Drinking Coffee May Reduce Chances of Developing Alzheimer's Disease: Systematic Literature Review and Meta-Analysis

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Abstract

Coffee is a popular beverage, and it contains caffeine, a psychoactive substance. Consuming coffee may reduce the risk of developing Alzheimer's disease (AD). However, the association between the reduced risk of developing AD and the consumption of coffee is controversial. Therefore, we conducted a systematic literature review and quantitative synthesis meta-analysis that included dose-response analysis on the relationship between the consumption of coffee and the risk of developing AD. Based on PRISMA guidelines, we analysed standard databases of journals published between January 1999 and May 2020. We included the two population-based cohort studies and one case-control study. All studies included looked at the association between consuming many cups of coffee, the amount of coffee consumed in milligrams per day and the risk of developing AD. The systematic literature review and meta-analysis had 1670 participants with follow-up years that ranged from 5 to 21. The consumption of moderate or 3-5 cups per day reduces the risk of developing AD. The pooled relative risk and 95% confidence interval of the 3 included studies were 0.63 (0.3, 1.54). Dose-response curve analysis appears to be U-shaped. The results of the forest plot showed that there is low heterogeneity between the studies. Plotting the funnel plot and the Galbraith plot demonstrated publication bias of the three included studies. More prospective and long-term studies have to be conducted in other countries to determine the exact risk of developing AD.

Keywords: Coffee; Caffeine; Alzheimer's disease; Dementia; Cognitive

1 Introduction

The aging population worldwide is the most critical driver of the increase in age-related disorders such as Alzheimer's disease (AD), dementia and other late-life cognitive disorders (Panza et al., 2015). Dementia disorders affect 6.4% of European people older than 65 years old, with AD being the most common cause of dementia (Beydoun et al., 2014). More than 40% of 85-year olds and older develop AD, compared to less than 1% by those less than 60 years old (Beydoun et al., 2014). AD is a neurodegenerative disorder, and it is considered an emotional and economic burden to the individual affected by AD and the families of the individual affected by this disease (Rosso et al., 2008). AD begins with loss in mem-

ory and other cognitive skills (Winblad et al., 2007). AD significantly interrupts the structure and function of a normal brain (Korolev, 2014). The rate of AD progression is due to both environmental and genetic risk factors (Marques et al., 2011).

Coffee is a ubiquitous beverage consumed by many people. Studies have shown that coffee is able to protect from neurodegenerative disorders, it has pharmacological properties and it can also regulate the neurotransmitter and the receptor systems (Barranco Quintana et al., 2007).

Caffeine in coffee is a psychoactive drug and acts as an adenosine receptor antagonist (Cappelletti et al., 2015; Marques et al., 2011). Caffeine reduces the risk of developing AD as it does not allow the amyloid- β-peptide (Aβ-P) to accumulate inside and around the cerebral blood vessels of the brain (Cappelletti et al., 2015). It helps reverse the cognitive dysfunctional skills and helps to decline the brain Aβ-P levels in transgenic mice diagnosed with AD. The consumption of 3-5 cups of coffee in a day during midlife reduces the risk of developing AD by 65% in late life. It has been reported to protect the rabbit hippocampus against oxidative stress the and the rise in the function of mitochondria that includes blocking melatonin signalling. Men who consume more caffeine are less likely to develop AD-related lesions than men who consume less caffeine (Cappelletti et al., 2015). Consumption of coffee can improve cognition in older people and it may also have neuroprotective effects against AD (Rosso et al., 2008). When caffeine is consumed daily, it blocks and deactivates the adenosine receptors, blocking cell response and can cause reduced risk of developing AD (Flaten et al., 2014). The role of the adenosine receptors is to control the transmission of the synapse and plasticity.

Epidemiological and experimental studies show that the caffeine component in coffee, when administered in the human body, has beneficial effects against some neurological disorders such as stroke, Parkinson's disease, AD, dementia and amyotrophic lateral sclerosis (Panza et al., 2015). Caffeine affects the cardiovascular system by increasing the heart rate and heart conductivity, and affects the central nervous system by improving cognitive skills and causes increased alertness and wakefulness (Cappelletti et al., 2015). Cross-sectional studies show that consumption of coffee in the younger generation and the older generation is related to better cognitive skills (Arendash & Cao, 2010). The inhibition of Aβ-P production and cognitive improvements is not only in rabbits but also in brain of rats or mice (Panza et al., 2015). The data of many epidemiological studies such as the Finland Italy Netherlands Elderly study (FINE study), the Three-City Study and the Canadian Study of Health and Aging have shown that the consumption of coffee can help to slow down the progression of AD and also reduce the risk of developing AD (Flaten et al., 2014).

Since there is less pharmacological treatment available in the medical field to treat neurodegenerative diseases, it is essential to identify environmental factors such as lifestyle factors to prevent such neurodegenerative diseases. Dietary factors are often related to reduced or more risk of cognitive disorders (Wu et al., 2017). The consumption of coffee is inversely related to the risk of developing AD (Yenisetti & Muralidhara, 2016). AD patients consumed less caffeine in the 20 years compared to controls (Araújo et al., 2015). There is no cure for AD (Xu et al., 2015). Since there is no cure for AD hence, it may contribute to being a neuroprotective factor, reduce the risk of developing AD with fewer side effects (Rosso et al., 2008; Xu et al., 2015).

Therefore, we conducted a systematic literature review and quantitative synthesis meta-analysis to pool the evidence and summarize the three selected studies (1 case-control and 2 population-based cohort studies). These studies looked at the association between consumption of coffee and AD. We also carried out a meta-analysis to detect heterogeneity of the 3 included studies concerning consumption of coffee and AD using the forest plot. Furthermore, we also plotted a dose-response curve analysis to critically evaluate the dose-response patterns of the relationship between consuming coffee and the risk of developing AD. We evaluated publication bias by analysing the funnel plot and the Galbraith plot.

2 Methods

The standard protocol criteria that were followed for conducting and reporting this systematic literature review and meta-analysis was the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" PRISMA protocol. The literature search strategy and selection process were conducted by using five databases namely, PubMed, EBSCOhost, Ovid, ScienceDirect and SpringerLink. The literature search of the articles were those published between January 1999 and May 2020 that dealt with coffee consumption and the incidence of Alzheimer's disease. The mesh terms which were utilized to write up this systematic literature review and meta-analysis were "coffee", "caffeine", "caffeinated", "decaffeinated", "dementia", "Alzheimer disease", and "cognitive".

The literature search was used to identify the mesh terms the combination risk and the outcomes of interest: coffee AND Alzheimer's disease, coffee OR caffeine OR caffeinated OR decaffeinated AND Alzheimer's disease, coffee AND dementia, coffee OR caffeine OR caffeinated OR decaffeinated AND dementia, coffee AND cognitive, coffee OR caffeine OR caffeinated OR decaffeinated AND cognitive. The PRISMA flowchart in Figure 1 shows the workflow and the detailed literature search strategy and selection process for the eligible articles. The full-text articles were grouped into systematic literature reviews and meta-analysis, clinical trial study designs, newsletters, poster presentations and a case report.

2.1 Selection Criteria

When duplicate study design articles were detected in more than one database or more than one article, the article was eliminated. The types of articles that were excluded were laboratory studies, no appropriate outcome, articles about Parkinson disease, no coffee consumption intervention and articles written in a different language. The PICOS (participants, intervention, comparison, outcome and study design) methodology was used to conduct the inclusion criteria and selection of the eligible articles. Only studies that met the following inclusion criteria were included to write this systematic literature review and meta-analysis: (i) articles or papers which were published from 1999; (ii) the main participants who were involved in the study were those who had AD or who have signs and symptoms of the disease; (iii) the intervention exposure was coffee consumption; (iv) the comparison was no treatment or placebo; (v) the outcomes were changes in Alzheimer's signs and symptoms, prevention or treatment; (vi) the study conducted was a proper clinical trial study design.

Quality Assessment

The relative risks (RRs) were utilized to measure the effect size of the articles which, were included in the meta-analysis (Table 1). The data collected were categorized into 0 cups of coffee consumed per day, 0-2 cups of coffee consumed per day, >1 cup of coffee consumed per day, 3-5 cups of coffee consumed per day and >5 cups of coffee consumed per day. The data extraction of the eligible studies of interest was included in the study characteristics table. Meta-analysis graphs such as the forest plot, the dose-response curve, the funnel plot and the Galbraith plot were plotted for the 3 included articles using Microsoft Excel software. Egger test was used to detect for publication bias of the 3 included articles.

3 Results and Discussion

The characteristics of the study design were shown in Tables 2 and 3 according to the inclusion criteria present in this study. The year of publication of these 3 included articles ranged from 2002 to 2009. The number of years of follow-up of the duration of these 3 included articles ranged from 5 to 21 years. All the 3 included articles included both male and female participants. The first study was conducted in Finland, the second in Canada and the other study was in Portugal. The type of study design of the 2 included articles which were conducted in Finland and Canada were the population-based cohort studies and the type of study design of the 1 article which was conducted in Portugal was the case-control study. The baseline age of
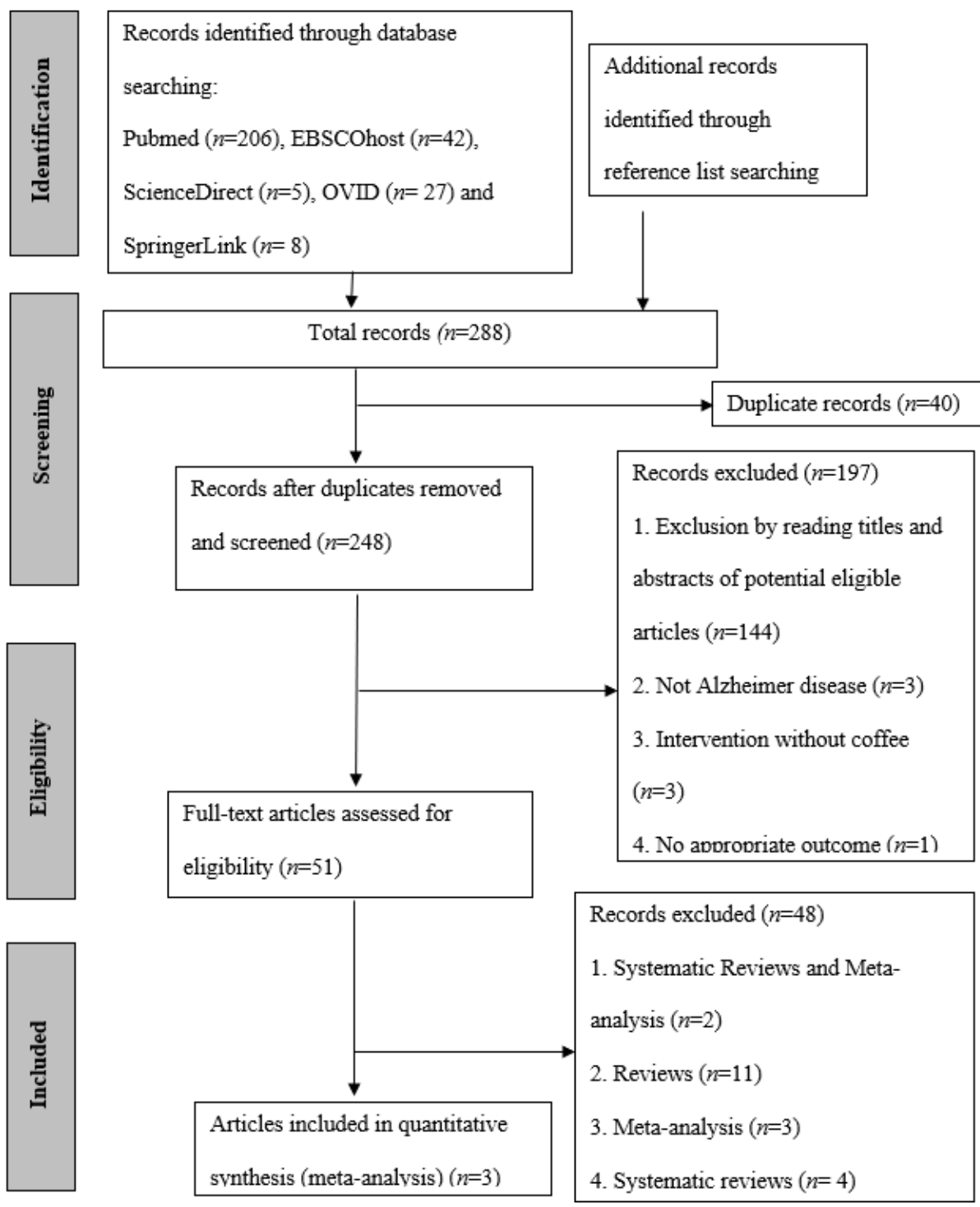
Figure 1: Literature search strategy and selection process, PRISMA flowchart.

Table 1: The Newcastle-Ottawa Scale used to grade the quality of each study (Wells et al., 2000) (maximum = 9 stars)

First author, year	Selection	Comparability	Outcome	Total
(Eskelinen et al., 2009)	**	**	**	******
(Lindsay et al., 2002)	***	**	*	******
(Maia & de Mendonca, 2002)	***	**	***	********

Footnote: Symbols indicate the star rating according to the Newcastle-Ottawa Scale. Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain. Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain. Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain.

the participants were 50 years or above in all the 3 included articles. The participant sample size ranged from 146 to 4615 for a total number of 6170 participants. The method of assessment for coffee intake for all 3 included articles was a self-administered questionnaire. The range of coffee intake was from 0 to greater than 5 cups per day (Table 2).

This systematic literature review and quantitative synthesis meta-analysis were conducted on 3 included articles that involved a total sample size of 6170 participants and a total number of 296 cases diagnosed with AD. According to the meta-analysis forest plot results, there was low heterogeneity of all the 3 included studies. Consumption of moderate or 3-5 cups of coffee in a day was inversely associated with the occurrence of AD. The consumption of low or 1-2 cups of coffee in a day was not significantly related to AD. A non-linear association was observed between AD and coffee consumption and a U-shaped dose-response curve was obtained. According to the dose-response curve results, moderate, or 3-5 cups of coffee consumed in a day was associated with a reduced risk of developing AD. Publication bias for the 3 included were analysed with Egger's test and were inspected visually after plotting the funnel plot and Galbraith plot. The funnel plot was asymmetrical showing uneven distribution of the selected 3 studies and in the Galbraith plot 2 studies were scattered away from the line of origin (Table 3).

3.1 Coffee consumption and the risk of Alzheimer's disease

The relative risks in Eskelinen's study with 3-5 cups and with more than 5 cups are: 0.42 (0.12, 1.46) and 1.01 (0.33, 3.09) respectively (Figure 2) (Eskelinen et al., 2009). The box represents the relative risk with corresponding confidence intervals. The left-hand panel shows the study ID, the last name of the first author and the year of publication of every included article. The right-hand panel shows the relative risk and 95% confidence intervals (lower and upper) of every included article. The right side of the graph favours the control group and the left side of the graph favours the experimental group. The x-axis is labelled as Relative Risk (95% CIs) and the y-axis is labelled as the line of no effect.

The results of the quantitative synthesis meta-analysis of the 3 included studies have shown that consuming coffee was non-significantly associated with the risk of developing AD and these results coincide with other studies. The summary risk estimates of these 3 studies between AD and coffee is 0.63 (0.3, 1.54) and this value is also quite close to other systematic literature reviews and meta-analyses conducted. The first meta-analysis which was conducted on 4 studies reported that consuming coffee was inversely related to the risk of developing AD with a summary risk estimate of 0.73 (95% CI: 0.58, 0.92) (Panza et al., 2015). A 2007 quantitative review that was conducted on 4 studies, 2 control studies

Table 2: The study design characteristics of the 3 included articles

The first author (year)	Country (years)	Follow-up (minimum-maximum)	Gender	Age Range of Participants	Study design	No.
(Eskelinen et al., 2009)	Finland	21	Both	65-79	population-based cohort	1409
(Lindsay et al., 2002)	Canada	5	Both	≥ 65	population-based cohort	4615
(Maia & de Mendonca, 2002)	Portugal	20	Both	50 - >75	case-control	146

and 2 case-cohort studies to determine the association between coffee consumption and AD had a summary risk estimate of 0.70 (0.55, 0.90) and reduces the risk of AD by 30% (Barranco Quintana et al., 2007). There was a systematic literature review and meta-analysis that was conducted on 11 studies to determine the association between coffee consumption and the risk of developing AD and reported that consuming more than 1 cup of coffee in a day was inversely associated with AD, the summary risk estimate 1.02 (0.95, 1.08) (Liu et al., 2016). Another systematic literature review and meta-analysis that was conducted on 11 studies reported that drinking coffee or caffeine intake was inversely associated with the risk of developing AD. The summary relative risk and 95% confidence interval were 0.84 (0.72, 0.99) (Santos et al., 2010). A meta-analysis conducted on 20 observational studies showed that the relative risk and confidence interval of consuming coffee on cognitive decline was 0.82 (0.67, 1.01) (Kim et al., 2015). A meta-analysis conducted on 3 observational studies has also shown that consuming coffee plays a protective role from the risk of getting other cognitive disorders (Wu et al., 2017). Honolulu–Asian Aging Study did not determine any relationship between the intake of caffeine and the risk of developing dementia. The autopsy on patients who consumed a high amount of coffee (>277.5 mg/day) did not have any type of pathological lesions that were related to Alzheimer's disease such as microvascular ischemic lesions, cortical Lewy bodies, hippocampal sclerosis, or generalized atrophy (Paganini-Hill et al., 2016). In this study, among the 3494 men, 418 of them were deceased and were used for autopsy purposes (Gelber et al., 2011).

3.2 Dose-response curve analysis

The relative risk of all studies with cups of coffee consumed is 1 (Figure 3). The relative risk is higher when consuming 1-2 cups of coffee per day than when consuming 3-5 cups of coffee per day. The relative risk is higher when consuming >5 cups of coffee per day than when consuming 3-5 cups of coffee per day. A non-linear association is observed and the dose-response curve is U-shaped.

According to the U-shaped dose-response curve results (Figure 3), a moderate consumption of 3-5 cups of coffee in a day is associated with a reduced risk of developing AD than when consuming 1-2 or >5 cups of coffee. This dose-response result matches the results of several epidemiological studies. One study by Andersen et al. (2006), suggested that the post-menopausal women who consumed a moderate or 3-5 cups of coffee in a day had a 30% reduced risk of developing an inflammatory disease such as AD with a summary risk estimate of 0.67 (95% CI: 0.50, 0.90) (Andersen et al., 2006). Also, a review conducted in 2010 reported that consuming 3-5 cups of coffee in a day reduces the risk of AD by 64% (Wierzejska, 2017). A cohort study conducted in 3 European countries reported that the consumption of 3-5 cups of coffee in a day reduces the risk of dementia (Wierzejska, 2017). The Women's Antioxidant Cardiovascular Study reported that drinking 4 cups of coffee a day was associated with improved cognitive maintenance during the 5-year follow up (Panza et al., 2015). The FINE study was conducted on old European men and the study suggested that consuming 3 cups of coffee per day showed the least decline in cognitive skills after a J-shaped dose-response curve was obtained (van Gelder et al., 2007). Ritchie et al. mentioned in the three city study that women who consumed more than 3 cups of coffee a day
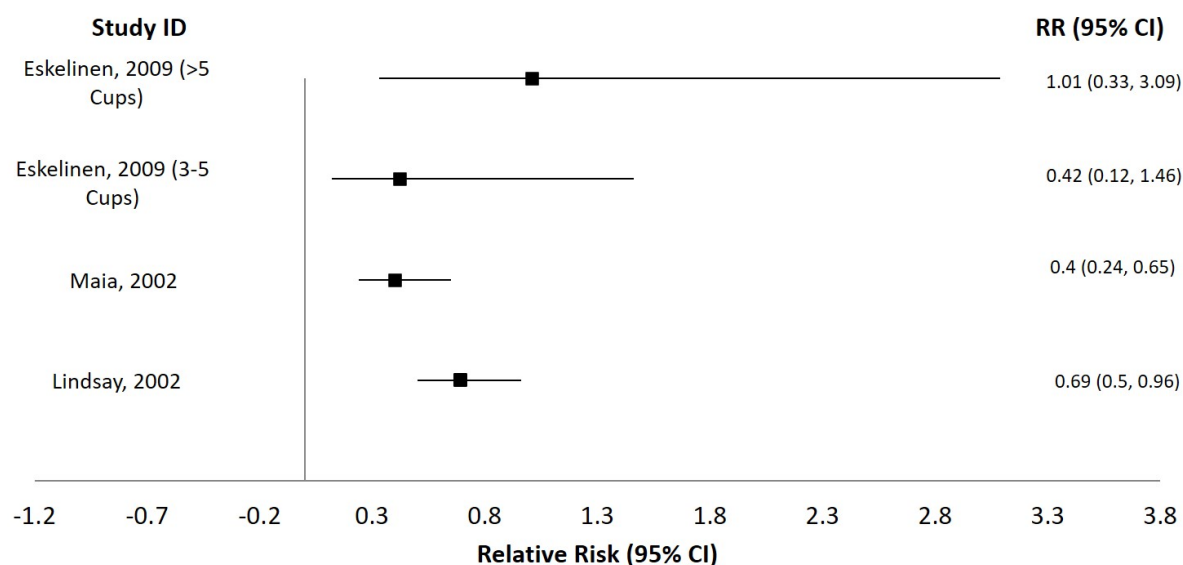
Figure 2: Meta-analysis forest plot for the relationship of coffee consumption with the risk of developing Alzheimer's disease.

had improved verbal retrieval and visuospatial memory (Ritchie et al., 2007). Paganini-Hill et al. reported in the 90+ study of elderly people that consuming 200+ milligrams of caffeine per day reduces the risk of developing dementia or AD by 34% (Paganini-Hill et al., 2016).

There are also experimental studies that prove that moderate consumption or 3-5 cups of coffee consumed in a day is related to a reduced risk of developing AD. In an experimental study, when mice diagnosed with AD were fed with caffeine that was added to drinking water, caffeine caused a decline in the levels of blood $A\beta$-P in the mice (Arendash & Cao, 2010). This experimental study results also match with the U-shaped dose-response curve results, which shows that a moderate number of 3-5 cups of coffee consumption per day contributes to protection against AD. There are some case-control, cross-sectional and population-based studies that were conducted to determine the long-term effects of caffeine and these studies suggest that caffeine has a protective contribution to dementia or AD (Panza et al., 2015). These study results are also similar to the results of this systematic literature review and meta-analysis studies. Five prospec-

tive studies suggested that consuming a moderate number or 3-4 cups of coffee a day (>300mg) is associated with a decreased risk of developing AD or dementia (Carman et al., 2014). The other prospective study that was conducted on 7000 elderly people who had an average age of 74 showed that drinking 3 or more cups of coffee in a day was related to improved verbal retrieval and improved visuospatial test scores (Kromhout et al., 2014).

3.3 Publication bias

The standard errors (z) for Eskelinen (3-5 Cups), Lindsay and Maia are 0.01, 0.08 and 0.03 respectively (Figure 4). Every blue dot in the figure is represented by the study ID (the last name of the first author and the year published). The grey dot represents the combined effect size and the orange dot represents the adjusted combined effect size. The grey and orange dots have corresponding confidence intervals. The funnel plot is inverted. The y-axis is labelled as standard error (z) and the x-axis is labelled as correlation (z). The inverse standard errors for (3-5 Cups) Es-
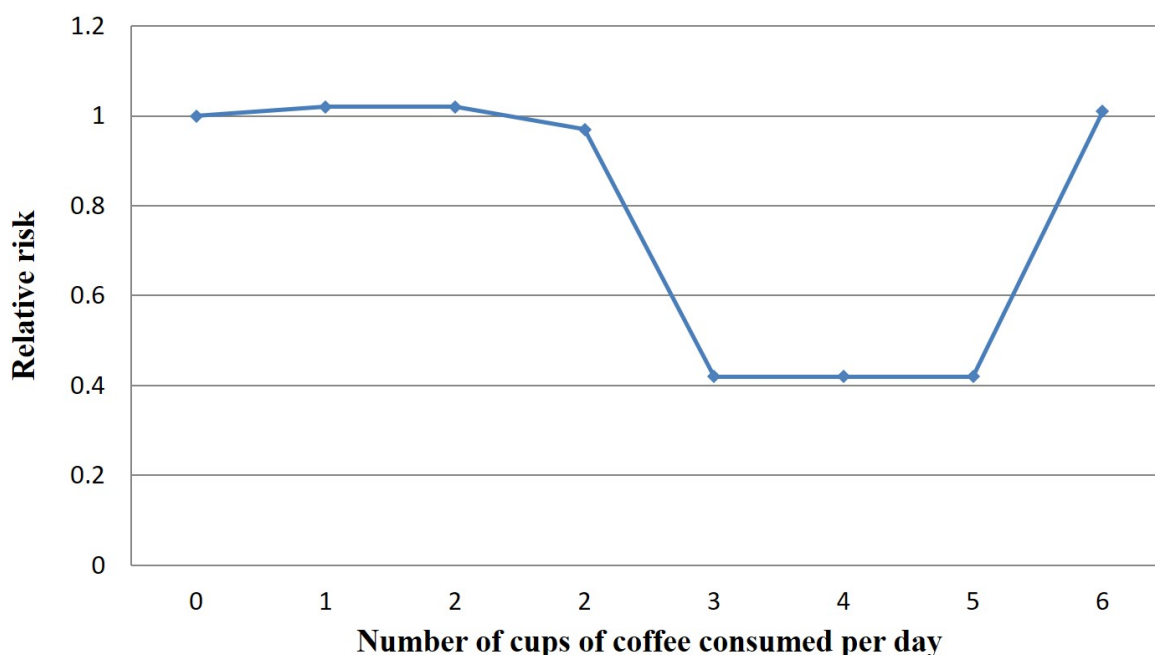
Figure 3: Dose-response curve relationship of coffee consumption (number of cups per day) with the risk of developing Alzheimer's disease.

kelinen, Lindsay and Maia are 67.91, 11.96 and 37.50 respectively (Figure 5). Every blue dot in the figure is represented by the study ID (the last name of the first author and the year published). The y-axis is labelled as z-score and the x-axis is labelled as inverse standard error. The darker line is the line of origin. The light lines are the 95% confidence intervals. Maia and de Mendonca (2002) is within the light line (Maia & de Mendonca, 2002). However, Eskelinen et al. (2009) and Lindsay et al. (2002) are away from the light lines.

3.4 Clinical and Animal Experimental Studies Correlation

The results of the included studies can also be justified by certain theoretical and practical facts, evidence such as experimental studies, bioactive components that can be found in coffee and its properties, epidemiological stud-ies and genetic studies. The laboratory experimental studies on transgenic mice showed that caffeine and the other bioactive components that are present in coffee possesses neuroprotection on cognitive dementia and cognitive decline (Liu et al., 2016). Numerous bioactive components can be found in coffee which, include caffeine, polyphenols like chlorogenic acids, ferulic acid and caffeic acid. These bioactive components have antioxidant properties (Cropley et al., 2012). The experimental studies have shown that caffeine has effects on the rise in alertness and it also reduces extreme tiredness or fatigue (Cropley et al., 2012). One of the studies suggested that the individuals who consumed 1 to 2 cups of coffee in a day have mild cognitive impairment with increased levels of caffeine and had lesser progress to dementia when compared with the individuals who had decreased levels of caffeine in the blood (Cao et al., 2012). When experiments were conducted on animal models, there was proof that caffeine has neu-
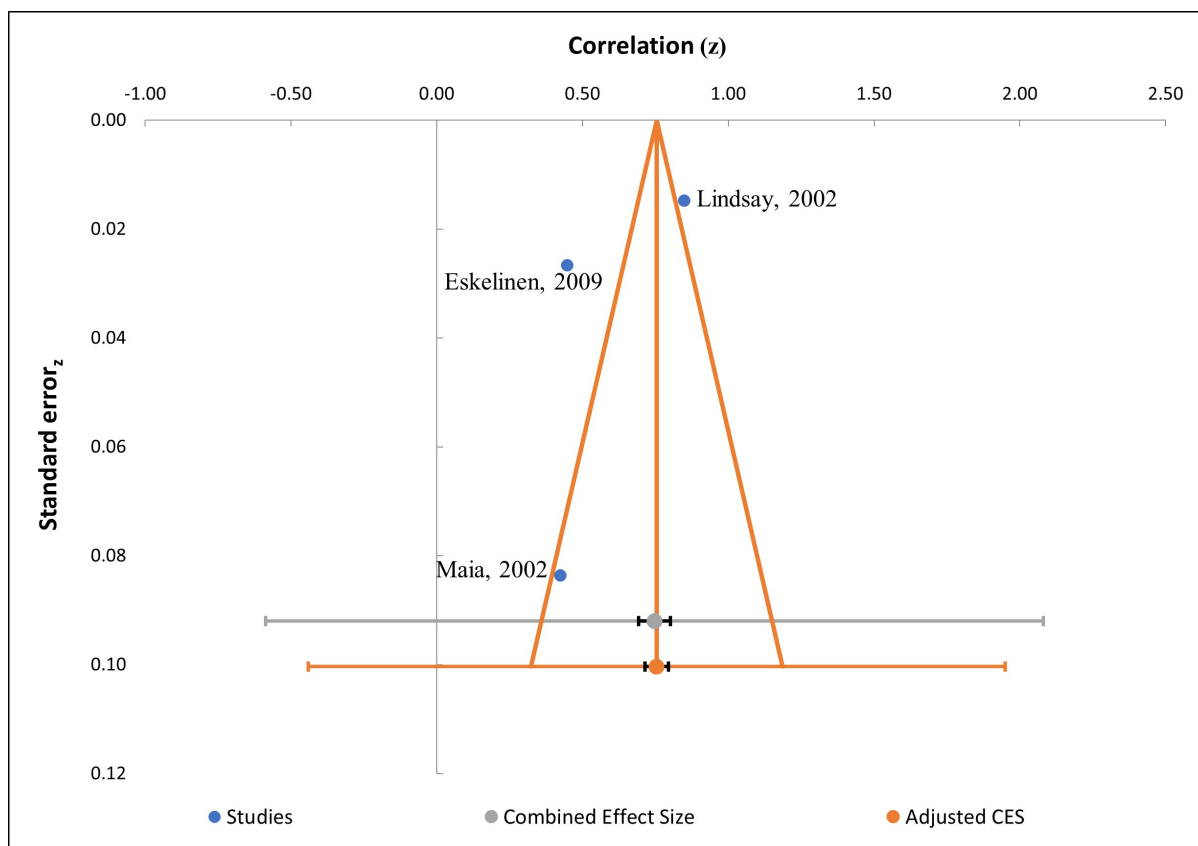
Figure 4: Funnel plot analysis of coffee consumption and Alzheimer's disease with 3 studies.

roprotective properties and regulates the Aβ-P metabolism (Carman et al., 2014). There are also genetic studies that discovered the E4 allele of the apolipoprotein E (APOE), a gene that is known to cause progress to late-onset AD. The locus of this E4 allele of the apolipoprotein E (APOE) gene was identified as rendering the carrier vulnerable to late-onset Alzheimer's disease (Barberger-Gateau et al., 2012). The 3C study is a genome-wide association study that discovered more hereditary genetic risk factors for Alzheimer's disease. Around 537,039 autosomal single nucleotide polymorphisms were genotyped on 2032 individuals who were diagnosed with Alzheimer's disease (Barberger-Gateau et al., 2012).

A case-control study involved 124 participants, and in the initial visit, the participants were neurologically assessed and blood samples were collected from them (Cao et al., 2012). After centrifugation of the blood, the blood plasma was measured for caffeine concentration using Enzyme-linked immunosorbent assay laboratory technique and the participants were monitored during the 2-4-year duration of follow-up. The caffeine level in the blood plasma was 51% lower in the participants who progressed from mild cognitive impairment to dementia than the participants who did not progress to dementia from mild cognitive impairment (Barberger-Gateau et al., 2012; Cao et al., 2012). The participants diagnosed with AD in these studies could have inherited the APOE gene which is a genetic risk factor to progression to AD (Lindsay et al., 2002). A study was conducted on 41,836 postmenopausal women with 15 years of follow up
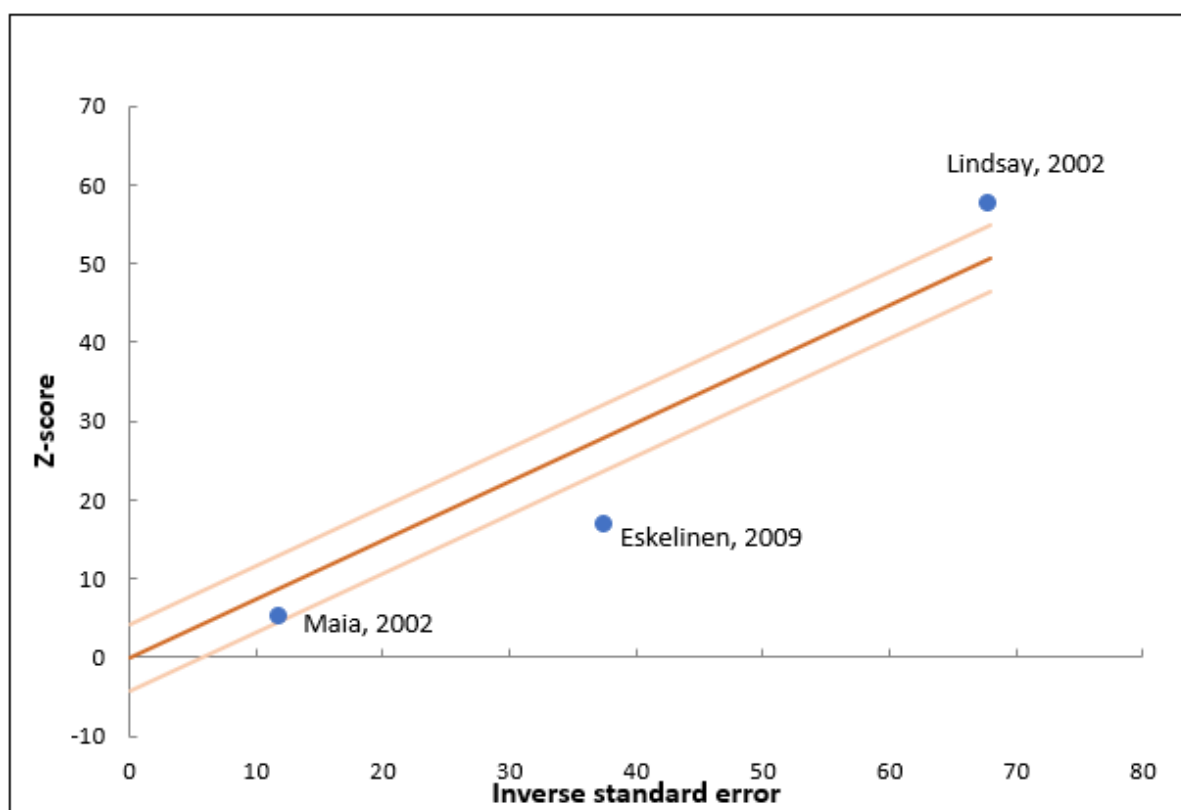
Figure 5: Galbraith plot analysis of coffee consumption and Alzheimer's disease with 3 studies.

(Andersen et al., 2006). This study showed that a moderate consumption of 3-5 cups of coffee in a day had a 30% reduced risk of developing an inflammatory disease or Alzheimer's disease with a summary risk estimate of 0.67 (0.50, 0.90) (Andersen et al., 2006). A review showed that consuming 3-5 cups of coffee in a day reduces Alzheimer's disease by 64% and 3 cups of coffee in a day prevents vascular dementia, meta-analysis on case control and cohort studies had an inverse association, and a literature review pointed out that coffee is a medical boon against Alzheimer's disease (Wierzejska, 2017).

The 90+ longitudinal study with 587 participants was conducted in California and had a 3 years duration of follow-up (Paganini-Hill et al., 2016). This study showed that elderly people who consumed 200+ mg/day caffeine per day reduced the risk of developing dementia to 34%,

and the summary risk estimate was 0.66 (0.43, 0.99) (Paganini-Hill et al., 2016). A longitudinal study was conducted in Italy with a total sample size of 1445 (Solfrizzi et al., 2015), the method of assessment of coffee intake was an interviewer-administered questionnaire and food free questionnaire. This study suggested that when consuming 1-2 cups of coffee per day, the relative risk of developing cognitive impairment was the lowest, risk estimate being 0.11 (0.02, 0.84) (Solfrizzi et al., 2015). A cohort study was conducted in Japan on 13,137 Japanese participants and the duration of follow up was 5.7 years (Sugiyama et al., 2015). The method of assessment of coffee intake was a self-administered and food free questionnaire. The study showed that when 1-2 cups of coffee per day are consumed, there was a minimum risk of getting incident dementia, and the risk estimate was 0.58 (0.43, 0.78) (Sugiyama

et al., 2015). The three-city study was a cohort study conducted in France with a 3.47 years follow-up and a sample size of 7017 (Ritchie et al., 2007). The method of assessment coffee intake was a standarized interview. The study showed that women who consumed more than 3 cups of coffee in a day had improvements in verbal retrieval, with a summary risk estimate of 0.67 (0.53, 0.85) and visuospatial memory, risk estimate 0.73 (0.53, 1.02) (Ritchie et al., 2007). A population-based study was conducted in the Netherlands and the method of assessment of coffee intake was a home interview and a partially food free questionnaire. The sample size was 5408 and the number of years of follow-up was 13.2 years (Mirza et al., 2014). This study showed that consuming coffee cannot progress to incident dementia in the long run (Mirza et al., 2014). The Rancho Bernardo was a cross-sectional study and the sample size was 1528 participants (Rosso et al., 2008). The female participants who were over 80 years of age who drink coffee regularly performed well on 11 cognitive tests (Rosso et al., 2008). A study that was conducted on 716 Finnish men reported that low coffee consumption was related to a reduction in cognitive decline after the participants were assessed by the Mental Status Questionnaire (MSQ) during the 25-year follow-up (Panza et al., 2015).

There are also epidemiological animal studies and clinical studies which have reported that caffeine helps to reduce cognitive decline in elderly patients diagnosed with Alzheimer's disease (van Gelder et al., 2007). In an animal study, when rats or transgenic mice were treated with caffeine, it was noted that they had bigger dendritic length and bigger spine density in distal dendritic branches in the basal dendrites of CA1 pyramidal neurons (Arab et al., 2013). Caffeine can inhibit GABA receptor signaling, increase intracellular calcium release, inhibit multiple phosphodiesterases, has pleiotropic effects on the central nervous system and can decrease $A\beta$ production in rodents (Carman et al., 2014).

Caffeine acts as a neuro-stimulatory substance

Methylxanthine caffeine has a psychostimulant property by acting on neurotransmission in different parts of the brain like an antagonist of the adenosine receptors A1 and A2A subtypes (Flaten et al., 2014; Haller et al., 2014). Caffeine can also act as an excitatory neurostimulator, controls the cerebral perfusion and is a vasoconstrictor that causes a low pressure of cerebral blood flow in the participants (Haller et al., 2014). When the 3C cohort study was conducted, women who consumed caffeine showed an inverse dose-response association towards cognitive decline (Barberger-Gateau et al., 2012). The side effects of caffeine include cardiovascular side effects, inhibition of phosphodiesterase, and rise in intracellular calcium but these side effects disappear after 3-4 days and consuming a moderate number of cups of coffee per day (Marques et al., 2011). This also indicates the corroboration with other studies with the results of this systematic literature review and meta-analysis, consuming a moderate number of cups of coffee a day prevents side effects in the participants of the included studies. Caffeine can also protect against a diagnosis of AD by increasing the activity of the Na^+-K^+-ATPase pump and also there is a rise in cerebrospinal fluid production (Yenisetti & Muralidhara, 2016).

The significant hallmarks of Alzheimer's disease are that the amyloid plaques and neurofibrillary tangles are deposited, the neurons disappear and the synapse does not function properly (Marques et al., 2011). The amyloid-β plaques are heterogeneous peptides produced from the amyloid-β protein precursor and these plaques can lead to excess accumulation of $A\beta42$ (Marques et al., 2011; Tabaton, 2009). The neurofibrillary tangles arise from the hyperphosphorylation of the tau protein which damages the neurons and the function of the synapse also ceases. In tau pathology, $A\beta$ deposits occur which is eventually followed by the late tangle pathology stages of AD (Marques et al., 2011). Factors that can trigger or that can occur in Alzheimer's disease include inflammation, tau protein phosphorylation or amyloid precursor protein expression and processing; together all these can lead to changes

Table 3: The study characteristics of the 3 included articles

First author (year)	Coffee Intake		Incident cognitive Disorders				
	Method of Assessment	Coffee Consumption	Type	Method of Ascertainment	No of cases	Coffee consumption → Risk estimate (95% CI)	Adjustment factor
(Eskelinen et al., 2009)	Self-administered questionnaire	0-2;				0-2 cups/day → 1.0 (Reference)	dementia and Alzheimer's disease, age, sex, education, follow up time, community of residence, midlife smoking, systolic blood pressure, serum total cholesterol, BMI, physical activity, ApoEe4, late-life myocardial infarction, stroke, diabetes mellitus, beck depressive scale
		3-5;	Dementia; Alzheimer's	DSM-IV; NINCDS-ADRDA	61; 48	3-5 cups/day → 0.42(0.12-1.46)	
		>5 cups/day				>5 cups/day → 1.01(0.33-3.09)	
(Lindsay et al., 2002)	Self-administered questionnaire	0;	Alzheimer's	NINCDS-ADRDA	194	Regular vs. not regular coffee consumption → 0.69 (0.50-0.96)	age, sex, education
(Maia & de Mendonca, 2002)	Self-administered questionnaire	>1 cup/day Average daily intake (mg) in 20 yrs before AD; cases, 73.9 [97.9] controls, 198.7 [35.7]. Average daily intake (mg) from 25 yrs old to 20 yrs before AD; cases, 69.6 [94.1] controls, 184.5[137.2]. Average daily intake after AD; cases, 36.3[64.1] controls, 177.1[123.7]	Alzheimer's	MMSE, NINCDS-ADRA	54	Coffee in mg → 0.40(0.24-0.65)	sex, age, hypertension, diabetes, stroke, head trauma, smoking habits, alcohol consumption, non-steroid anti-inflammatory drug use, vitamin E, gastric disorder, heart disease, education and family history of Alzheimer's disease

Abbreviations: AD; Alzheimer's Disease; DSM; Diagnostic and Statistical Manual of Mental Disorders; MMSE; Mini-Mental State Examination; NINCDS-ADRDA; National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association; mg; milligrams; Ave; Average; yrs; years

in the neurotransmission, synaptic loss, neurodegeneration including clinical and neuropathological changes (Profenno et al., 2010). Caffeine can also increase the use of cerebral glucose rate which helps to improve cognitive functioning (Rosso et al., 2008). Caffeine possesses the ability to bind to many types of receptors that are found in the synaptic membranes for cytoplasmic phosphodiesterases (Santos et al., 2010). Caffeine is a nonselective antagonist of adenosine receptors (van Gelder et al., 2007). Caffeine can block A2A receptors that reduce the synaptotoxic effect of Aβ (van Gelder et al., 2007). The mechanism of caffeine as a protective factor against Alzheimer's disease is that it initially enters the circulatory system, then acts like an antagonist on the A2A adenosine receptors that are located in the brain and this action immediately stimulates the cholinergic neurons which have the ability and play the role of defending against β-amyloid induced neurotoxicity, the precursor of

cognitive decline (Rosso et al., 2008).

Systematic Literature Review and Meta-Analysis of Population-Based Cohort Studies and Case-Control Study

The significant result that was obtained from the dose-response curve was a non-linear inverse correlation between coffee consumption or coffee intake and the risk of developing AD. The case-control study that was selected had the sources of caffeine specified such as coffee (5 oz), instantaneous coffee and decaffeinated (Maia & de Mendonca, 2002). All the included studies had relative risk and 95% confidence intervals stated. The number of follow-ups in years was long for Eskelinen et al. (2009) study and Maia and de Mendonca (2002) study. The sample size was the largest for Lindsay et al. (2002) study. All the 3 included studies used the self-administered

questionnaire method for assessing coffee intake for both male and female genders. The study were prospective studies (Eskelinen et al., 2009; Lindsay et al., 2002).

The epidemiologic studies conducted on humans and animals show that coffee is a neurostimulant, coffee consumption plays a significant role in neuroprotection and has a reduced risk of developing AD. The results of the 3 included studies graphically plotted on the forest plot helped to detect any heterogeneity between the studies and the results between the studies was homogenous and more reliable. The results of the 3 included studies graphically plotted on the funnel plot and the Galbraith plot helped to detect publication bias between the studies. In conclusion, most of the studies are based on study data from 2 population-based cohort studies and 1 case-control study, an exact relationship between consuming coffee and the risk of developing AD cannot be judged with the current systematic literature review and meta-analysis which has been conducted.

4 Conclusions

The major strengths of the current systematic literature review and meta-analysis are the inclusion of 2 population-based cohort studies and 1 case-control study. The large sample size with a total number of 6170 participants and a total number of 296 cases diagnosed with AD helped plot the dose-response curve. The large sample size from a population makes the study data more reliable, less uncertainty and errors are avoided. In conclusion, the results and the current systematic literature review and meta-analysis of the 3 included studies which were conducted gives evidence that consuming a moderate number of 3-5 cups of coffee per day has a reduced risk of developing Alzheimer's disease. The Forest plot graphically summarized the results of the 3 included studies and the 3 studies had low heterogeneity. A U-shaped curve was obtained after plotting the dose-response curve. Publication bias between the studies exists after plotting the funnel plot and the Galbraith plot. Epidemiological studies such as human and animal studies prove that coffee can be a therapeutic agent for Alzheimer's disease. More prospective and long-term studies have to be conducted in other regions of the world to determine the exact relationship between coffee and Alzheimer's disease. The mechanism of how coffee carries out its neuroprotective effects in the human body might guide to invent new treatments for Alzheimer's disease in the future.

Acknowledgements

References

Andersen, L. F., Jacobs, D. R., Carlsen, M. H., & Blomhoff, R. (2006). Consumption of coffee is associated with reduced risk of death attributed to inflammatory and cardiovascular diseases in the Iowa Women's Health Study. *The American Journal of Clinical Nutrition*, *83*(5), 1039–1046. https://doi.org/10.1093/ajcn/83.5.1039

Arab, L., Khan, F., & Lam, H. (2013). Epidemiologic Evidence of a Relationship between Tea, Coffee, or Caffeine Consumption and Cognitive Decline. *Advances in Nutrition*, *4*(1), 115–122. https://doi.org/10.3945/an.112.002717

Araújo, L. F., Giatti, L., Reis, R. C. P., Goulart, A. C., Schmidt, M. I., Duncan, B. B., Ikram, M. A., & Barreto, S. M. (2015). Inconsistency of Association between Coffee Consumption and Cognitive Function in Adults and Elderly in a Cross-Sectional Study (ELSA-Brasil). *Nutrients*, *7*(11), 9590–9601. https://doi.org/10.3390/nu7115487

Arendash, G. W., & Cao, C. (2010). Caffeine and Coffee as Therapeutics Against Alzheimer's Disease (R. A. Cunha & A. de Mendonça, Eds.). *Journal of Alzheimer's Disease*, *20*(s1), 117–126. https://doi.org/10.3233/JAD-2010-091249

Barberger-Gateau, P., Lambert, J.-C., Féart, C., Pérès, K., Ritchie, K., Dartigues, J.-F., & Alpérovitch, A. (2012). From Genetics to Dietetics: The Contribution of Epidemiology to Understanding Alzheimer's Disease (G. Perry, X. Zhu, M. A. Smith, A. Sorensen, & J. Avila, Eds.). *Journal of Alzheimer's Disease*, *33*(s1), 457–463. https://doi.org/10.3233/JAD-2012-129019

Barranco Quintana, J. L., Allam, M. F., Serrano Del Castillo, A., & Fernández-Crehuet Navajas, R. (2007). Alzheimer's disease and coffee: a quantitative review. *Neurological Research*, *29*(1), 91–95. https://doi.org/10.1179/174313206X152546

Beydoun, M. A., Beydoun, H. A., Gamaldo, A. A., Teel, A., Zonderman, A. B., & Wang, Y. (2014). Epidemiologic studies of modifiable factors associated with cognition and dementia: systematic review and meta-analysis. *BMC Public Health*, *14*(1), 643. https://doi.org/10.1186/1471-2458-14-643

Cao, C., Loewenstein, D. A., Lin, X., Zhang, C., Wang, L., Duara, R., Wu, Y., Giannini, A., Bai, G., Cai, J., Greig, M., Schofield, E., Ashok, R., Small, B., Potter, H., & Arendash, G. W. (2012). High Blood Caffeine Levels in MCI Linked to Lack of Progression to Dementia. *Journal of Alzheimer's Disease*, *30*(3), 559–572. https://doi.org/10.3233/JAD-2012-111781

Cappelletti, S., Daria, P., Sani, G., & Aromatario, M. (2015). Caffeine: Cognitive and Physical Performance Enhancer or Psychoactive Drug? *Current Neuropharmacology*, *13*(1), 71–88. https://doi.org/10.2174/1570159X13666141210215655

Carman, A. J., Dacks, P. A., Lane, R. F., Shineman, D. W., & Fillit, H. M. (2014). Current evidence for the use of coffee and caffeine to prevent age-related cognitive decline and Alzheimer's disease. *The journal of nutrition, health and aging*, *18*(4), 383–392. https://doi.org/10.1007/s12603-014-0021-7

Cropley, V., Croft, R., Silber, B., Neale, C., Scholey, A., Stough, C., & Schmitt, J.

(2012). Does coffee enriched with chlorogenic acids improve mood and cognition after acute administration in healthy elderly? A pilot study. *Psychopharmacology*, *219*(3), 737–749. https://doi.org/10.1007/s00213-011-2395-0

Eskelinen, M. H., Ngandu, T., Tuomilehto, J., Soininen, H., & Kivipelto, M. (2009). Midlife Coffee and Tea Drinking and the Risk of Late-Life Dementia: A Population-Based CAIDE Study. *Journal of Alzheimer's Disease*, *16*(1), 85–91. https://doi.org/10.3233/JAD-2009-0920

Flaten, V., Laurent, C., Coelho, J. E., Sandau, U., Batalha, V. L., Burnouf, S., Hamdane, M., Humez, S., Boison, D., Lopes, L. V., Buée, L., & Blum, D. (2014). From epidemiology to pathophysiology: what about caffeine in Alzheimer's disease? *Biochemical Society Transactions*, *42*(2), 587–592. https://doi.org/10.1042/BST20130229

Gelber, R. P., Petrovitch, H., Masaki, K. H., Ross, G. W., & White, L. R. (2011). Coffee Intake in Midlife and Risk of Dementia and its Neuropathologic Correlates. *Journal of Alzheimer's Disease*, *23*(4), 607–615. https://doi.org/10.3233/JAD-2010-101428

Haller, S., Montandon, M.-L., Rodriguez, C., Moser, D., Toma, S., Hofmeister, J., Sinanaj, I., Lovblad, K.-O., & Giannakopoulos, P. (2014). Acute Caffeine Administration Effect on Brain Activation Patterns in Mild Cognitive Impairment. *Journal of Alzheimer's Disease*, *41*(1), 101–112. https://doi.org/10.3233/JAD-132360

Kim, Y.-S., Kwak, S. M., & Myung, S.-K. (2015). Caffeine Intake from Coffee or Tea and Cognitive Disorders: A Meta-Analysis of Observational Studies. *Neuroepidemiology*, *44*(1), 51–63. https://doi.org/10.1159/000371710

Korolev, I. O. (2014). Alzheimer's Disease: A Clinical and Basic Science Review. *Medical Student Research Journal*, *4*(Fall), 24–33.

Kromhout, M. A., Jongerling, J., & Achterberg, W. P. (2014). Relation between caffeine and behavioral symptoms in elderly patients with dementia: An observational study. *The journal of nutrition, health and aging*, *18*(4), 407–410. https://doi.org/10.1007/s12603-013-0417-9

Lindsay, J., Laurin, D., Verreault, R., Hébert, R., Helliwell, B., Hill, G. B., & McDowell, I. (2002). Risk Factors for Alzheimer's Disease: A Prospective Analysis from the Canadian Study of Health and Aging. *American Journal of Epidemiology*, *156*(5), 445–453. https://doi.org/10.1093/aje/kwf074

Liu, Q.-P., Wu, Y.-F., Cheng, H.-Y., Xia, T., Ding, H., Wang, H., Wang, Z.-M., & Xu, Y. (2016). Habitual coffee consumption and risk of cognitive decline/dementia: A systematic review and meta-analysis of prospective cohort studies. *Nutrition*, *32*(6), 628–636. https://doi.org/10.1016/j.nut.2015.11.015

Maia, L., & de Mendonca, A. (2002). Does caffeine intake protect from Alzheimer's disease? *European Journal of Neurology*, *9*(4), 377–382. https://doi.org/10.1046/j.1468-1331.2002.00421.x

Marques, S., Batalha, V. L., Lopes, L. V., & Outeiro, T. F. (2011). Modulating Alzheimer's Disease Through Caffeine: A Putative Link to Epigenetics (G. B. Britton, M. A. Smith, G. Perry, K. Sambamurti, & K. Jagannatha Rao, Eds.). *Journal of Alzheimer's Disease*, *24*(SUPPL. 2), 161–171. https://doi.org/10.3233/JAD-2011-110032

Mirza, S. S., Tiemeier, H., de Bruijn, R. F. A. G., Hofman, A., Franco, O. H., Jong, J. K.-d., Koudstaal, P. J., & Ikram, M. A. (2014). Coffee consumption and incident dementia. *European Journal of Epidemiology*, *29*(10), 735–741. https://doi.org/10.1007/s10654-014-9943-y

Paganini-Hill, A., Kawas, C. H., & Corrada, M. M. (2016). Lifestyle Factors and Dementia in the Oldest-old. *Alzheimer Disease and Associated Disorders*, *30*(1), 21–26. https://doi.org/10.1097/WAD.0000000000000087

Panza, F., Solfrizzi, V., Barulli, M. R., Bonfiglio, C., Guerra, V., Osella, A., Seripa, D., Sabbà, C., Pilotto, A., & Logroscino, G. (2015). Coffee, tea, and caffeine consumption and prevention of late-life cognitive decline and dementia: A systematic review. *The journal of nutrition, health and aging*, *19*(3), 313–328. https://doi.org/10.1007/s12603-014-0563-8

Profenno, L. A., Porsteinsson, A. P., & Faraone, S. V. (2010). Meta-Analysis of Alzheimer's Disease Risk with Obesity, Diabetes, and Related Disorders. *Biological Psychiatry*, *67*(6), 505–512. https://doi.org/10.1016/j.biopsych.2009.02.013

Ritchie, K., Carriere, I., de Mendonça, A., Portet, F., Dartigues, J. F., Rouaud, O., Barberger-Gateau, P., & Ancelin, M. L. (2007). The neuroprotective effects of caffeine: A prospective population study (the Three City Study). *Neurology*, *69*(6), 536–545. https://doi.org/10.1212/01.wnl.0000266670.35219.0c

Rosso, A., Mossey, J., & Lippa, C. F. (2008). Review: Caffeine: Neuroprotective Functions in Cognition and Alzheimer's Disease. *American Journal of Alzheimer's Disease and Other Dementiasr*, *23*(5), 417–422. https://doi.org/10.1177/1533317508320083

Santos, C., Costa, J., Santos, J., Carneiro, A. V., & Lunet, N. (2010). Caffeine Intake and Dementia: Systematic Review and Meta-Analysis (R. A. Cunha & A. de Mendonça, Eds.). *Journal of Alzheimer's Disease*, *20*(s1), S187–S204. https://doi.org/10.3233/JAD-2010-091387

Solfrizzi, V., Panza, F., Imbimbo, B. P., D'Introno, A., Galluzzo, L., Gandin, C., Misciagna, G., Guerra, V., Osella, A., Baldereschi, M., Di Carlo, A., Inzitari, D., Seripa, D., Pilotto, A., Sabbá, C., Logroscino, G., & Scafato, E. (2015). Coffee Consumption Habits and the Risk of Mild Cognitive Impairment: The Italian Longitudinal Study on Aging (P. Kehoe, Ed.). *Journal of Alzheimer's Disease*, *47*(4), 889–899. https://doi.org/10.3233/JAD-150333

Sugiyama, K., Tomata, Y., Kaiho, Y., Honkura, K., Sugawara, Y., & Tsuji, I. (2015). Association between Coffee Consumption and Incident Risk of Disabling Dementia in Elderly Japanese: The Ohsaki Cohort 2006 Study (K. Anstey, Ed.). *Journal of Alzheimer's Disease*, *50*(2), 491–500. https://doi.org/10.3233/JAD-150693

Tabaton, M. (2009). Coffee "Breaks" Alzheimer's Disease. *Journal of Alzheimer's Disease*, *17*(3), 699–700. https://doi.org/10.3233/JAD-2009-1089

van Gelder, B. M., Buijsse, B., Tijhuis, M., Kalmijn, S., Giampaoli, S., Nissinen, A., & Kromhout, D. (2007). Coffee consumption is inversely associated with cognitive decline in elderly European men: the FINE Study. *European Journal of Clinical Nutrition*, *61*(2), 226–232. https://doi.org/10.1038/sj.ejcn.1602495

Wells, G. A., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M., & Tugwell, P. (2000). *The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses*, Otawa Hospital Research Institute. https://www.ohri.ca//programs/clinical_epidemiology/oxford.asp

Wierzejska, R. (2017). Can coffee consumption lower the risk of Alzheimer's disease and Parkinson's disease? A literature review. *Archives of Medical Science*, *3*, 507–514. https://doi.org/10.5114/aoms.2016.63599

Winblad, B., Jones, R. W., Wirth, Y., Stöffler, A., & Möbius, H. J. (2007). Memantine in Moderate to Severe Alzheimer's Disease: a Meta-Analysis of Randomised Clinical Trials. *Dementia and Geriatric Cognitive Disorders*, *24*(1), 20–27. https://doi.org/10.1159/000102568

Wu, L., Sun, D., & He, Y. (2017). Coffee intake and the incident risk of cognitive disorders: A dose–response meta-analysis of nine prospective cohort studies. *Clinical Nutrition*, *36*(3), 730–736. https://doi.org/10.1016/j.clnu.2016.05.015

Xu, W., Tan, L., Wang, H.-F., Jiang, T., Tan, M.-S., Tan, L., Zhao, Q.-F., Li, J.-Q., Wang, J., & Yu, J.-T. (2015). Meta-analysis of modifiable risk factors for Alzheimer's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, *86*, 1299–1306. https://doi.org/10.1136/jnnp-2015-310548

Yenisetti, S. C., & Muralidhara. (2016). Beneficial Role of Coffee and Caffeine in Neurodegenerative Diseases: A Minireview. *AIMS Public Health*, *3*(2), 407–422. https://doi.org/10.3934/publichealth.2016.2.407