Additional Table 1: Clinical trials investigating the effects of caffeine on cognitive function in dementia

Study	Study design	Number of subjects	Age (yr)	Caffeine	Cognitive assessment	Adjusted by	Caffeine's effect on cognition	Caffeine as a cognitive normalizer	Sex differences	Main outcomes
Sugiyama et al. (2016)	Longitudinal	13,137 dementia free subjects. Men = 5922 Female = 7215	≥ 65	FFQ at baseline: Never/ occasionally/1–2 cups/d/≥ 3 cups/d	Long-term Care Insurance database after a 5.7-year follow up	Baseline age, BMI, education, green tea consumption, CVD history, fractures, stroke, diabetes, smoking, alcohol intake, and social support	Positive		The lower risk of dementia was more remarkable among women	Coffee consumption was associated with a lower incidence risk of dementia
Driscoll et al. (2016)	Longitudinal	6467 females	65 – 80	FFQ at enrolment: < 75 mg/75 – 174 mg/175 – 189 mg/≥ 190 mg	Annually testing for 10 years using a 100-point mMMSE Dementia questionnaire	Age, race, BMI, education, diabetes, hypertension, history of CVD, depression, hormone therapy, sleep quality index, smoking, and alcohol habits	Positive		N/A	Women with above-median (175 mg/ d) caffeine intake had a lower risk of developing dementia or any cognitive impairment compared to those who consuming below median amounts
Arab et al. (2011)	Longitudinal	4799 dementia free subjects Male = 2077 Female = 2722	≥ 65	Tea or coffee consumption under FFQ at baseline: < 5×/yr/5 – 10×/yr/1 – 3×/mon/1 – 4×/wk/≥ 5×/wk	Annually assessment using a mMMSE for 7.9 years follow up	Age, education, socioeconomic status, depression, medical history, APOE 4 genotype, and smoking	Positive		The beneficial effect was only found in women	Attenuated rate of cognitive decline among some female tea and coffee consumers compared with female non-consumers
Ritchie et al. (2007)	Longitudinal	7017 dementia free subjects Male = 2820 Female = 4197	≥ 65	Standardized interview with questions by health professional at baseline: 0 – 100 mg/ d/100 – 200 mg/d/200 – 300 mg/d/> 300 mg/d	MMSE, Issacs set test, Benton visual retention test, and Diagnostic and Statistical Manual of Mental Disorders-IV over 4 years follow up	Age, sex, BMI, medical history, education, diet, lifestyle, alcohol, and tobacco use	Positive		The protective effect was only observed in women	Women with 300 mg/d coffee showed less decline in verbal retrieval and visuospatial memory than women consuming ≤ 1 cup/d
Gelber et al. (2011)	Longitudinal	3734 cognitive healthy Japanese American male and 418 autopsy sub-group	71 – 93	24 h dietary recall questionnaire at baseline: 0 – 137.0 mg/d/138.5 – 231.0 mg/d/251.5 – 391.5 mg/d/411.0 – 1872.5 mg/d	100-point Cognitive Abilities Screening Instrument	Age, BMI, physical activity index, cigarette smoking, alcohol consumption, education, number of childhood years spent in Japan, occupational complexity, marital status, elevated cholesterol, hypertension, diabetes, CVDs, and APOEε4 genotype	No effect		N/A	No association between coffee intake in midlife and risk of cognitive impairment. Higher coffee consumption (≥ 411.0 mg/d) is associated with any type of brain lesions from 418 subgroup autopsy

Additional Table 1: Continued

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Mirza et al. (2014)	Stratified longitudinal	5408 cognitively healthy subjects (1989 – 1991) Male = 2216 Female = 3192 4368 cognitively healthy subjects (1997 – 1999) Male = 1791 Female = 2577	0 – 1 cup/d: 70.3±8.6 > 1 – 3 cups/d: 69.5±7.8 > 3 cups/d: 66.3±7.	Baseline and follow-up questionnaire: 0 – 1 cup/d/> 1 – 3 cups/d/> 3 cups/d	MMSE, geriatric mental schedule, and Cambridge assessment for mental disorders for short (0–4 yr) and long (4–21 yr) follow-up	Age, BMI, health, lifestyle, alcohol, and tobacco use	No effect			In the follow-up stratum of 0 – 4 yr, > 3 cups/d coffee consumption was associated with a lower risk of dementia then < 1 cup/d Coffee consumption is not associated with incident dementia during long term
Araújo et al. (2016)	Longitudinal and cross-sectional subgroup	Longitudinal: 2454 subjects Male = 1104 Female = 1350 Cross-sectional: 2914 subjects Male = 1306 Female = 1608	59.3 ± 7.2	FFQ at baseline: 0 – 1 cup/d/> 1 – 3 cups/d/> 3 cups/d	Letter digit substitution task, the Stroop test, Word Fluency test, the 15-Word Learning test, and the Purdue Pegboard both hands for 5 year follow-up	Educational attainment, BMI, hypertension, diabetes mellitus type 2, alcohol consumption, smoking habits, coronary heart disease history, depression, and psycho-analeptic drug use	No effect			No association found longitudinally. Higher coffee consumption was associated with a lower prevalence of lacunar infarcts, smaller hippocampal volume, and better cognitive performance cross-sectionally
Vercambre et al. (2013)	Longitudinal	2475 cognitive normal female with CVD risk	≥ 65	Willett semi-quantitative food questionnaire at baseline: < 30 mg/d/30 – 111 mg/d/112 – 203 mg/d/204 – 371 mg/d/> 371 mg/d	Telephone Interview of Cognitive Status, a telephone adaptation of the MMSE, 10-word list (immediate and delayed recall), the East Boston Memory Test (immediate and delayed recall), and category fluency test every second year (mean time = 5.4 years)	Age, education, marital status, alcohol intake, physical activity, use of multivitamin supplements, smoking, BMI, history of depression, CVDs, revascularization surgery, angina, transient ischemic attack, diabetes, hypertension, and hyperlipidaemia	Positive		N/A	Caffeine intake was related to better cognitive maintenance over 5 years follow-up among ≥ 65 years old women with vascular deficits
Solfrizzi et al. (2015)	Longitudinal	1445 cognitively normal subjects Male = 815 Female = 630	65 – 84	FFQ at 1992 – 1993 and 1995 – 1996: 0 – 1 cup/d/1 – 2 cups/d/> 2 cups/d	The Babcock Story Recall Test and MMSE	Age, sex, pack years cigarettes, current alcohol intake, coronary artery disease, stroke, type 2 diabetes, hypertension, APOE A-I, MMSE score at first survey, geriatric depression scalre score, and tea consumption	Positive and negative			Constant habit of 1 – 2 cups/d of coffee per day had a reduced rate of MCI incidence than those who have < 1 cup/d, while the change of habitual drinking pattern increased the risk of MCI
Eskelinen et al. (2009)	Longitudinal	1409 subjects Male = 534 Female = 875	65 – 79	Survey questionnaire at baseline: 0 – 2 cups/d/3 – 5 cups/d/> 5 cups/d	MMSE	Age, sex, education, follow-up time, community of residence, midlife smoking, systolic blood pressure, serum total cholesterol, body mass index, physical activity, APOEε4, late-life myocardial infarction/stroke/diabetes mellitus, and Beck depressive scale	Positive		No sex difference between coffee/tea drinking and the risk of dementia/AD	Coffee but not tea consumption at midlife had a significantly reduced risk of developing dementia and AD

Additional Table 1: Continued

Study	Study design	Number of subjects	Age (yr)	Caffeine	Cognitive assessment	Adjusted by	Caffeine's effect on cognition	Caffeine as a cognitive normalizer	Sex differences	Main outcomes
Santos et al. (2010b)	Longitudinal	531 subjects Follow-up: male = 128 and female = 181	≥ 65	FFQ at baseline: < 22 mg/d/22 – 62 mg/d/> 62 mg/d	MMSE at the baseline and at follow-up	Age, education, diabetes, smoking, alcohol drinking, BMI, and hypertension	Positive		No correlation found in men	> 62 mg/d caffeine intake was associated with a lower risk of cognitive decline than < 22 mg/d among women only
West et al. (2019)	Cross-sectional	638 subjects with T2D Male = 394 Female = 244	Young: 64 – 71.5 Old: 71.5 – 86	FFQ at baseline and estimated: 204.2 ± 114.5 mg/d for all participants, 214.94 ± 125.4 g/d for young group, and 193.64 ± 101.7 mg/d for older group	Neuropsychological test battery examining episodic memory, working memory, executive function, and semantic categorization	Age, sex, years of education, LDL and HDL cholesterol, systolic and diastolic blood pressure, T2D, APOE genotype, serum albumin, serum thyroid-stimulating hormone, smoking, and CVDs	Positive	The overall cognitive improvement associated with higher caffeine intake were more significant in the older group		Higher caffeine intake was associated with better overall cognition
Paganini-Hill et al. (2016)	Longitudinal	587 cognitively normal subjects	90 – 103	Self-reported questionnaire at baseline and Leisure World Cohort health survey (1981 – 1985): < 50 mg/50 – 199 mg/> 200 mg	Neurological examination, MMSE, informant questionnaires, Cognitive Abilities Screening Instrument and Dementia Questionnaire	Age, sex, education, smoking, alcohol consumption, exercise and other activities	Positive			Consumers of ≥ 200 mg/d caffeine had a 34% lower risk of dementia compared with those who consuming < 50 mg/d
Cao et al. (2012)	Longitudinal	124 subjects *n* = 81 in Miami cohort, *n* = 43 in Tampa cohort	65 – 88	Baseline plasma caffeine level measurement in two combined cohorts: Normal: 1750 ng/mL, MCI: 900 ng/mL, Dementia: 1100 ng/mL	MMSE, Three-trial Fluid Object Memory Evaluation, and Hopkins's verbal Learning Test for 2–4 years follow up	N/A	Positive			Plasma caffeine levels were significantly lower in MCI subjects who progressed to dementia in during follow up than stable MCI subjects
Haller et al. (2017)	Longitudinal	45 elderly controls Male = 20, Female = 25 18 with MCI Male = 11, Female = 7	Stable controls = 70.0 ± 4.3 Deteriorating controls = 73.4 ± 5.9 MCI = 71.6 ± 4.7	Self-reported chronic coffee consumers (200 mg)	MMSE, working memory (n-back) and functional MRI at the baseline with the follow-up period of 18 mon	Age, sex, and education	Positive	Reduced sensitivity of caffeine effects only in deteriorating control subjects		Deteriorating control group showed a less pronounced acute caffeine-induced brain activation compared to stable controls
Haller et al. (2018)	Longitudinal	145 cognitively preserved subjects Male = 65 Female = 80	Stable-stable = 73 ± 3 Intermediate = 73 ± 3 Deteriorating-deteriorating = 74 ± 4	Substance questionnaire at baseline: Light = 0 – 28 cups/mon; Moderate = 29 –60 cups/mon; Heavy = 61 – 168 cups/mon	MMSE, attention (Digit-Symbol Coding, Trail Making Test A), working memory (verbal: Digit Span. Forward), visuo-spatial (Visual Memory Span (Corsi), episodic memory (verbal: RI-48 Cued Recall Test), visual (Shapes test), executive functions (Trail Making Test B, Wisconsin Card Sorting Test and Phonemic Verbal Fluency Test), language (Boston Naming), visual gnosis (Ghent Overlapping Figures), and praxis (ideomotor, reflexive, and constructional) at the baseline and during 3-year follow-up	Age, sex, education level, and MMS	Positive	Protective effects of caffeine against cognitive decline only in stable-stable		Moderate coffee consumption was associated with better white matter preservation and cerebral blood flow in cognitively stable elders only

Additional Table 1: Continued

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Fischer et al. (2018)	Longitudinal	2622 dementia-free subjects Male = 910 Female = 1712	≥ 75	8-item cognitive health food questionnaire at baseline: Never/< 1 time/wk /1 time/wk/ Several times/ wk/Everyday	Structured interview for the diagnosis of dementia of the Alzheimer type, ten-item Word List Immediate Recall subtest, ten-item Word List Delayed Recall subset, and ten-item Word List Recognition subtest during eight follow-up visits for 10 yr (with an 18-mon interval between each follow-up)	Age, sex, BMI, education, APOEε4, smoking status, physical activity, depression, hypercholesterolemia, and modified Charlson comorbidity index	No effect			No association between coffee/tea intake with memory decline or AD incidence
Cornelis et al. (2020a)	Cross-sectional	445,786 self-reported cognitively healthy subjects	35 – 73	Tea or coffee under Touchscreen questionnaire: None/< 1 cup/d/1 cup/d/2 – 3 cups/d /4 – 5 cups/d/6 – 7 cups/d/≥ 8 cups/d	Self-administered cognitive functioning tests using a touchscreen system (2006–2010, prospective memory, fluid intelligence and Pairs Matching) or on home computers (2014, symbol digit substitution, and Trail making test B)	Age, sex, baseline smoking, Townsend deprivation index, education, income, employment status, homeownership, self-reported health, waist-to-hip ratio, physical activity, fasting time and intakes of alcohol, water, fish, red meat, fruit, and vegetables, and tea consumption	No effect			Consumption of ≥ 1 cups/d coffee significantly decreased performance on all cognitive function tests
Cornelis et al. (2020b)	Cross-sectional	434,900 self-reported cognitively normal subjects	35 – 73	Touchscreen questionnaire: Cups of coffee per day/< 1 cup/ d/Do not know/ Prefer not to answer Type of coffee: Decaffeinated coffee (any type)/ Instant coffee/ Ground coffee	Prospective Memory Test, Pairs Matching Test, Fluid Intelligence Test, and Reaction Time Test	Age, sex, smoking, Townsend deprivation index, education, income, employment status, home-ownership, self-reported health, alcohol intake, water intake, fish intake, red meat intake, fruit intake, vegetable intake, waist-to-hip ratio, physical activity, fasting time, and habitual coffee and tea intake	No effect			No significant and consistent effect between caffeine intake and memory/ cognition was established among white and non-white subjects
Dong et al. (2020)	Cross-sectional	2513 subjects Male = 1214 Female = 1299	≥ 60	2× 24-h dietary recall interview: Caffeinated coffee intake: No caffeinated coffee intake, intake/1 – 384.8 g/d/384.8 g/d or more Decaffeinated coffee consumption: no decaffeinated coffee intake and more than 0 g/d	CERAD Word Learning sub-test, the Animal Fluency test and the DSST	Age, sex, race, education level, marital status, poverty-income ratio, BMI, total energy, drinking status, smoking status, hypertension, diabetes, and stroke	Positive			Only caffeinated coffee was associated with improved cognition
Iranpour et al. (2020)	Cross-sectional	1440 cognitively normal subjects Male = 700 Female = 740	≥ 60	24 h dietary recall survey Quartiles of caffeine intake for CERAD score immediate recall: 164.1 11.7/153.2 9.4/168.5 11.04/170.9 11.8 For CERAD score delayed recall: 139.8 10.5/153.6 13.0/197.6 11.3/165.7 14.2	CERAD Word List Learning Test, CERAD Word List Recall Test, the Animal Fluency test, and the DSST	Sex, race, education, marital status, family poverty income ratio, home status, employ status, age, total number of people in the household, self-rated health, history of stroke, physical activity, diabetes, vitamin D, vitamin K, phosphorus, magnesium, sodium, protein, dietary fibre, lycopene, lutein + zeaxanthin, niacin, total choline, added vitamin B12, vitamin A, vitamin C, retinol activity equivalents, depression, alcohol, carbohydrate, added alpha-tocopherol, folic acid, total polyunsaturated fatty acids, thyroid, and copper	Positive		The positive association between caffeine and cognition is stronger among men	Caffeine intake was significantly associated with improved CERAD word list recall test

Additional Table 1: Continued

Study	Study design	Number of subjects	Age (yr)	Caffeine	Cognitive assessment	Adjusted by	Caffeine's effect on cognition	Caffeine as a cognitive normalizer	Sex differences	Main outcomes
Ritchie et al. (2010)	Cross-sectional	641 subjects Male = 317 Female = 324	≥ 65	Caffeine intake questions in interview: ≤ 100 mg/d/200 – 300 mg/d/> 300 mg/d	WML volume and ratio of WML to cranial volume	Age, education, mobility, confinement to home and neighbourhood, height, weight, alcohol consumption, tobacco use, history of respiratory disorders, cancer, hypertension, hypercholesterolemia, diabetes, stroke, angina pectoris, myocardial infarction, cardiac and vascular surgery, and BMI	Positive		The significant positive association between caffeine consumption and lower cognitive alteration is only found in women	Those women who consumed > 300 mg/d caffeine have significantly lower mean log transformed white matter lesion/cranial volume ratios than consuming 200 – 300 mg/d or ≤ 100 mg/d
Kyle et al. (2010)	Cross-sectional	351 dementia-free subjects Male = 175 Female = 176	64	MONICA food frequency questionnaire: Quartiles of caffeine intake (mg/d): 226 – 504/505 – 634/635 – 751/743 – 1134	MMSE, Raven's Standardized Progressive Matrices, Digit Symbol, Block Design subtests of the Wechsler Adult Intelligence Scale-revised, and Rey Auditory Verbal Learning Test	Gender, SES, childhood intelligence, education, neuroticism, HADS-anxiety, and -depression	No effect			Self-reported caffeine intake has no effect on cognitive performance
Ritchie et al. (2014)	Cross-sectional	1193 cognitively healthy subjects Male = 473 Female = 720	≥ 65	Caffeine questionnaire at baseline interview: ≥ 300 mg/d	MMSE	Age, sex, education, CVDs, hypertension, BMI, HDL, triglycerides, mobility, baseline depressive symptoms, respiratory pathologies, and baseline diabetes	No effect			No statistically significant association between caffeine and Aβ levels
Kim et al. (2019)	Cross-sectional	411 (282 cognitively normal subjects + 129 MCI subjects) Male = 179 Female = 232	55 – 90	Coffee intake questions in interview: < 2 cups/d/≥ 2 cups/d	Korean version of the Consortium to Establish a Registry for Alzheimer's Disease Assessment Packet	Age, sex, education, APOEε4, clinical diagnosis, LCA score, occupational complexity, annual income status, VRS, GDS score, smoking status, alcohol status, duration of coffee intake, and age of first coffee intake,	Positive			≥ 2 cups/d coffee intake was significantly associated with lower Aβ positivity compared to < 2 cups/d
Haller et al. (2014)	Randomized control	17 MCI 17 healthy controls	MCI: 68.3 ± 2.8 Healthy controls: 70.7 ± 4.6	Caffeine tablets (200 mg) and placebo tablets	MMSE, attention (Trail Making Test A), working memory (verbal: Digit Span Forward, visuo-spatial: Visual Memory Span (Corsi), episodic memory (verbal:RI-48 Cued Recall Test), executive functions (Trail Making Test B, Wisconsin Card Sorting Test, and Phonemic Verbal Fluency test), language (Boston Naming, visual gnosis (Ghent Overlapping Figures), and constructional praxis (CERAD Figures copy)	Age, sex, handedness, and education	Positive	In MCI, a significant-caffeine related enhancement in the activation of the prefrontal cortex, supplementary motor areas, ventral premotor, parietal cortex, basal ganglia, and cerebellum compared to healthy individuals		Acute caffeine administration induced a more prefrontal activation in healthy individuals and a more diffuse posteromedial activation in MCI
Lin et al. (2021)	Randomized control	20 healthy subjects	18 – 35	3 × 150 mg/d	N-back test	Total cerebral blood flow	Positive			Higher caffeine intake induced a significant reduction in grey matter volumes in the medial temporal lobe

Note: FFQ: food frequency questionnaire; AD: Alzheimer's disease; Aβ: amyloid-β; MMSE: mini-mental state evaluation/examination; mMMSE: modified mini-mental state evaluation; BMI: body mass index; APOEε4: apolipoprotein Eε4; LDL: low-density lipoprotein; HDL: high-density lipoprotein; CERAD: Consortium to Establish a Registry for Alzheimer's Disease; CVD: cardiovascular disease; MCI: mild cognitive impairment; MONItor trends in cardiovascular diseases; N/A: not applicable; T2D: type 2 diabetes; MRI: magnetic resonance imaging; DSST: Digit Symbol Substitution Test; SES: socioeconomic status; LCA: lifetime cognitive activity; GDS: geriatric depression scale; VRS: vascular risk score.