APPENDIX A

Search Terms

From Web of Science:

TI= (“Alzheimer” OR “Dement*” OR “Senile dementia” OR “Alzheimer’s disease” OR “Cognition”) AND TI= (“Flavonoid” OR “Bioflavonoid” OR “Flavone” OR “Flavonol” OR “Flavanonies” OR “flavanoies” OR “isoflavonoid” OR “isoflavones” OR “catechins” OR “anthocyanidins” OR “chalcones” OR “Neoflavonoid” OR “Polyphenol” OR “Polyhydroxyphenol” OR “Provinol”)

From PubMed:

(Alzheimer [MeSH Terms] OR Dementia [MeSH Terms] OR Senile dementia [MeSH Terms] OR Alzheimer’s disease [MeSH Terms] OR Cognition [MeSH Terms]) AND (Flavonoid [MeSH Terms]OR Bioflavonoid [MeSH Terms] OR Flavone [MeSH Terms] OR Flavonol [MeSH Terms] OR Flavanonies [MeSH Terms] OR flavanoies [MeSH Terms] OR isoflavonoid [MeSH Terms] OR isoflavones [MeSH Terms] OR catechins [MeSH Terms] OR anthocyanidins [MeSH Terms] OR chalcones [MeSH Terms] OR Neoflavonoid [MeSH Terms] OR Polyphenol [MeSH Terms] OR Polyhydroxyphenol [MeSH Terms] OR Provinol [MeSH Terms])

APPENDIX B

Quality Evaluation Sheet

1. Study design

- Studies with cross-sectional data collection: 0 points
- Studies with longitudinal data collection (prospective): 1 point
- Intervention studies: 2 points

2. Sample size

- Small population for analysis: N<100: 0 points
- Intermediate population for analysis: N= 100-1000: 1 point
- Large population for analysis: N=1000: 2 points

3. Exposure

Observational studies

- If exposure is not measured: 0 points
- If exposure is measured through dietary questionnaires: 1 point (19)
- If exposure is measured through biomarkers (e.g. fluid biomarkers test, amyloid PET imaging, CSF Aβ42, tHcy levels, or presence or absence of *APOE ε4*): 2 points (19)

Intervention studies

- If the intervention was not blinded: 0 points
- If the intervention was single blinded: 1 point
- If the intervention was adequately double-blinded: 2 points

4. Outcome

- If the study used no appropriate outcome measurement method or if not reported: 0 points
- If the study used moderate quality outcome measurement methods (e.g. cognitive tests, mental and mood status testing): 1 point (1)

- If the study used adequate outcome measurement methods to rule out other causes of dementia-like symptoms (e.g. fluid biomarkers test, amyloid PET imaging, CSF Aβ42, tHcy levels, or presence or absence of *APOE ε4*): 2 points (1)

5. Adjustments

- If findings are not controlled for at least key confounders: 0 points
- If findings are controlled for key confounders (e.g. gender, family history, baseline diet, obesity, diabetes, smoking, etc.): 1 point
- If findings are controlled for additional confounders (e.g. key confounders + ethnicity, socioeconomic background, etc.): 2 points

APPENDIX C

Quality Evaluation Results

Table 2. Quality Evaluation.

Study	*Year*	*Study Design*	*Sample Size*	*Exposure*	*Outcome*	*Adjustments*	*Total*
Alharbi M.H. et al.	2016	2	0	2	1	1	**6**
Arab H. et al.	2016	2	0	0	2	2	**6**
Baum L. et al.	2008	2	0	2	2	1	**7**
Brickman A.M. et al.	2014	2	0	0	2	0	**4**
Butchart C. et al.	2011	0	2	1	1	2	**6**
Desideri G. et al.	2012	2	1	2	1	1	**7**
Devore E.E. et al.	2010	1	2	1	1	1	**6**
Devore E.E. et al.	2012	1	2	1	1	2	**7**
Downey L.A. et al.	2013	2	0	2	1	1	**6**
Gleason C.E. et al.	2015	2	0	0	2	2	**6**
Henderson V.W. et al.	2012	2	1	2	2	1	**8**
Ide K. et al.	2016	2	0	2	2	0	**6**
Ide K. et al.	2014	2	0	0	2	1	**5**
Kent K. et al.	2017	2	0	1	1	2	**6**
Kesse-Guyot E. et al.	2011	1	2	1	1	1	**6**
Krikorian R. et al.	2010	2	0	1	1	1	**5**
Morillas-Ruiz J.M. et al.	2010	2	1	2	2	0	**7**
Nooyens A.C.J. et al.	2015	1	2	1	1	2	**7**
Ringman J. et al.	2012	2	0	2	2	1	**7**
Root M. et al.	2015	1	2	1	1	2	**7**
Ryan J. et al.	2008	2	1	2	2	2	**9**
Turner R.S. et al.	2015	2	1	2	2	1	**8**
Wightman E.L et al.	2012	2	0	2	2	0	**6**
Yimam M. et al.	2016	2	0	0	1	1	**4**

APPENDIX D
Data Extraction Tables

Table 3.1 Clinical Trials. Part 1

Study	Year	Country	Population Age	Population Size	Aim	Duration of Supplementation	Type and Amount of Supplementation
Alharbi M.H. et al.	2016	UK	30-65	24	To investigate whether consumption of FR orange juice is associated with acute cognitive benefits.	8 weeks	240-ml FR orange juice (272 mg); placebo
Arab H. et al.	2016	Iran	67-91	30	To investigate the influence of green tea consumption on markers of oxidative stress in AD.	2 month	2 g/day of green tea pills
Baum L. et al.	2008	China	≥50	34	To examine curcumin's safety and effects on biochemical and cognitive measures in AD.	6 months	1 g/day or 4 g/day curcumin powder; 4 g/day color-matched placebo powder.
Brickman A.M. et al.	2014	US	50–69	41	To test whether high flavanol dietary intervention would enhance dentate gyrus' function in older humans.	3 months	High dietary flavanol: 900-mg/day of cocoa flavanols + 138 mg/day of epicatechin. Low dietary flavanol: 45mg/day of cocoa flavanols + <2 mg/day of epicatechin.
Desideri G. et al.	2012	Italy	64-81	90	To test whether dietary flavanols might improve cognitive function in subjects with mild cognitive impairment.	8 weeks	~990 mg/day (high flavanols), ~520 mg/day (intermediate flavanols), or ~45 mg/day (low flavanols) of cocoa flavanols.

Study	Year	Country	Population Age	Population Size	Aim	Duration of Supplementation	Type and Amount of Supplementation
Downey L.A. et al.	2013	Australia	μ 76.5	24	To assess the acute effects of a specific extract of *Bacopa monnieri* on cognitive performance.	6 weeks	320 mg or 640 mg of *Bacopa monnieri* on each testing day; placebo.
Gleason C.E. et al.	2015	US	≥60	65	To examine the potential cognitive benefits of soy isoflavones in patients with Alzheimer's disease.	6 months	100mg/day soy isoflavone; placebo.
Henderson V.W. et al.	2012	US	45–92	350	To determine the cognitive effects of long-term dietary soy isoflavones in a daily dose comparable to that of traditional Asian diets.	4 years	25 g/day of isoflavone-rich soy protein; milk-matched placebo
Ide K. et al.	2014	Japan	70-98	12	To investigate the effects of green tea consumption on cognitive dysfunction.	3 months	2 g/day of green tea powder.
Ide K. et al.	2016	Japan	μ 84.8	33	To assess the effects of green tea consumption on cognitive dysfunction	12 months	2 g/day of green tea powder; placebo powder.
Kent K. et al.	2017	Australia	≥70	49	To assess relationship between daily consumption of anthocyanin-rich and changes in cognitive function , blood pressure and anti-inflammatory effects in dementia patients.	12 weeks	200 ml/day of cherry juice (anthocyanin).
Krikorian R. et al.	2010	US	μ 76.2	16	To investigate the effects of daily consumption of wild blueberry juice on cognition.	12 weeks	Individuals weighing 54 to 64 kg were prescribed 444 mL/day, those weighing between 65 and 76 kg consumed 532 mL/day, and those weighing between 77 and 91 kg consumed 621 mL/day. Placebo juice.

Study	Year	Country	Population Age	Population Size	Aim	Duration of Supplementation	Type and Amount of Supplementation
Morillas-Ruiz J.M. et al.	2010	Spain	μ 76.5	100	To determine the effect of an antioxidant beverage rich in polyphenols on the plasmatic levels of tHcy in Alzheimer's patients.	8 months	200 mL/day) of antioxidant drink or placebo drink
Ringman J. et al.	2012	US	>49	36	To generate tolerability and preliminary clinical and biomarker efficacy data on curcumin in persons with AD.	24 weeks	2 gm/day, or 4 gm/day of Curcumin C3 Complex; placebo
Ryan J. et al.	2008	Australia	60-85	101	To examine the effects of the flavonoid antioxidant Pycnogenol (PYC) on a range of biochemical and cognitive measures.	3 months	150 mg/day of Pycnogenol; placebo.
Turner R.S. et al.	2015	US	>49	119	To test the safety, tolerability and effects of resveratrol on several biomarkers, volumetric MRI outcomes and clinical outcomes.	13 months	500 mg/day of Resveratrol (with dose escalation by 500-mg increments every 13 weeks); placebo.
Wightman E.L et al.	2012	UK	18-30	27	To assess the effects of oral ingestion of the 'green tea' polyphenol epigallocatechin gallate (EGCG) on cognitive performance, mood and localized cerebral blood flow (CBF) parameters in healthy human adults.	21 days	2 doses (135 and 270 mg) of EGCG in counterbalanced order on separate days; placebo.
Yimam M. et al.	2016	US	35-65	83	To analyse the effects of UP326 and assess the impact of the composition on speed and accuracy of processing complex information.	30 days	UP326 300mg/day; placebo.

Table 3.2. Clinical Trials. Part 2.

Study	Year	Quality Score	P-value 95% CI	Main Findings
Alharbi M.H. et al.	2016	6	$P < 0.05$	Performance on tests of executive function and psychomotor speed was significantly better following the FR drink compared to the placebo
Arab H. et al.	2016	6	$P = 0.000$	Increased levels of MDA, 8-OHdG and carbonyl, and increased antioxidant capacity of plasma.
Baum L. et al.	2008	7	$P = 0.36$	Curcumin intake resulted safe for patients however no statistically significant change was detected between treatment and control groups with respect to plasma Aβ 40.
Brickman A.M. et al.	2014	4	$P = 0.038$	A high-flavanol intervention was found to enhance DG function, as measured by fMRI and by cognitive testing.
Desideri G. et al.	2012	7	$P < 0.05$	Time required to complete cognitive and verbal tests was significantly lower in the high and intermediate flavonol groups, compared to the low flavonol group.
Downey L.A. et al.	2013	6	$P < 0.05$	The 320 mg dose of BM improved performance at the first, second, and fourth repetition post-dosing.
Gleason C.E. et al.	2015	6	$P = 0.15$	No significant differences in treatment effects emerged between treatment groups or genders.
Henderson V.W. et al.	2012	8	$P \leq 0.11$ [0.13-0.35]	There was no significant between-group difference on change from baseline in global cognition. Secondary analyses indicated greater improvement on a visual memory factor in the isoflavone group, but not for other cognitive factors or test scores.
Ide K. et al.	2014	5	$P = 0.03$	After three months of green tea consumption, the participants' MMSE-J scores were significantly improved.
Ide K. et al.	2016	6	$P = 0.59$; [−2.97, 1.74]	Green tea consumption did not significantly alter cognitive dysfunction, but it did prevent an increase in oxidative stress.
Kent K. et al.	2017	6	$P \leq 0.001$	Improvements in verbal fluency ($p = 0.014$), short-term memory ($p = 0.014$) and long-term memory ($p \leq 0.001$). Reduction in systolic blood pressure and trend for diastolic blood pressure. No significance alterations for markers of inflammation.

Study	Year	Quality Score	P-value 95% CI	Main Findings
Krikorian R. et al.	2010	5	$P = 0.03$	Improved paired associate learning ($p = 0.009$) and word list recall ($p = 0.04$).
Morillas-Ruiz J.M. et al.	2010	7	$P \leq 0.05$	Higher tHcy levels were observed in the AD moderate phase patients than in the AD initial phase patients and in the control group. Lower folate levels were observed in the AD moderate phase patients than in the AD initial phase patients and in the control group. Antioxidant drink *vs* placebo drink attenuated the tHcy increase in the control group and AD patients.
Ringman J. et al.	2012	7	$P = 0.41$	No evidence of efficacy of Curcumin C3 Complex in AD
Ryan J. et al.	2008	9	$P < 0.01$	Statistically significant interactions were found for memory-based cognitive variables and lipid peroxidation products. No change was evident for other aspects of cognitive performance, such as concentration or psychomotor abilities.
Turner R.S. et al.	2015	8	$P = 0.002$	Resveratrol was safe, well-tolerated, and altered some AD biomarkers (Aβ40, Aβ42, brain volume).
Wightman E.L et al.	2012	6	---	135 mg EGCG resulted in reduced CBF in the frontal cortex, but that this is not associated with changes in cognitive performance or mood.
Yimam M. et al.	2016	4	$P < 0.05$	Improvement in speed and accuracy of processing complex information compared to placebo group.

Table 4.1 Observational Studies. Part 1

Study	Year	Country	Population Age	Population Size	Aim	Study Design	Duration of Study	Measurements*
Butchart C. et al.	2011	Scotland	70	1091	To investigate the potential role of different subclasses of flavonoids in reducing cognitive decline, after adjusting for prior cognitive ability and other potential confounding variables.	Cross-sectional	3 years	Version 7.0 of the Scottish Collaborative Group FFQ, with 168 food items. The Moray House Test to test IQ. Other cognitive tests include: National Adult Reading Test (NART), Wechsler Adult Intelligence Scale-III UK (WAIS), Wechsler Memory Scale-III UK (WMS).
Devore E.E. et al.	2010	The Netherlands	≥55	5395	To study consumption of major dietary antioxidants in relation to long-term risk of dementia.	Prospective Cohort	14 years	Mini-Mental State Examination (MMSE) and Geriatric Mental State schedule (GMS) for dementia assessment. Home interviews, SFFQs for dietary assessment of 170 food items.
Devore E.E. et al.	2012	US	≥70	16010	To evaluate whether greater long-term intakes of berries and flavonoids are associated with slower rates of cognitive decline in older women.	Cohort	21 years	Willet SFFQ of 61 food items.
Kesse-Guyot E. et al.	2011	France	35-60	6850	To evaluate the long-term association between total and class-specific polyphenol intake and cognitive performance.	Cohort	2 years	24-h dietary record; cued recall test, RI-48, for memory evaluation; Forward and Backward Digit Span for working memory; Delis-Kaplan TMT for mental flexibility.

*Assessments of dietary intake and cognitive decline at baseline and follow-up.

Study	Year	Country	Population Age	Population Size	Aim	Study Design	Duration of Study	Measuraments*
Root M. et al.	2015	US	45–64	10,041	To test whether high intake of dietary flavonols in middle-aged adults is associated with decreased rates of cognitive decline over time.	Prospective cohort	11 years	FFQ with 60 food items. (WAIS-R), the delayed word recall test, Multilingual Aphasia Examination.
Nooyens A.C.J. et al.	2015	The Netherlands	43–70	2613	To assess the relationship between dietary intake of antioxidants (vitamin C, vitamin E, b-carotene, lutein, flavonoids and lignans) and cognitive decline at middle age.	Cohort	20 years	4 cognitive tests; FFQ on habitual consumption of 178 food items.

*Assessments of dietary intake and cognitive decline at baseline and follow-up.

Table 4.2. Observational Studies. Part 2.

Study	Year	Quality Score	P-value 95% CI	Main Findings
Butchart C. et al.	2011	6	$P = 0.003$	The associations were no longer statistically significant after adjusting for confounding factors, including childhood IQ.
Devore E.E. et al.	2010	6	HR, 0.75* [0.59–0.95]	Lower risk for AD among those with greater consumption of vitamin E. Vitamin C, beta carotene, and flavonoid intakes were unrelated to AD risk.
Devore E.E. et al.	2012	7	$P = 0.029$ [0.00–0.07]	Greater intakes of blueberries, strawberries, anthocyanidins and total flavonoids were associated with slower rates of cognitive decline.
Kesse-Guyot E. et al.	2011	6	$P = 0.01$	High total polyphenol intake was associated with better language and verbal memory ($P = 0.01$) but not with executive functioning ($P = 0.09$).
Root M. et al.	2015	7	$P < 0.001$	Total flavonols across quintiles of intake were positively associated with preserved combined cognitive function ($P < 0.001$).
Nooyens A.C.J. et al.	2015	7	$P = 0.01$	Higher lignan intake was linearly associated with less decline in global cognitive function ($P=0.01$), memory ($P<0.01$) and processing speed ($P=0.04$).Higher flavonoid intake was associated with greater decline in cognitive flexibility. Intake of other antioxidants was not associated with cognitive decline.

*HR = hazard ratio. It is the ratio of the hazard rates corresponding to the conditions described by two levels of an explanatory variable.

APPENDIX E

Medical Glossary

Amyloid beta-peptide accumulations = type of proteins which fold into polypeptides in the shape of β-sheet structures that aggregate into long fibers.

Antioxidant = a molecule that inhibits the oxidation of other molecules.

Apolipoprotein E (APOE) = a class of proteins involved in the metabolism of fats in the body.

Apolipoprotein E (APOE) gene = a gene which provides instructions for making a protein called apolipoprotein E.

Atherosclerosis = a disease of the arteries characterized by the deposition of fat, cholesterol, calcium, and other substances on the inner of their walls.

Beta-carotene = phytonutrient found in dark green and yellow fruits and vegetables.

Cancer = a disease caused by an uncontrolled division of abnormal cells in a part of the body.

Cardiopathies = any disorder which affects the heart. Heart diseases include: arrhythmia; congenital heart disease; coronary artery disease (CAD); dilated cardiomyopathy; myocardial infarction; heart failure; hypertrophic cardiomyopathy; mitral regurgitation; mitral valve prolapse; pulmonary stenosis.

Cardiovascular diseases = group of diseases affecting the heart or blood vessels. Cardiovascular diseases include: arteriosclerosis; coronary artery disease; heart valve disease; arrhythmia; heart failure; hypertension; orthostatic hypotension; shock; endocarditis; diseases of the aorta and its branches; disorders of the peripheral vascular system; and congenital heart disease.

Cerebral Blood Flow (CBF) = a measurement or parameter of the ability of blood to perfuse brain tissue adequately.

Cellular ageing = the progressive decline in the resistance to stress and other cellular damages, causing a gradual loss of cellular functions and resulting eventually in cell death.

Cholesterol = a compound required by the body as a building block for cell membranes and for hormones such as estrogen and testosterone.

Chronic inflammation = a prolonged inflammatory response that involves a progressive change in the type of cells present at the site of inflammation. It is characterized by the simultaneous destruction and repair of the tissue from the inflammatory process.

Cognitive dysfunction = the loss of intellectual functions such as thinking, remembering, and reasoning of sufficient severity to interfere with daily functioning.

Cognitive functioning = a set of cognitive processes that are necessary for the cognitive control of a behaviour and consequent attainment of one's goal.

Cognitive performance = the ability to utilize the knowledge acquired by mental processes in our brains.

Dentate gyrus = part of a brain region known as the hippocampus which is involved in the formation of new memories.

Depression = a medical condition which involves the body, mood, and thoughts of an individual, usually affecting the way a person eats, sleeps, feels about himself or herself, and thinks about things.

Diabetes = a disease in which the body is not capable to produce or respond to insulin adequately, resulting in elevated levels of glucose in the blood.

Down Syndrome = a congenital disorder arising from a defect in chromosome 21, causing intellectual impairment and physical abnormalities.

Geriatric diseases = diseases mostly affecting the elderly.

Heart disease = any disorder which affects the heart. See definition of "Cardiopathies".

Head trauma = any trauma to the scalp, skull, or brain.

Hyperhomocysteinemia = medical condition characterized by an abnormally high level of homocysteine in the blood, conventionally described as above 15 μmol/L.

Hypertension = a condition in which blood pressure is abnormally high.

Incidence = measure of new cases arising in a population over a given period of time, such as month or year.

***In vitro* studies** = studies which are performed with microorganisms, cells, or biological molecules outside their normal biological context.

***In vivo* studies** = studies in which the effects of various biological entities are tested on whole, living organisms or cells, usually animals, including humans, and plants, as opposed to a tissue extract or dead organism.

Kidney degeneration = a type of kidney disease in which there is gradual loss of kidney function over a period of months or years.

Kinetics = the rates of chemical or biochemical reaction.

Liver degeneration = a type of liver disease in which there is gradual loss of liver function over a period of months or years, causing the liver to fail.

Malnutrition = it can refer to "under-nutrition", which includes stunting (low height for age), wasting (low weight for height), underweight (low weight for age) and micronutrient deficiencies or insufficiencies (a lack of important vitamins and minerals); it can also refer to overweight, obesity and diet-related non-communicable diseases

Metabolic syndrome = group of conditions that occur together, including: high blood pressure, increased blood sugar, excessive body fat around the waist, and abnormal cholesterol level or triglyceride levels.

Metabolism = the chemical processes that occur within a living organism in order to sustain life, including the digestion and the transport of substances between different cells.

Mild cognitive impairment (MCI) = an intermediate stage between the expected cognitive decline of normal aging and the more-serious decline of dementia. It involves problems with memory, language, and thinking that are usually greater than normal age-related changes.

Muscle depletion = loss of muscle tone, due to ageing, diet, lack of sleep, lack of physical activity or illness.

Neurodegeneration = the progressive loss of function and structure of neurons, including death of neurons.

Neurotoxicity = a form of toxicity in which a biological, chemical, or physical agent produces an adverse effect on the structure or function of the central and/or peripheral nervous system.

Obesity = a medical condition where excessive fat has accumulated to the extent that is harmful for human health. A person is usually defined obese when has a BMI equal to or higher than 30 km/m^2.

Osteoporosis = a disease which causes thinning of the bones and reduction in bone mass, due to depletion of calcium and bone protein. Osteoporosis can lead to fractures, which often do not heal properly.

Oxidation = a chemical reaction which, if free radicals are produced, can lead to damage of the cells.

Oxidative stress = imbalance between production of free radicals and antioxidant defences, which can produce cells' damage.

Prevalence = proportion of a population affected by a certain disease or condition.

Weight loss = a reduction of the total body mass, due to either a mean loss of fluid, body fat or adipose tissue, or because of loss of lean mass, namely bone mineral deposits, muscle, tendon, and other connective tissue.

Reference

[1] H. Posner, R. Curiel, C. Edgar, S. Hendrix, E. Liu, D.A Lowenstein, et al., Outcomes assessment in clinical trials of Alzheimer's disease and its precursors: readying for short-term and long-term clinical trial needs, Innoy Clin Neurosci 14, 2017, 22-29·