Neurodegenerative Diseases

Overview

Research suggests that a lifelong, regular and moderate intake of coffee/caffeine may have an effect on physiological, age-related cognitive decline: in women, and those over 80 years old in particular[1-23]. Moderate coffee consumption is typically defined as 3-5 cups per day, based on the European Food Safety Authority's review of caffeine safety[24].

In the case of Alzheimer's Disease (AD), research points to an inverse association between lifelong coffee consumption and the risk of developing this condition[24-35]. However, as research in this area is still limited, further studies are required. A number of studies have suggested that caffeine may be involved in the observed effect[36-41], but other coffee constituents such as trigonelline[42-44] and polyphenols[45-46] are also of interest.

Epidemiological studies also suggest an inverse association between coffee consumption and the risk of developing Parkinson's Disease (PD) [47-63]. Research has indicated that caffeine may be involved in the potential preventative effect coffee consumption has on PD[54,64-67]. Caffeine may play a role by antagonising adenosine A2A receptors. Such antagonists are thought to have neuro-protective properties[54,68-70]. Several studies have also reported that coffee consumption may have a protective effect on the risk of stroke[71-76], especially in women[72].

The content in this Overview was last edited in July 2019. Papers in the Latest Research section and further resources are added regularly.

Background Information

Cognitive functions remain relatively stable until an individual reaches approximately 60 years old, at which point they tend to slow down, particularly between 60 and 80 years[77]. There is some evidence that brain function can start to deteriorate as early as 45 years old. In addition, older adults are susceptible to developing neurodegenerative disorders, including Alzheimer's and Parkinson's diseases, for which there is no treatment at present[77].

This has triggered extensive research into various preventative factors, mainly related to diet and lifestyle. Caffeine is known to have stimulating properties on human cognitive function, including positive effects on alertness and concentration[78], learning, memory and mood[79]. Caffeine is also known to stimulate motor activity in animals and humans. Because of these properties, caffeine is considered a likely candidate for delaying and/or preventing physiological, age-related cognitive decline as well as a number of

neurodegenerative disorders – Alzheimer's and Parkinson's Diseases, as well as stroke. However, more research is needed before any firm conclusions can be drawn.

Caffeine and Cognitive performance

Unhealthy lifestyles, vascular diseases, genetic factors, oxidative stress and inflammation all accelerate cognitive decline and suggest that cognitive decline could, at least partly, be modifiable. It has been hypothesized that caffeine could, in part, compensate for this decline because of its effects on vigilance, mainly in situations of reduced alertness[80-83]. However, young and elderly subjects appear to respond to the effects of caffeine differently.

Two early studies on both elderly and adult subjects found that caffeine improves attention span, psychomotor performance and cognitive function, as well as feelings of well-being in the elderly. The elderly appeared more sensitive to the protective effects of caffeine on declining mental performance over time than younger subjects[1,2].

In younger subjects (18-37 years), caffeine has been shown to improve performance during distraction, rather than during simple tasks. In elderly subjects (60-75 years) however, caffeine improved performance during more complex tasks requiring sustained attention. Interestingly, improving performance during complex tasks is usually less effective in elderly subjects than in younger participants[3].
It is suggested that caffeine may help to reverse the effects of cognitive aging by stimulating the energy resources of elderly subjects[4].

A British study of 9,003 adult subjects reported a dose-related improvement in cognitive performance with higher levels of coffee consumption. Higher overall caffeine consumption (from coffee and tea) improved simple and choice reaction times, incidental verbal memory and visuo-spatial reasoning. Older people appeared more susceptible to the performance-enhancing effects of caffeine on mental performance than the younger subjects[5].

Analysis from the Baltimore Longitudinal Study of Aging, a prospective cohort study, also suggested that caffeine intake was associated with better baseline cognition in adults over 70 years of age[6]. Two Dutch studies on subjects aged 24-81 years also found positive effects of caffeine on cognition, mainly reaction time and verbal memory, but no age-related differences were observed[7,8].

Other components in coffee may also enhance cognitive performance in older adults. A pilot study on 39 healthy participants, aged 53-79 years, found that decaffeinated coffee enriched with chlorogenic acids improved mood and some mood-related behaviours, compared to regular decaffeinated coffee. The effect was less robust than the one triggered by caffeine, but reflects the potential cognitive-related activity of chlorogenic acids and warrants further investigation[9].

Effects of coffee on cognitive decline

Further studies have considered the specific effect of coffee consumption, suggesting that habitual coffee consumption may boost the cognitive reserve of older adults, particularly in women.

A 2010 meta-analysis of 9 studies looked at the effects of coffee/caffeine on different measures of cognitive impairment and/or decline including AD, cognitive impairment and cognitive decline. The authors found a reduced risk of cognitive decline across different measures of cognitive impairment (mean risk ratio 0.84) with caffeine intake, with moderate heterogeneity[10]. Although the outcome of this meta-analysis ranged from cognitive decline to AD, the analyses showed a clear protective role of coffee. It should be noted that many papers devoted to the effects of coffee on age-related cognitive decline were not included in this review.

A further systematic literature review published in 2013 suggested that, for all studies on tea and most of those on coffee, estimates of cognitive decline were lower among consumers but there was no evidence of a dose response. Research has also suggested a stronger effect in women than men[11].

However, a 2018 meta-analysis of prospective studies indicated no statistically significant association between coffee consumption and the risk of dementia[12].

A number of large studies have also considered associations between coffee intake and cognitive decline.

- The Rancho Bernardo study with 1,538 participants – 890 healthy women and 638 healthy men from South California with a mean age of 73 years – reported that higher caffeine consumption in a lifetime was associated with better performance in women in 6 out of 12 cognitive tests, with a trend in two other tests. Among women aged 80 or older, lifetime coffee intake was associated with better performance in 11 out of 12 tests. Current caffeinated coffee intake was also associated with improved performance. No relation was found between coffee intake and cognitive function in men, or between decaffeinated coffee intake and cognitive function in either sex[13].

- The longitudinal prospective Three City cohort study of 4,197 healthy women and 2,820 healthy men over 65 years, suggested that women consuming more than 3 cups of caffeinated coffee per day for 4 years showed a smaller decline in verbal retrieval and visuo-spatial memory than women consuming one cup of coffee or less per day. The protective effect of caffeine increased with age, with a maximal effect in women over 80 years. No relation was found between caffeine intake and cognitive decline in men[14].

- A cohort of 648 adults aged 65 years old and living in Portugal, with a caffeine intake of more than 62 mg/day (the equivalent of 1 regular cup or more) compared to less than 22 mg/day was associated with a lower risk of cognitive decline in women only[15].

- Another study of 4,809 participants aged 65 and older suggested that subjects who did not consume tea or coffee declined mentally every year by 1.30 points (women) and 1.11 points (men) on standard scores. In fully adjusted models, tea, coffee or caffeine consumption modestly attenuated the rate of cognitive decline in women, with no consistent effect on men[16].

- A further prospective study looked at the 10-year cognitive decline of 676 healthy men born between 1900 and 1920 in three European countries (Finland, Italy and The Netherlands). Men who consumed coffee experienced a 10-year cognitive decline of 4%. Non-coffee drinkers experienced an additional decline of 4.7%. The authors reported an inverse J-shaped curve between the number of cups of coffee consumed and the extent of cognitive decline, with the lowest cognitive decline (2%) reported for 3 daily cups of coffee. This decline was 4.3 times smaller than in non-coffee drinkers[17].

- A cohort study of 923 healthy adults from Scotland (Lothian Birth Control 1936 Study), assessed the IQ of children at 11 years old and latterly at the age of 70. The authors found association between total caffeine intake (through coffee, tea, and dietary caffeine) and general cognitive ability and memory. After adjustment for IQ at age 11 and social class, a robust positive association remained between drinking ground coffee (filter or espresso) and reading performance. No gender effects were observed, contrary to several previous studies[18].

- A general survey performed in Taiwan found that among all lifestyle factors examined, there was an inverse relationship between cognitive impairment and the intake of vegetables and fruits, coffee, and tea. The authors considered that the subjects who did not drink coffee were at a significantly higher risk of cognitive impairment[19].

- Further work as part of the Women's Antioxidant Cardiovascular Study showed that consumption of caffeinated coffee but not other caffeinated products such as tea, cola and chocolate, was significantly related to slower cognitive decline in older women with vascular disorders[20].

Research suggests that regular coffee/caffeine consumption can help to reduce cognitive decline in older adults, particularly women. Further research is required to clarify the differences between men and women, and potential mechanisms.

Coffee and Alzheimer's Disease

Background

Alzheimer's Disease (AD) is the most frequent cause of dementia. It is estimated that between 50-70% of people with dementia suffer from AD[84-87]. In addition, approximately one person out of 20 over the age of 65 suffers from AD, as opposed to less than one person in a thousand under the age of 65[85]. Approximately 44 million people globally suffer from AD[86]. The 2015 World Alzheimer's Report suggested that approximately 10.5 million people in Europe suffer with AD and the number is predicted to increase to 13.4 million by 2030 and to 18.7 million by 2050[87].

In 2014 Alzheimer Europe published an updated systematic review of papers reporting the prevalence of dementia. The authors concluded that that for the majority of age groups, dementia prevalence has not changed significantly over the last few decades. However, they did report a higher prevalence in older females than was previously thought[88].

AD, a neurodegenerative disease, leads to progressive cognitive decline and the accumulation of β-amyloïd peptide (Aβ) in the brain. Some forms of AD are due to the mutation of genes coding for the precursor of Aβ, presenilin 1 and 2. Genetic factors interact with surrounding environmental factors and the influence of these additional factors, deleterious or protective, remains largely unknown[89].

Coffee, caffeine and risk of Alzheimer's disease

The majority of studies suggest that regular coffee/caffeine consumption over a lifetime reduces the risk of developing AD, particularly in the elderly, however some studies show varying results. It seems that coffee/caffeine consumption may be particularly beneficial before the occurrence of the disease i.e. during the pre-morbid phase.

A number of meta-analyses and reviews have been undertaken which together support the view that coffee consumption is associated with a reduced risk of AD.

- A 2007 review of observational studies suggested that coffee consumption was associated with a reduced risk of AD by approximately by 30% as compared to non-coffee consumers[29]. Four studies carried out between 1990 and 2002 were included in this review (2 case-control and 2 cohort studies)[25-28]. Overall, the

results suggested a protective effect of coffee consumption, however, there was a large heterogeneity across the studies.

- A further meta-analysis of the relation between coffee/caffeine intake and the risk of AD, suggested that the summary risk ratio reached 0.80-0.83 for Alzheimer's disease after adjustment for smoking and hypertension[10].

- A 2010 review also suggested that daily intake of 3-5 cups of coffee in middle age may lower the risk of the dementia and AD by about 65% as compared to lower amounts of coffee. However, the author also highlighted the fact that some findings are inconsistent[30].

- A 2017 review concluded that reports indicate that moderate coffee consumption may in fact lower the risk for common neurodegenerative conditions including AD. However, the authors concluded that methodological differences in studies mean comparisons and conclusions can be difficult to reach and further well constructed research is required[31].

- A 2017 theoretical review suggested an association between genetically predicted higher coffee consumption and higher odds of AD. The role of genetic polymorphisms in diet and disease warrants further investigation[32].

- A further 2018 meta- analysis of prospective studies that focused on Alzheimer's disease revealed no association between coffee consumption and Alzheimer's disease and no deviations from a linear trend. The relative risk of Alzheimer's disease per 1 cup/day increment of coffee consumption was 1.01[12].

Larger studies that have also considered associations between coffee consumption and AD.

- A study of 4,615 subjects followed over 5 years (194 AD cases, 3,894 cognitively 'normal' controls, and 527 exclusions) found that the use of non-steroidal anti-inflammatory drugs, wine consumption, coffee consumption, and regular physical activity were associated with a reduced risk of AD (risk ratio of 0.69 for coffee). Interestingly, there was no protection for tea consumers in this study[26].

- A further study of 1,409 individuals aged 65 to 79 were examined after 21 years' follow-up. Coffee consumption in midlife decreased the risk of AD and dementia in the elderly, with the lowest risk (65% decrease) found in people who drank 3-5 cups/day[33].

However, other studies have not shown an association between coffee consumption and a reduced risk of AD. Both a Finnish study[34] and the Honolulu-Asia Aging Study[35], found no link between coffee consumption and dementia or cognitive impairment.

Mechanism of action for caffeine

A number of animal studies point to possible mechanisms of action behind coffee/caffeine's effects on AD risk.

In one study, caffeine in drinking water, given to transgenic mice that develop AD-like symptoms around 8 months of age, improved learning and memory and reduced the concentration of Aβ peptide and presenilin in the hippocampus, the main brain structure involved in memory[36].

Moreover, these effects were also found when caffeine treatment was started late i.e. once the mice had already developed cognitive deficits. Caffeine seemed to act by reducing the mediators of inflammation[37,38].

Caffeinated coffee increased plasma levels of granulocyte-colony stimulating factor (GCSF), which seemed to improve the cognitive performance of AD transgenic mice with the recruitment of bone marrow cells, enhanced synaptogenesis, and increased neurogenesis. Neither a caffeine solution alone, nor decaffeinated coffee, provided this effect. The authors hypothesize that caffeine might interact with another component in coffee to selectively elevate GCSF[39].

Caffeine may also be active at a different level. In an animal study, the long-term consumption of caffeine in drinking water by rats increased cerebrospinal fluid (CSF) production and cerebral blood flow, which directly affects the production of CSF[35]. Defective CSF production and turnover, with diminished clearance of Aβ, may be one mechanism implicated in the pathogenesis of AD[36]. This may partly explain the caffeine-induced reduction of brain levels of Aβ peptide although it is not yet known whether this effect also occurs in humans[40,41].

A further hypothesis suggests that the modulation of adenosine receptors, namely, the A_{2A}receptor, affords neuroprotection through the control of microglia reactivity and neuroinflammation. Again, further work is required to explore this hypothesis[42].

A role for other coffee constituents

Other coffee constituents, which may be involved in coffee's beneficial effect on AD risk, besides caffeine, have also been studied.

Several animal studies suggest that trigonelline may have neuro-protective properties and improve memory retention[43-45].

The polyphenol antioxidant ferulic acid found in coffee, given to mice in drinking water, has been found to protect against cognitive deficits, mainly spatial and working memory, suppress inflammation and prevent the loss of acetylcholine from the cerebral cortex – all factors that characterize the disease[46].

There is an increasing number of experimental and human scientific studies suggesting a potentially protective role for caffeine – and potentially also for other coffee compounds e.g. anti-oxidants or anti-inflammatory agents – in the development of AD. However, further studies aimed at identifying the different coffee compounds that appear to be active against the disease, and the mechanism of action, are needed before firm conclusions can be drawn.

Coffee and Parkinson's disease

Background

Parkinson's Disease (PD) is a debilitating neurodegenerative disorder. In Europe, almost 1.2 million people are estimated to have PD, with about 75,000 new cases diagnosed every year[90]. The age of onset of PD is usually over 60, but it is estimated that one in 10 cases are diagnosed before the age of 50, with slightly more men than women affected[91].

The cardinal features of PD are the slowing down of motor function, resting tremor, muscular rigidity, gait disturbances, and postural reflex impairment. The underlying pathological lesion is the progressive destruction of dopaminergic neurons in the midbrain. There is currently no available treatment to either prevent or slow down this neuronal loss and the resulting dopamine decrease in the midbrain.
Experimental and epidemiological research has focused on lifestyle, dietary and environmental risk factors, including coffee consumption.

Coffee, caffeine and risk of Parkinson's disease

A large number of epidemiological studies report an inverse, dose-responsive relationship between coffee/caffeine consumption and the risk of developing PD. Coffee consumption appears to reduce or delay the development of PD and caffeine is most likely the causal factor. In women, however, the interaction between caffeine and hormonal therapy still needs further clarification.

As early as 1968, a study reported a higher percentage of non-coffee consumers in the control compared to the affected group[47]. Subsequent studies performed in Spain[48], Sweden[49] and Germany[50] found an inverse relationship between coffee consumption and PD, and a lower coffee consumption before disease onset.

The first prospective study on 8,004 Japanese American men living in Hawaii (the Honolulu Heart Program), carried out over a median duration of 27 years, reported an inverse association between PD incidence with a five-fold reduced risk for those drinking more than 4 cups of coffee per day when compared to non-consumers. The same inverse relationship was shown for caffeine from non-coffee sources[51]. A smaller case control study published in 2014 suggested only a weak inverse association between coffee intake and the risk of PD[52].

A number of meta-analyses and reviews have been undertaken which together support the view that coffee consumption is associated with a reduced risk of Parkinson's Disease.

- A 2002 meta-analysis of 20 studies reported that the global risk of developing PD decreased by 31% (relative risk 0.69)[53] in coffee drinkers compared to non-coffee drinkers. Some of the individual studies found very strong risk reductions, up to 80% with the consumption of over 4 cups of coffee per day.
- A further 2010 meta-analysis of 26 studies[54] found that the overall risk of developing PD fell by 24-32% per 300 mg increase in caffeine intake (i.e. with every 3 cups of coffee, approximately).
- A 2012 review of 304,980 participants in the National Institutes of Health-AARP Diet and Health Study suggested that higher caffeine intake was associated with subsequent lower PD risk in both men and women. The authors conducted a meta-analysis of prospective studies and confirmed that caffeine intake was inversely associated with PD risk in both men and women and suggested that there was no gender difference in the relation between caffeine and PD[55].
- A 2014 dose, response meta-analysis showed a linear relationship between risk reduction of PD with tea and caffeine consumption, however, the association with coffee intake reached a maximum at approximately 3 cups of coffee a day[56].
- A 2018 literature review also confirmed that most reports indicate that moderate coffee consumption may in fact lower the risk for common neurodegenerative conditions, including PD[31].

In women, the data are more equivocal. One study found a U-shaped relation, with moderate consumption of coffee/caffeine being the most protective[57-59]. Postmenopausal hormone use seems to affect the impact of coffee consumption on risk of PD.

A study performed on 77,713 women, followed up for 18 years, reported that in those not taking postmenopausal hormones (PMH), coffee was as protective against PD as in men. In women taking estrogens, the risk for PD was similar to men in case of low coffee consumption, but significantly increased four-fold in women drinking 6 or more cups of coffee a day when compared to non-coffee drinkers[57]. A case-control study, part of the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS), did not find convincing evidence that variations in the genes coding for caffeine metabolism (CYP1A2 and NAT2) or estrogen receptors (ESR1 and ESR2) could predict the risk of PD linked to hormone replacement therapy use[60].

Further analysis from the same data sets supported previous findings that increased caffeine intake may be associated with a decreased PD risk in men and also in women who have never used PMH[61].

Additional work has considered the effect of coffee consumption on the symptoms associated with PD. A randomised control trial evaluated the effects of caffeine intake on the symptoms of PD, including daytime somnolence, motor severity and other non-motor features. The results showed improved objective motor measures, but only equivocal effects of caffeine on somnolence in PD; further evidence is required[62]. A further study of non-motor symptoms in patients with PD suggested that coffee drinking was significantly inversely associated with the prevalence of lack of motivation, anhedonia, and lack of pleasure, which were less frequent in coffee drinkers. In particular, coffee drinking was significantly associated with a reduced severity of the mood/cognition domain of non-motor symptoms[63].

Mechanism of action

Experimental studies have identified a mechanism of action for caffeine's preventative role in the development of PD.

Low doses of caffeine antagonize mainly adenosine A2A receptors, which are located with D2 dopaminergic receptors in the striatum, i.e. the cerebral region involved in the control of locomotion and movement and in which dopaminergic neurontransmission is dramatically impaired in patients with PD. In the striatum, the blockade of A2A receptors increases motor activity and improves motor deficits in models of PD, via the stimulation of D2 receptors[64,65].

In animals, caffeine counteracts the symptoms of PD induced in rats and mice and enhances the effects of the classical treatment of PD, the precursor of dopamine, L-DOPA[66,67].

Data obtained from several preclinical studies point to the beneficial effects of chronic A2A receptor antagonists (such as caffeine) on PD motor disability and on motor

complications produced by long-term L-DOPA treatment, suggesting that they will be effective in the symptomatic treatment of PD58[54,67].

Moreover, the A2A antagonists, including caffeine and D2 agonists, have neuroprotective properties and can attenuate the degeneration of dopaminergic cells in various animal models[54,68].

The role of genetic polymorphisms has been considered in a number of areas. One assessment of PD incidence and prevalence with lifetime coffee consumption and polymorphisms in the ADORA2A and CYP1A2 suggested that associations with daily coffee consumption were strongest among carriers of variant alleles in both ADORA2A and CYP1A2[69]. However, a further study of interactions between GRIN2A and CYP1A2 polymorphisms did not show an interaction with caffeine intake in determining PD risk[70]. Clearly further research on genetic polymorphisms is required to understand the associations in more detail.

Coffee and stroke

The World Heart Federation states that every year 15 million people worldwide suffer a stroke. Nearly 6 million die and another 5 million are left permanently disabled. Stroke is the second leading cause of disability after dementia. Globally, stroke is the second leading cause of death above the age of 60 years, and the fifth leading cause of death in people aged 15 to 59 years old[92].

In many developed countries the incidence of stroke is declining even though the actual number of strokes is increasing because of the aging population. In the developing world, however, the incidence of stroke is increasing.

Research shows that moderate coffee consumption may reduce the risk of stroke, and limit the deleterious consequences of suffering a stroke.

A prospective study of 26,556 male Finnish smokers reported that the relative risk of developing a non-hemorrhagic stroke was significantly reduced by 12% with the consumption of 4-5 cups of coffee per day. The risk was reduced further to 23% in the heaviest consumers (≥ six cups per day) compared to those who drank less than 2 cups per day. However, coffee consumption did not protect against intra-cerebral or subarachnoid hemorrhage[71].

This association was extended to women in a study where 34,670 women were followed up prospectively. Coffee consumption (2-5 cups per day) was associated with a significant 22-25% risk reduction of total stroke, cerebral infarction, and subarachnoid hemorrhage but not intra-cerebral hemorrhage[72].

The prospective Nurses' Health Study of 83,076 women also reported a 20% reduced risk of stroke with the consumption of 2-4 cups coffee per day, compared to 1 cup per month. The association was stronger among never and past smokers, with a risk reduction of 43% with 4 cups a day. Other drinks containing caffeine, such as tea and caffeinated soft drinks, were not associated with stroke[73].

A 2011 meta-analysis including 11 prospective studies, with 10,003 cases of stroke among 479,689 participants, found that moderate coffee consumption may be weakly, non-linearly, inversely associated with risk of stroke[74].

In a further study, 10 patients who suffered a cortical stroke were given a caffeinol mixture injection (approximately 8-9 mg/kg caffeine – the equivalent of 5-7 cups of coffee – with 0.3-0.4 g/kg ethanol, or 2 doses of strong alcohol), and fibrinolysis with tissular plasminogen activator (t-PA), in the 134 min following the first clinical signs. The efficacy of the cocktail was optimal when administered during the first 95 minutes. Among the 10 patients treated with caffeinol, six had preserved activities and autonomy, while this was only the case in 26% of the 90 patients treated in a classical manner[75]. The mechanisms of action underlying these effects could involve the inhibition of adenosine receptors by caffeine, and the receptors of the main inhibitory neurotransmitter, GABA, by ethanol but await further validation.

A systematic review of stroke risk in relation to the consumption of different foods concluded that a high consumption of nuts, fruits, vegetables, dairy foods, fish and tea, and moderate consumption of coffee and chocolate demonstrated a protective effect against stroke risk[76].

Conclusion

The lifelong, regular and moderate intake of coffee/caffeine (the equivalent of 3-5 regular cups of caffeinated coffee) appears to have a beneficial effect on our cognitive abilities. It may preserve our cognitive potential as we age, have preventative effects on the development of neurodegenerative diseases such as Alzheimer's and Parkinson's disease, and limit both the risk, and the deleterious consequences, of stroke. However, further research is needed before any firm conclusions can be drawn.

References

1. Swift C.G. & Tiplady B. (1988) The effects of age on the response to caffeine. *Psychopharmacology*, 94:29-31.
2. Rees K. et al. (1999) The influences of age and caffeine on psychomotor and cognitive function. *Psychopharmacology*, 145:181-188.
3. Hogervorst E. et al. (1998) Caffeine improves memory performance during distraction in middle-aged, but not in young or old subjects. *Hum Psychopharmacol*, 13:277-284.
4. Lorist M.M. et al. (1995) Aging, caffeine, and information processing: an event-related potential analysis. *Electroencephalogr Clin Neurophysiol*, 96:453-467.

5. Jarvis M.J. (1993) Does caffeine intake enhance absolute levels of cognitive performance? *Psychopharmacology*, 110:45-52.
6. Beydoun M.A. et al. (2014) Caffeine and Alcohol Intakes and Overall Nutrient Adequacy Are Associated with Longitudinal Cognitive Performance among U.S. Adults. *J Nutr*, 144(6):890-901.
7. Hameleers P.A. et al. (2000) Habitual caffeine consumption and its relation to memory, attention, planning capacity and psychomotor performance across multiple age groups. *Hum Psychopharmacol*, 15:573-581.
8. van Hooren S.A. et al. (2005) Influence of cognitive functioning on functional status in an older population: 3- and 6-year follow-up of the Maastricht Aging Study. *Int J Geriatr Psychiatry*, 20:883-888.
9. Cropley V. et al. (2011) Does coffee enriched with chlorogenic acids improve mood and cognition after acute administration in healthy elderly? A pilot study. *Psychopharmacology*, 219(3):737-49.
10. Santos C. et al. (2010) Caffeine intake and dementia: systematic review and meta-analysis*. J Alzheimers Dis*, 20 Suppl 1:S187-204.
11. Arab L. et al. (2013) Epidemiologic Evidence of a Relationship between Tea, Coffee, or Caffeine Consumption and Cognitive Decline. *Adv Nutr, vol. 4:115-122.*
12. Larsson S.C., Orsini N. (2018) Coffee Consumption and Risk of Dementia and Alzheimer's Disease: A Dose-response Meta-Analysis of Prospective Studies. *Nutrients*, Volume 10 (10).
13. Johnson-Kozlow M. et al. (2002) Coffee consumption and cognitive function among older adults. *Am J Epidemiol*, 156:842-850.
14. Ritchie K. et al. (2007) The neuroprotective effects of caffeine: a prospective population study (the Three City Study). *Neurology,* 69:536-545.
15. Santos C. et al. (2010) Caffeine intake is associated with a lower risk of cognitive decline: a cohort study from Portugal. *J Alzheimers Dis*, 20 Suppl 1:S175-85.
16. Arab L. et al. (2011) Gender Differences in Tea, Coffee, and Cognitive Decline in the Elderly: The Cardiovascular Health Study. *J Alzheimers Dis,* 2011;27(3):553-66.
17. van Gelder B.M. et al. (2007) Coffee consumption is inversely associated with cognitive decline in elderly European men: the FINE Study*. Eur J Clin Nutr*, 61:226-32.
18. Corley J. et al. (2010) Caffeine consumption and cognitive function at age 70: The Lothian birth cohort 1936 study. *Psychosom Med,* 72:206-14.
19. Wu M.S. et al. (2011) Socio-demographic and health-related factors associated with cognitive impairment in the elderly in Taiwan. *BMC Public Health*, 11:22.
20. Vercambre M.-N. et al. (2013) Caffeine and Cognitive Decline in Elderly Women at High Vascular Risk. *J Alzheimers Dis,* 35(2):413-21.
21. Wu L. et al. (2016) Coffee Intake and the Incident Risk of Cognitive Disorders: A Dose-response Meta-Analysis of Nine Prospective Cohort Studies. *Clin Nutr*, 36(3):730-736.
22. Liu Q.-P. et al. (2016) Habitual coffee consumption and risk of cognitive decline/dementia: A systematic review and meta-analysis of prospective cohort studies, *Nutr*, 32(6):628-36.
23. EFSA (2015) Scientific Opinion on the Safety of Caffeine, *EFSA Journal,* 13(5):4102.
24. Cao C. et al. (2012) High blood caffeine levels in MCI linked to lack of progression to dementia. *J Alzheimers Dis*, 30:559-572.
25. Maia L & de Mendonça A. (2002) Does caffeine intake protect from Alzheimer's disease? *Eur J Neurol,* 9:377-82.
26. Lindsay J. et al. (2002) Risk factors for Alzheimer's disease: a prospective analysis from the Canadian Study of Health and Aging. *Am J Epidemiol*, 156:445-53.
27. Broe G.A. et al. (1990) A case-control study of Alzheimer's disease in Australia. *Neurology,* 40:1698-707.
28. Tyas S.L. et al. (2001) Risk factors for Alzheimer's disease: a population-based, longitudinal study in Manitoba, Canada, *Int J Epidemiol*; 30:590-7.
29. Barranco Quintana J.L. et al. (2007) Alzheimer's disease and coffee: a quantitative review. *Neurol Res*, 29:91-5.
30. Eskelinen M.H, Kivipelto M. (2010) Caffeine as a protective factor in dementia and Alzheimer's disease. *J Alz Dis*, 20 Suppl 1:S167-74
31. Wierzejska R. (2017). Can coffee consumption lower the risk of Alzheimer's disease and Parkinson's disease? A literature review, *Arch Med Sci*, Volume 13 (3)
32. Larsson S.C. et al. (2017) Modifiable pathways in Alzheimer' s disease: Mendelian randomisation analysis. *BMJ* ,359:j5375.
33. Eskelinen M.H. et al. (2009) Midlife coffee and tea drinking and the risk of late-life dementia: a population-based CAIDE study. *J Alzheimers Dis*, 16:85-91.
34. Laitala V.S. et al. (2009) Coffee drinking in middle age is not associated with cognitive performance in old age. *Am J Clin Nutr*, 90:640-6.

35. Gelber R.P. et al. (2011) Coffee intake in midlife and risk of dementia and its neuropathologic correlates. *J Alzheimers Dis*, 23:607-15.
36. Arendash G.W. et al. (2006) Caffeine protects Alzheimer's mice against cognitive impairment and reduces brain β-amyloid production. *Neuroscience*, 142:941-52.
37. Arendash G.W. et al. (2009) Caffeine reverses cognitive impairment and decreases brain amyloid-β levels in aged Alzheimer's disease mice. *J Alzheimers Dis*, 17:661-80.
38. Cao C. et al. (2009) Caffeine suppresses amyloid-β levels in plasma and brain of Alzheimer's disease transgenic mice. *J Alzheimers Dis*, 17:681-97.
39. Cao C. et al. (2011) Caffeine synergizes with another coffee component to increase plasma GCSF: linkage to cognitive benefits in Alzheimer's mice. *J Alzheimers Dis*, 25(2):323-35.
40. Han M.E. et al. (2009) Regulation of cerebrospinal fluid production by caffeine consumption. *BMC Neurosci*, 10:110.
41. Wostyn P. et al. (2011) Increased cerebrospinal fluid production as a possible mechanism underlying caffeine's protective effect against Alzheimer's disease. *Int J Alzheimers* Dis, 2011:617420.
42. Madeira M.H. et al. (2017) Having a Coffee Break: The Impact of Caffeine Consumption on Microglia-Mediated Inflammation in Neurodegenerative Diseases. *Mediators Inflamm, 2017*:4761081.
43. Tohda C. et al. (2005) Search for natural products related to regeneration of the neuronal network. *Neurosignals*, 14:34-45.
44. Tohda C. et al. (1999) Trigonelline-induced neurite outgrowth in human neuroblastoma SK-N-SH cells. *Biol Pharm Bul,* 22:679-82.
45. Kim H.S. et al. (2004) Inhibitory effects of long-term administration of ferulic acid on microglial activation induced by intracerebroventricular injection of beta-amyloid peptide (1-42) in mice. *Biol Pharm Bull*, 27:120-1.
46. Cho J.Y. et al. (2005) Inhibitory effects of long-term administration of ferulic acid on astrocyte activation induced by intracerebroventricular injection of beta-amyloid peptide (1-42) in mice. *Prog Neuropsychopharmacol Biol Psychiatry*, 29:901-7.
47. Nefzger M.D. et al. (1968) A retrospective study of smoking in Parkinson's disease. *Am J Epidemiol*, 88:149-158.
48. Jimenez-Jimenez F.J. et al. (1992) Premorbid smoking, alcohol consumption, and coffee drinking habits in Parkinson's disease: a case-control study. *Mov Disord*, 7:339-44.
49. Fall P.A. et al. (1999) Nutritional and occupational factors influencing the risk of Parkinson's disease: a case-control study in southeastern Sweden. *Mov Disord*, 14:28-37.
50. Hellenbrand W. et al. (1996) Diet and Parkinson's disease. I. A possible role for the past intake of specific foods. Results from a self-administered food-frequency questionnaire in a case-control study. *Neurology*, 47:636-43.
51. Webster Ross G. et al. (2000) Association of coffee and caffeine intake with the risk of Parkinson disease. *JAMA*, 283:2674-2679.
52. van der Mark M. et al. 2014, A Case-Control Study of the Protective Effect of Alcohol, Coffee, and Cigarette Consumption on Parkinson Disease Risk: Time-Since-Cessation Modifies the Effect of Tobacco Smoking, *PLoS One*, 9(4):e95297.
53. Hernan M.A. et al. (2002) A meta-analysis of coffee drinking, cigarette smoking, and the risk of Parkinson's disease. *Ann Neurol*, 52:276-84.
54. Costa J. et al. (2010) Caffeine exposure and the risk of Parkinson's disease: a systematic review and meta-analysis of observational studies. *J Alzheimers Dis*, 20 Suppl 1:S221-38.
55. Liu R. et al. (2012) Caffeine intake, smoking, and risk of Parkinson disease in men and women. *Am J Epidemiol*, 175(11):1200-7.
56. Qi H. et al. (2014) Dose–response meta-analysis on coffee, tea and caffeine consumption with risk of Parkinson's disease. *Geriatr Gerontol Int,* (2):430-9.
57. Ascherio A. et al. (2001) Prospective study of caffeine consumption and risk of Parkinson's disease in men and women. *Ann Neurol*, 50:56-63.
58. Ascherio A. et al. (2003) Caffeine, postmenopausal estrogen, and risk of Parkinson's disease. *Neurology*, 60:790-5.
59. Palacios N. et al. (2012). Caffeine and Risk of Parkinson's Disease in a Large Cohort of Men and Women. *Movement Disorders*, 27(10):1276-82.
60. Palacios N. et al. (2010) Polymorphisms of caffeine metabolism and estrogen receptor genes and risk of Parkinson's disease in men and women. *Parkinsonism Relat Disord*, 16:370-5.
61. Kim I.Y. et al. (2017) Differences in Parkinson's Disease Risk with Caffeine Intake and Postmenopausal Hormone Use, *J Parkinsons Dis*, 7(4):677-684.

62. Postuma R.B. et al. (2012), Caffeine for treatment of Parkinson disease: A randomized controlled trial. *Neurology*, 79(7): 651–658.
63. Cho B.H. et al. (2018) Association of Coffee Drinking and Non-motor Symptoms in Drug Naive, Early Stage Parkinson's Disease, *Parkinsonism & Related Disorders*,50:42-47.
64. Kuwana Y. et al. (1999) Antiparkinsonian activity of adenosine A2A antagonists in experimental models. *Adv Neurol*, 80:121-3.
65. Fenu S. & Morelli M. (1998) Motor stimulant effects of caffeine in 6-hydroxydopamine-lesioned rats are dependent on previous stimulation of dopamine receptors: a different role of D1 and D2 receptors. *Eur J Neurosci*, 10:1878-84.
66. Chen J.F. et al. (2001) Neuroprotection by caffeine and A(2A) adenosine receptor inactivation in a model of Parkinson's disease. *J Neurosci*, 21:RC143.
67. Morelli M. et al. (2009) Adenosine A2A receptors and Parkinson's disease. *Handb Exp Pharmacol,* 193:589-615.
68. Iida M. et al. (1999) Dopamine D2 receptor-mediated antioxidant and neuroprotective effects of ropinirole, a dopamine agonist. *Brain Res*, 838:51-9.
69. Chuang Y.H. et al. (2017) Gene-Environment Interaction in Parkinson's Disease: Coffee, ADORA2A, and CYP1A2, *Neuroepidemiol*, 47(3-4):192-200
70. Kim I.Y. et al. (2018) Interaction between caffeine and polymorphisms of glutamate ionotropic receptor NMDA type subunit 2A (GRIN2A) and cytochrome P450 1A2 (CYP1A2) on Parkinson's disease risk. *Mov Disord*, 33(3):414-420.
71. Larsson S.C. et al. (2008) Coffee and tea consumption and risk of stroke subtypes in male smokers. *Stroke*, 39:1681-7.
72. Larsson S.C. et al. (2011) Coffee consumption and risk of stroke in women. *Stroke*, 42:908-12.
73. Lopez-Garcia E. et al. (2009) Coffee consumption and risk of stroke in women. *Circulation*, 119:1116-23.
74. Larsson S.C. & Orsini N. (2011) Coffee consumption and risk of stroke: A dose-response meta-analysis of prospective studies. *Am J Epidemio*l, 174(9):993-1001.
75. Piriyawat P. et al. (2003) Pilot dose-escalation study of caffeine plus ethanol (caffeinol) in acute ischemic stroke. *Stroke*, 34:1242-5.
76. Deng C. et al.(2017) Stroke and food groups: an overview of systematic reviews and meta-analyses. *Pub Health Nutr*, 21(4):766-776.
77. Singh-Manoux A. et al. (2011) Timing of onset of cognitive decline: results from Whitehall II prospective cohort study. *BMJ*, 343:d7622.
78. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) (2011) Scientific Opinion on the substantiation of health claims related to caffeine and increased fat oxidation leading to a reduction in body fat mass (ID 735, 1484), increased energy expenditure leading to a reduction in body weight (ID 1487), increased alertness (ID 736, 1101, 1187, 1485, 1491, 2063, 2103) and increased attention (ID 736, 1485, 1491, 2375) pursuant to Article 13(1) of Regulation (EC) No 1924/20061.*EFSA Journal*, 9(4):2054.
79. Nehlig A. (2010) Is Caffeine a Cognitive Enhancer? *J Alzheimers Dis*, 20(S1):85-94.
80. McLellan T.M. et al. (2016) A review of caffeine's effects on cognitive, physical and occupational performance. *Neuro & Biobehav Revs*, 71:294-312.
81. Ryan L. et al. (2002) Caffeine reduces time-of-day effects on memory performance in older adults. *Psychol Sci*, 13:68-71.
82. Smith A.P. (1994) Caffeine, performance, mood and status of reduced alertness. *Pharmacopsychoecologia*, 7:75-86.
83. Smith A.P. (2005) Caffeine in *Nutritional Neuroscience*, Lieberman H, Kanarek R, Prasad C, eds. Taylor & Francis, Boca Raton, FL;pp. 335-359.
84. Alzheimer Europe (2010) 'Alzheimer's disease. Available at: http://www.alzheimer-europe.org/EN/Dementia/Alzheimer-s-disease
85. Alzheimer Europe (2009) 'Who is affected by Alzheimer's disease?' Available at: http://www.alzheimer-europe.org/Dementia/Alzheimer-s-disease/Who-is-affected-by-Alzheimer-s-disease
86. GBD Dementia Collaborators (2016) Global, regional, and national burden of Alzheimer's disease and other dementias, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet*, 18(1): 88-106.
87. Alzheimer's Disease International (2015) World Alzheimer Report 2015 The Global Impact of Dementia- An AnalysIs of prevalence, Incidence, cost and trends. Available at: https://www.alz.co.uk/research/WorldAlzheimerReport2015.pdf

88. Alzheimer Europe (2014) 'Prevalence of dementia in Europe' Available at: http://www.alzheimer-europe.org/Research/European-Collaboration-on-Dementia/Prevalence-of-dementia/Prevalence-of-dementia-in-Europe
89. O'Brien R.J., Wong P.C. (2011) Amyloid Precursor Protein Processing and Alzheimer's Disease. *Ann Rev Neurosci*, 34:185-204.
90. European Parkinson's Disease Association (2011) 'EPDA Annual report 2010-2011.' Available at: http://www.epda.eu.com/EasySiteWeb/GatewayLink.aspx?alId=14888
91. European Parkinson's Disease Association 'What is Parkinson's' Available at: https://www.epda.eu.com/about-parkinsons/what-is-parkinsons/
92. World Heart Federation, 'Cardiovascular Health: Stroke' Available at: http://www.world-heart-federation.org/cardiovascular-health/stroke/