tremolizzo et al., 2017).

Cardio-metabolic and inflammatory factors and neurodegenerative diseases

The aim of one study was to see the effects of cardio-metabolic factors on PD progression and survival. One hundred and fifty patients were evaluated for body mass index, body fat percentage, waist circumference and impedance, serum lipids, fasting glucose and transaminases. A direct inverse correlation was found between PD duration and body fat percentage, as well as body mass index. On the other hand, higher levels of high-density lipoprotein levels which are supposed to be protective, were associated with an increased duration of the disease. No other correlations were statistically significant in this study (Cassani et al., 2013).

With regard to cardiometabolic and inflammatory factors, the study highlighted that body mass index, high-density lipoprotein and C-reactive protein levels were inversely associated with AD incidence, while low-density lipoprotein and total cholesterol were positively associated with it (Larsson et al., 2017).

In a population-based autopsy study conducted by Dublin et al. (2017), patients with atrial fibrillation were more likely to have AD, than those without atrial fibrillation, apparently because atrial fibrillation was not associated with AD neuropathological changes. However, none of these associations were statistically significant.

About 25% of all human body cholesterol is found in the brain. Since cholesterol levels in brain influence the synthesis, clearance and toxicity of amyloid-β peptide, a recent study aimed to analyse the direct relationship between serum levels of cholesterol and amyloid-β deposition in the brain. Data from the study showed that higher levels of low-density lipoprotein and lower levels high-density lipoprotein were both associated with greater deposition of brain amyloid, independently of Apo E genotype (Reed et al., 2014).

A recent study followed the prevalence of cardio-metabolic factors in a group of 58 patients diagnosed with amyotrophic lateral sclerosis (ALS) compared to the general population. ALS patients expressed a good cardiometabolic profile, with heart rate, blood pressure, PR and QT intervals in the normal range. Body mass index analysis revealed that there were fewer obese women and more men within the normal body mass index interval in the ALS group compared to the general population. Both of these were statistically significant. Dyslipidaemia was less frequent and a higher number of individuals never smoked in the ALS cohort than in the general population (Timmins et al., 2017).

Dementia, stroke and glucose metabolism

Pase and colleagues studied the Framingham Heart Study Offspring cohort of 5124 volunteers, comprising 9 cycles of examination, every 4 years, starting in 1971 and concluding in 2014. Regarding the sugar- and artificially-sweetened beverages, the participants responded to a Harvard semi-quantitative food frequency questionnaire that included several types of beverage and their frequency of consumption in the previous year. The results show a correlation between increased intake of artificially sweetened drinks and a higher risk for stroke and dementia. Total sugary beverages or sugar sweetened soft drinks were also associated with an increased risk for dementia or stroke (Pase et al., 2017).

In 2017, a study was published that investigated the effects of long-term administration of regular or long-acting insulin on biomarkers of AD. The results of this randomized, dou-

ble-blind, placebo-controlled study showed that the regular insulin-treated group had improved memories after two months of treatment. No significant effects were observed in the long-acting insulin treated group (Craft et al., 2017).

A prospective cohort study over 19 months followed 450 sporadic amyotrophic lateral sclerosis patients, 223 of whom died. The baseline included the lab findings for HbA1c and fasting blood glucose at the first meeting. A higher risk of mortality was associated with increased baseline levels of HbA1c, with a direct correlation between them, each additional unit (%) of HbA1c augmenting the risk of mortality by 50%. No significant association was found between fasting blood glucose levels and the risk of mortality, even though a similar trend was observed (Wei et al., 2017).

A study conducted on data from the Danish Registers system showed a protective association between prior diabetes diagnosis and ALS. Obesity in unadjusted and adjusted models for other risk factors showed the same correlation, but when diabetes was taken into consideration, the association was weaker and no longer significant. This does not apply for diabetes, which remains protective regardless of the obesity indicator. No significant association was observed between hypercholesterolaemia or hyperlipidaemia and ALS diagnosis (Kioumourtzoglou et al., 2015). A study on data from the Swedish Patient Register found an inverse association between prior diabetes diagnosis and ALS, with similar results after adjusting for socioeconomic status and education. The association was powerful for the noninsulin dependent cases, but not for the insulin dependent ones, which also correlated with age at diabetes diagnosis. An inverse correlation was observed for older individuals, i.e., in the under 50 years old group insulin dependent diabetes implies a higher risk for ALS (Mariosa et al., 2015).

Obesity, inflammation and rehabilitation odds in stroke patients

The obesity paradox has been described as an inverse relationship between body mass index and mortality in stroke patients (Olsen et al., 2008; Towfighi and Ovbiagele, 2009; Ovbiagele et al., 2011; Ryu et al., 2011; Vemmos et al., 2011; Andersen and Olsen, 2015). Thus, a cohort study from the China National Stroke Registry analyzed the relationship between body mass index, mortality and post-stroke functional recovery at 3 months after disease onset in 10,905 patients with acute ischemic stroke. Favourable functional recovery was seen in 52.4% of underweight (body mass index 18.5 kg/m^2), 55% of normal weight (body mass index 18.5–22.9 kg/m^2), 61% of overweight (body mass index 23–27.4 kg/m^2), 59,2% of obese (27.5–32.4 kg/m^2) and 60.3% of severely obese (body mass index > 32.5 kg/m^2) stroke survivors. Indeed, obesity, but not severe obesity, showed a protective trend in terms of 3-month functional recovery in the AIS survivors. Severe obesity was associated with higher mortality at 3 months after stroke (Zhao et al., 2014).

Another study has focused on the effect of body mass index on stroke rehabilitation in 819 patients admitted to an acute rehabilitation hospital. Again, overweight patients had better functional progression than did patients in other weight categories (Burke et al., 2014).

Yet another study that included 510 patients with transient ischemic attack, showed that excess adiposity increases the risk of severe disability after ischemic stroke. Contradictory results were reported in a study from 2007, showing that functional improvement was better in patients of normal weight than that in overweight/obese patients (Razinia et al., 2007).

More recently, in a large retrospective cohort study from the Danish Stroke Register, 53,812 patients were analysed for correlations between obesity and age, sex, stroke severity, body mass index, cardiovascular profile, stroke subtype, and socioeconomic status. Although stroke incidence was higher in younger age patients with higher body mass index, a clear correlation could not be found in favour of the obesity paradox.

Finally, still another study on 451 patients hospitalized for ischemic stroke found no correlation between body mass index on admission and functional recovery on discharge (Tanizaki et al., 2000; Downes and Crack, 2010). Thus, it is risky to conclude that there is a protective effect of obesity alone on functional recovery after stroke. However, since patients with high body mass index seemed to have had less severe strokes (Ryu et al., 2011), it seems that the association between higher body mass index and favourable functional recovery might be influenced by stroke severity and some degree of adiposity is necessary to prevent severe disability in stroke survivors (Chiquete et al., 2010).

Using a C57B6/J mouse model maintained on normal or high fat diets with different levels of testosterone, Jayaraman et al. (2014) demonstrated that testosterone depletion exacerbates the negative effects on both metabolic and proinflammatory responses in the diet-induced obesity group.

Caloric restriction and rehabilitation odds in stroke patients

Caloric restriction is an important promoter of autophagy process and previous studies have demonstrated that non-pharmaceutical intervention can contribute to life-span extension in various organisms (Bishop and Guarente, 2007; Colman et al., 2009). Some recent studies reported positive effects of caloric restriction on primates by lowering age-related mortality and the incidence of age-related diseases (Colman et al., 2009). *In vivo* animal models also suggest that caloric restriction reduces the incidence of AD and PD (Fontana et al., 2010; Hutchison and Mattson, 2010).

Metabolic syndrome and neuroregeneration

Dietary and life habits along with food abundance and high income can lead to hypothalamus-mediated energy imbalance and weight gain. At the molecular level, hypothalamic O-GlcNAc transferase, which is a known intracellular sensor of glucose metabolism catalysing the transfer of β-N-acetylglucosamine from uridine-diphosphate-β-N-acetylglucosamine to the hydroxyl group of serine or threonine residues of nucleocytoplasmic proteins, controls body weight. In an experimental study, it could be shown that O-β-N-acetyl-

glucosamine transferase knock out exacerbated obesity and insulin resistance induced by a high-fat diet in adult mice. The feeding behaviour was accompanied by neuronal cell death including leptin receptor-expressing neurones, in the hypothalamus (Dai et al., 2018).

Moran et al. (2015) examined if there was a link between in vivo neurodegeneration biomarkers and T2DM. To this end they investigated a cohort of 124 patients with T2DM and 692 controls. They found that there was a statistically significant association between T2DM and p-tau protein levels in cerebrospinal fluid.

Chronic hyperglycemia in DM may lead to impaired neurogenesis and cognition deficits (Yu et al., 2019). The underlying mechanism could be long noncoding RNA (lncRNA)-induced apoptosis of hippocampal neurons. LncRNA H19, noncoding RNAs with lengths greater than 200 nucleotides, are implicated in development and growth control (Yu et al., 2019). A more recent study has shown that lncRNA H19 were upregulated in an experimental model of DM and induced apoptosis of hippocampal neurones by stimulating methylation in the promoter region of the IGF2 gene. At the same time, lncRNA H19 increased the expression of the anti-apoptotic factor Bcl-2 (Gao et al., 2014).

Physical activity and neurodegenerative protection

Stephen et al. (2017) reviewed the specific literature in order to investigate the association between AD and physical activity. Since AD is a multifactorial pathology, focusing on physical activity only in AD prevention has shown no beneficial results. Previous studies which included single lifestyle factor changes - physical activity (Ball et al., 2002; Lautenschlageret al., 2008; Sink et al., 2015), management of cardiovascular factors (Qiu et al., 2005; Ruitenberg et al., 2005) and diet (Martínez-Lapiscina et al., 2013) showed no or little benefit. The LIFE study showed no improvement in cognitive function in the group undergoing moderate-intensity physical activity compared with a healthy education group (Stephen et al., 2017).

More recent studies found a positive effect of 6 weeks aerobic exercise on functional ability compared to AD individuals versus the groups undergoing non-aerobic stretching and tonic control program. Aerobic training was associated with an increased performance in a 6-minute walking test as compared to control groups. Results from this study also showed an association between changes in peak VO_2 and changes in memory composite score with changes in bilateral hippocampal volume (Morris et al., 2017).

Conclusions

Lifestyle including high sugar diets, alcohol and tobacco addiction or high fat diets as well as some intrinsic factors such as ageing, neuroinflammation, brain injury and oxidative stress, negatively influence the onset, severity and duration of neurodegenerative diseases (**Figure 1**). Fortunately, there are several healthy dietary components such as polyunsaturated fatty acids and the anti-oxidants curcumin, resveratrol, blueberry polyphenols, sulphoraphane, salvionic acid as well as caloric restriction and physical activity which may counteract ageing and associated neurodegenerative diseases via increased autophagy (Fîlfan et al., 2017; Madeo et al., 2018) or increased neurogenesis in the adult brain (**Table 1**).

Author contributions: *Literature on dietary habits: DID, BC; literature on the lifestyle section: EBP and RS; literature on neurodegenerative diseases: DAD; manuscript design and editing: APW and WHF. All authors approved the final manuscript.*
Conflicts of interest: *The authors declare no conflicts of interest.*
Financial support: *None.*
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Peer review: *Externally peer reviewed.*

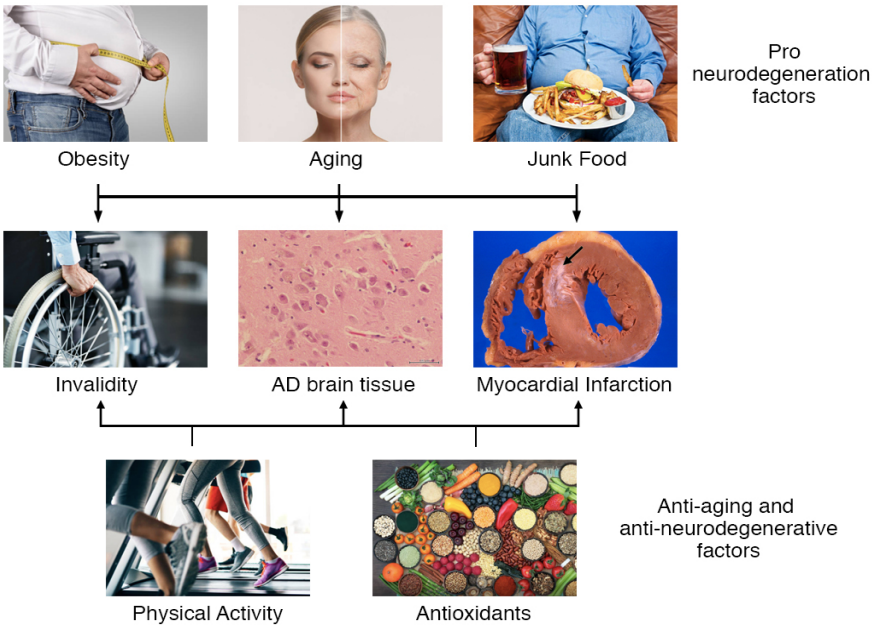


Figure 1 Prodegeneration factors including ageing, obesity and unhealthy diets could be balanced by physical activity, caloric restriction, and anti-oxidants to mitigate the onset, severity and duration of neurodegenerative diseases.
AD: Alzheimer's disease.

Table 1 The impact of life style and the severity of neurodegenerative diseases

Factor	AD	T2DM	Stroke	PD	ALS
Physical activity	+++	+	?	+	?
Calorie restriction	++	++	+	?	?
Alcohol consumption	–	++	–	+	–
Fatty Diet		++	+	–	–
Iron	–	–	–	+	–
Oxidative stress	–	+	–	+	+
Trace elements	–	–	–	+	–
Polyunsaturated fatty acids	–	–	–	–	–
Smoking	–	–	?	–	–
Coffee	+	–	–	–	–
High HDL-C	–	–	–	+	–
Low HDL	+	–	–	–	–
High LDL	+	+	+	–	–
Sugary beverages	–	+	+	–	–

AD: Alzheimer's disease; ALS: amyotrophic lateral sclerosis; HDL: high-density lipoprotein; HDL-C: high-density lipoprotein cholesterol; LDL: low-density lipoprotein; PD: Parkinson's disease; T2DM: type 2 diabetes mellitus.

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C-Editors: Zhao M, Li JY; T-Editor: Jia Y