High Coffee Consumption, Brain Volume and Risk of Dementia and Stroke

James S. Ritter

Department of Healthcare Informatics, Hahn School of Nursing

HCIN 549: Biostatistics

Professor Alexandrea Cronin

August 20, 2021

High Coffee Consumption, Brain Volume and Risk of Dementia and Stroke

Coffee is one of the most prevalent and recognizable beverages, ameliorating early mornings for millions worldwide. According to a survey conducted by the National Coffee Association (2020), 62% of Americans consume an average of three cups daily. Many identify the beloved beverage with the stimulating effects caused by the bean's intrinsic caffeine content, which acts on the central nervous system to improve cognition, promote wakefulness, and increase motor functioning (Gonzalez & Ramirez, as cited in Pham et al., 2021, p. 1). The stimulating effects of caffeine are due to its competitive inhibition of adenosine receptors in the brain, which help regulate various cognitive functions like sleep, arousal, and memory (Sebastiao & Ribeiro, 2009). Caffeine's propensity to block these receptors is associated with short-term increases in wakefulness and cognition, likely caused by the release of catecholamines (e.g., norepinephrine) that further enhance the stimulating effects that coffee drinkers so gladly welcome (Ribeiro & Sebastiao, 2010).

Caffeine's stimulating effects are well-understood, and its mechanism of action has been the subject of research projects for decades. Until recently, studies that examine the long-term effects of habitual caffeine ingestion on neurodegeneration have been scarce, featuring small sample sizes and supplying inconsistent results. Alarmingly, long-term adenosine receptor inhibition appears to be related to reductions in brain volume, increasing the risk of dementia and stroke. (Rebola et al., 2008, as cited in Pham et al., 2021, p. 1) Given coffee's pervasiveness in societies worldwide, the need for research regarding the risks associated with regular and long-term caffeine consumption is urgent. To this end, a team of researchers, based at the University of South Australia and led by Ph.D. Candidate Kitty Pham, performed a monumental secondary analysis of clinical data collected in the United Kingdom to investigate potential associations that

may exist between habitual coffee consumption, brain volume, and the incidence of dementia and stroke (Pham et al., 2021).

Clinical data formed the foundation of the study-in-focus. The researchers sourced health information from the UK Biobank, a comprehensive biomedical database aimed at tracking and improving patient outcomes while supplying an accessible data source for researchers. The UK Biobank (2021) comprises health information acquired through the organization's long-term cross-sectional study, that between 2006 and 2010, enrolled over half a million Britons. Participants consented to share personal health information with the organization during their initial assessment, submitted saliva, blood, and urine samples for genomic analysis, and completed questionnaires to assess various lifestyle factors. The database is regularly updated with depersonalized medical data gathered in follow-up assessments. In 2014, the UK Biobank also incorporated an imaging sub-study to conduct MRI scans for approximately 20% of the original cohort. Pham et al. pulled information from participant health records, self-reported lifestyle factors, and neuroimaging analyses to explore possible associations between coffee consumption, neurodegeneration, and the risk of dementia or stroke.

How the Research Was Conducted

The research team led by Pham conducted a secondary analysis of extant data provided by the UK Biobank to investigate any associations between habitual coffee consumption and risk of dementia or stroke. From the UK Biobank's original 502,504 participant cohort, Pham et al. enrolled 398,646 participants in the study. 54.3% of participants were female and 45.7% were male with ages ranging from 37 – 73 years old. The researchers defined exclusion criteria as prior diagnoses of dementia or stroke, non-response to questions regarding coffee consumption, and identification as non-Caucasian. The research team implemented the final exclusion

requirement because of the vast over-representation of white-British nationals in the original cohort. Unfortunately, critics frequently cite the Biobank's considerable selection bias toward healthy participants from higher socioeconomic backgrounds. Neither the original cohort nor the sample groups were representative of the British population. From the eligible participants, researchers then selected a sub-sample of 17,702 individuals for brain volume analysis on the condition that they had previously completed the Biobank-sponsored MRI neuroimaging sub-studies. Pham's research team was working with depersonalized clinical data and had no contact with the participants involved.

All eligible participants self-reported their daily coffee consumption through a survey that included a question asking, "How many cups of coffee do you drink a day?" Participants were also asked, "What type of coffee do you usually drink?" to identify and group decaffeinated (decaf) coffee drinkers. Based on these responses, the researchers organized participants into seven categories: non-drinkers, decaf coffee drinkers, less than 1 cup per day, 1 – 2 cups per day, 3 – 4 cups per day, 5 – 6 cups per day, and more than 6 cups per day. Regardless of the daily amount, decaf coffee drinkers were all grouped into the same category, highlighting the study's focus on habitual caffeine consumption.

Researchers collected information on the incidence of stroke and dementia through various sources, including data from electronic health records and national death registers. The team grouped dementia diagnoses into three main subtypes: vascular dementia, frontotemporal dementia, and Alzheimer's disease. All centrally adjudicated stroke and dementia diagnoses that occurred between the Biobank's initial assessment (2006 – 2010) and the follow-up assessment (2018) were included in the analysis.

Participants included in the Brain Volume sub-study completed MRI neuroimaging approximately 4-6 years after their initial assessment by the UK Biobank. All scans were completed and processed according to the UK Biobank's Brain Imaging Protocol. The resulting MRI scans allowed researchers to gather continuous data about volume measures for the total brain, white matter areas, gray matter areas, hippocampus, and white matter hypertrophies. The researchers excluded brain volumes that were not within three standard deviations of the mean.

Pham et al. identified 27 covariates with potential impacts on neurological health based on the participants' self-reported responses to the questionnaires completed at their initial assessment. Aside from the basic covariates of sex, age, age squared, and assessment center, researchers organized additional covariate groups relating to socioeconomic status, anthropometric measures, dehydration indicators, and lifestyle factors (see Appendix A for information about data collection and covariate categorization).

Collected Data, Analysis, and Results

Pham et al. decided to designate very light coffee drinkers (1 – 2 cups per day) as the control group for this study to avoid introducing bias from non-coffee drinkers who may choose to abstain due to poor health. The researchers used linear regression to understand the relationship between coffee consumption and brain volume, testing variance by including multiplicative variables relating to coffee consumption, age, and sex in the regression models. For the association between coffee consumption and incidence of dementia and stroke, the researchers employed logistic regression with similar variance testing. Both sets of models included adjustments for each covariate group. Coffee consumption, the primary independent variable in both sub-studies, was organized into the seven categories listed above. Brain volume measures were continuous

Researchers also conducted sensitivity analyses in subsets of the included sample to determine whether external factors had influenced the study in unexpected ways. For example, the team conducted sensitivity analyses using decaf coffee, organized with the same categorical variables as its caffeinated counterpart (i.e., none, 1 - 2 cups per day, etc.). Certain factors, like age and smoking, have been shown to increase the risk of neurological disease and were accordingly included as sensitivity analyses to ensure that they were not skewing the results. In addition, researchers completed sensitivity analyses organized by dementia subtype to see if coffee consumption was linked to specific presentations of the disease.

Missing variables were remedied using Multivariate Imputation by Chained Equations (MICE). This process creates multiple datasets by filling in missing information based on observed values for specific covariates to reduce variability in the sample. (Azur et al., 2011). Fortunately, most covariates were missing data points in less than 4.7% of participants, except for blood pressure (8.76%) and income (13.84%). Interestingly, approximately 30% of participants (n = 118,316) had incomplete data for at least one covariate measure.

Based on data from the baseline assessment, coffee consumption was associated with many covariates, like blood pressure and smoking status. Also, sex- and BMI-adjusted smaller brain volumes seemed to correlate with an increased incidence of dementia and stroke, especially in covariates that are known to be associated with a decreased brain volume, like depression status. Understandably, a history of chronic or mental illness was associated with an increased incidence of dementia and stroke (see Appendix B).

Coffee consumption presented an inverse linear association with brain volume. High consumption was correlated with a significant decrease in total brain, white matter, gray matter, and hippocampal volumes (see Appendix C). However, as the regression model was adjusted to

include each group of covariates, the significance level of the inverse linear association was slightly diminished (see Appendix D). However, this pattern did not hold true for the association between coffee consumption and white matter hypertrophy volumes ($P > 0.15$). Decaf coffee did not reflect this or any significant, inverse linear pattern (see Appendix E). Researchers modeled the relationship between coffee consumption and incidence of dementia and stroke using logistic regression. The risk of developing dementia displayed a non-linear association and seemed to follow a U-shaped pattern with increasing coffee consumption. While heavy coffee drinkers (> 6 cups per day) were correlated with the largest incidence of dementia (odds ratio = 2.17, odds $\text{ratio}_{adj} = 1.53$), participants who drank 1 – 2 cups per day presented the lowest odds ratio of developing dementia. (odds ratio = 1.00, odds $\text{ratio}_{adj} = 1.00$). In the model adjusted for basic covariates, non-coffee drinkers and decaf drinkers presented higher odds ratios (odds $\text{ratio}_{none} = 1.36$, odds $\text{ratio}_{decaf} = 1.23$) than very light-coffee drinkers (1 – 2 cups per day). The regression models did not reflect the same pattern when adjusted for all covariates, with decaf drinkers having a higher risk than both non-coffee drinkers and very light-coffee drinkers (odds $\text{ratio}_{none\ adj} = 1.36$, odds $\text{ratio}_{decaf\ adj} = 1.23$). In the case of stroke risk, the same general pattern was upheld, with very light-coffee drinkers (VL) presenting the lowest odds ratio, very-heavy (VH) coffee drinkers presenting the greatest odds, and non-coffee drinkers presenting in between (odds $\text{ratio}_{VL} = 1.00$, odds $\text{ratio}_{VH} = 1.60$, odds $\text{ratio}_{none} = 1.27$). Although adjusting for all covariates reduced the odds ratio for each category, the same general pattern was upheld (odds $\text{ratio}_{VL\ adj} = 1.00$, odds $\text{ratio}_{VH\ adj} = 1.17$, odds $\text{ratio}_{none\ adj} = 1.14$) (see Appendix F).

The sensitivity analyses for decaf-coffee drinkers, participants over 60 years old, and non-smokers all showed similar, U-shaped patterns of association between increased coffee consumption and incidence of dementia and stroke (see Appendices G, H, and I, respectively). In

addition, the association between coffee consumption and the incidence of Alzheimer's disease presented a similar pattern as in the aforementioned analyses (see Appendix J). Interestingly, tea consumption did not show a similar association pattern with the incidence of dementia or stroke (see Appendix K).

Conclusion

While coffee drinkers seem to enjoy the stimulating effects of caffeine, the molecule's inhibition of adenosine receptors in the brain may result in physiological changes associated with decreases in brain volume, over time, increasing the risk of dementia or stroke in caffeine users. In this study, Pham et al. performed a secondary analysis of the UK Biobank dataset for nearly 400,000 participants living in the UK to determine if any associations exist between coffee consumption and the incidence of dementia or stroke. To determine total and regional brain volumes, researchers analyzed MRI neuroimaging assays for approximately 17,000 participants, pulled from the original sample, then modeled the associations between coffee consumption and incidence of dementia/stroke using linear regression, and between coffee consumption and brain volume using logistic regression. The researchers also identified 27 covariates, divided into six main covariate groups, which were chosen for their potential to independently influence the incidence of dementia or stroke and brain volume.

Increased coffee consumption was associated with a decrease in brain volume in all regions of the brain, except white matter hypertrophies. However, increased coffee consumption did not show the same linear relationship with the incidence of dementia or stroke and instead presented in a U-shaped pattern. Participants who drank small amounts of coffee (< 4 cups per day) were associated with lower incidences of dementia and stroke, while non-drinkers, decaf coffee drinkers, very heavy coffee drinkers (>6 cups per day) correlated with an increased

incidence of dementia and stroke. Covariate adjustment did not impact this pattern for stroke incidence; however, it seemed to reduce the odds of developing dementia in non-coffee drinkers, compared to the unadjusted model.

Interestingly, the study suggests that both heavy caffeine consumption and no caffeine consumption may correlate with an increased incidence of dementia or stroke. Despite this, the inverse linear relationship between coffee consumption and brain volume would imply that non-coffee drinkers are at the lowest risk of developing dementia or stroke. This discrepancy may explain why Pham et al. (2021) chose to use light coffee drinkers (1 - 2 cups per day) as the control group in the study since "...individuals with poor health…may avoid coffee due to their health status" (p. 4). The baseline analysis of the data set shows that chronic illnesses are associated with an increased incidence of dementia and stroke and loosely associated with decreased brain volume. Further research needs to be completed to better understand this relationship.

Researchers also performed regression analysis in specific subsets of the original cohort, such as participants aged 60 years or older or participants who exclusively drink decaf coffee to see if the same relationships exist. While all subsets reflected relatively similar U-shaped association patterns between consumption and incidence, tea presented an entirely different association pattern for dementia incidence, with fully adjusted models showing that very heavy tea consumption is associated with a decreased incidence of dementia. This discrepancy might be attributed to the smaller caffeine content found in tea. Assuming equal beverage volumes, a heavy coffee drinker would ingest a significantly higher caffeine content than the heavy tea drinker. Hence, future studies should explore whether high caffeine consumption, in a purer form, replicates the results of this study.

Unfortunately, a significant design flaw lies in the nearly 400,000-participant-strong sample used in this study, which is not representative of the general population in the UK. Pham et al. elected to exclude non-Caucasian participants because of the UK Biobank's "healthy-volunteer bias" (p. 8) that preferentially selects individuals with greater access to and interest in healthcare and clinical research. During the UK Biobank's four-year recruitment period, staff actively contacted approximately 9 million individuals, yet only enrolled ~5% of them. (UK Biobank, 2016, as cited in Manufo et al., 2017). Consequently, previous studies have criticized the UK Biobank's sampling procedures, citing higher education rates, lower smoking rates, and lower mortality rates when comparing participants with the general population (Ganna et al., 2015, as cited in Munafo et al., 2017, p. 228).

According to Munafo et al. (2017), "[a participant] agreeing to take part in the UK Biobank study is associated with a number of characteristics that will reflect, for example, health status and social position..." (p. 228). This phenomenon could be attributed to the significant commitment required by the UK Biobank's participants, which could discourage low-income individuals from enrolling due to issues related to healthcare accessibility like grueling work schedules, financial hardship, and insufficient transportation. Also, individuals from disadvantaged minority communities with lower access to educational opportunities may disregard the value of clinical research or lack trust in the healthcare system entirely.

Indeed, the original cohort's considerable selection bias and over-representation of Caucasians can help justify the researcher's decision to exclude non-Caucasian participants from the study. In so doing, Pham et al. avoided much of the genotypic variability between ethnic groups that could have skewed the study's regression models in unpredictable ways. Since clinical data was readily available, Phan et al. could have included supplementary regression

models to incorporate the individuals excluded for not being white. Doing so would have illustrated the possible relationships that may exist between race/ethnicity and neurological diseases. Clearly, similar studies need to be completed using well-designed sampling procedures that accurately reflect the characteristics of the population. Studies with more diverse samples that replicate the results presented by Pham et al. would help confirm the U-shaped risk associated with long-term caffeine consumption. However, these studies will have to include a larger number of covariates due to genetic variation and sociocultural differences between ethnic groups.

Strengths and Weakness of the Selected Statistical Study

The researchers used Linear Regression models to examine the association between coffee consumption and brain volume. Given the large number of covariates, which act as independent variables in statistical analysis, and the continuous nature of the dependent variable, brain volume, Phan et al. were left with little option but to use linear regression models in this sub-study. While linear regression models can provide accurate results in more simple applications, the effectiveness of these models tends to diminish as the number of inputted independent variables increases. If these variables are closely related, the resulting multicollinearity will render the model essentially useless (Singh, 202). In a study containing 27 covariates based on responses to a questionnaire about lifestyle factors from 10 years prior, any similar covariates, especially those that could influence one another, must be reorganized to remove as much multicollinearity as possible, explaining why the researchers divided the covariates into specific covariate groups.

The researchers used logistic regression models to investigate the associations between coffee consumption and the incidence of depression or stroke. The dichotomous nature of the

dependent variable, incidence, makes logistic regression the best-suited analysis for this sub-study. However, logistic regression's dichotomous variable requirement can pose problems in real-world cases where dependent variables are not always black-and-white. For example, a simple dementia diagnosis would be dichotomous: either the patient has dementia or not. However, a more complex diagnosis might specify the severity or subtype (e.g., Alzheimer's Disease). Nuances like these are common in clinical data and serve as a weakness for logistic regression analyses. Moreover, the dichotomy requirement helps explain the additional sensitivity analyses completed by the research group for each dementia subtype.

References

Pham, K., Mulugeta, A., Zhou, A., O'Brien, J. T., Llewellyn, D. J., & Hyppönen, E. (2021). High coffee consumption, brain volume and risk of dementia and stroke. *Nutritional neuroscience*, 1–12. Advance online publication. https://doi.org/10.1080/1028415X.2021.1945858

Munafò, M. R., Tilling, K., Taylor, A. E., Evans, D. M., & Davey Smith, G. (2017, September 27). Collider scope: When selection bias can substantially influence observed associations. OUP Academic. https://doi.org/10.1093/ije/dyx206.

Singh, N. (2020, July 27). Advantages and disadvantages of linear regression. OpenGenus IQ: Computing Expertise & Legacy. https://iq.opengenus.org/advantages-and-disadvantages-of-linear-regression/.

National Coffee Association. (2020, March 26). NCA releases Atlas of American Coffee. NCA. https://www.ncausa.org/Newsroom/NCA-releases-Atlas-of-American-Coffee.

Ribeiro, J. A., & Sebastião, A. M. (2010). Caffeine and adenosine. *Journal of Alzheimer's disease : JAD*, *20 Suppl 1*, S3–S15. https://doi.org/10.3233/JAD-2010-1379

Sebastião, A. M., & Ribeiro, J. A. (2009). Adenosine receptors and the central nervous system. *Handbook of experimental pharmacology*, (193), 471–534. https://doi.org/10.1007/978-3-540-89615-9_16

UK Biobank. (2021, June 19). About us. https://www.ukbiobank.ac.uk/learn-more-about-uk-biobank/about-us.

Appendix A

Data Collection Methods and Categorization of Covariates (Pham et al., 2021)

	Data collection tool/method	Categorization of data
Basic Covariates		
Age	From reported date of birth	39 – 49 years, 50 – 59 years, 60 – 73 years
Sex	Sex recorded for the participant by the NHS and confirmed by the participant	Male, Female
Socioeconomic Status		
Education	Derived from the question: *"Which of the following qualifications do you have?"*	None, Intermediate (NVQ/CSE/A levels), High (degree/professional)
Townsend deprivation index	Calculated based on reported postcode and the preceding national census	Quartiles
Income	Derived from the question: *"What is the average total income before tax received by your household?"*	<£18,000, £18,000 – £30,999, £31,000 – £51,999, £52,000 – £100,000, >£100,000
Employment status	Derived from the question: *"Which of the following describes your current situation?"*	Paid, retired, unemployed
Disease Indicators		
History of common mental disorder (CMD)	Derived from the UK Biobank questionnaire and hospital record data, and has been previously described by Tyrrell et al. (2018) - https://doi.org/10.1093/ije/dyy223	Yes No
Systolic blood pressure	Automatic blood pressure measurements, measured using the Omron device at baseline assessment, corrected for use of blood pressure lowering medication	Below normal, normal, above normal
Sleep duration	Derived from the question: *"About how many hours sleep do you get in every 24 hours (please include naps)?"*	<5 hours, 6 hours, 7 hours, 8 hours, ≥9 hours

Insomnia	Derived from the question: *"Do you have trouble falling asleep at night or do you wake up in the middle of the night?"*	Never/rarely, sometimes, usually
Long-standing illness	Derived from the question: *"Do you have any long-standing illness, disability or infirmity?"*	No, yes
Anthropometric measures		
Body mass index	Calculated from weight and height measured at baseline assessment	Underweight (<18·5 kg/m^2), normal (18·5 – 25 kg/m^2), overweight (25 – 30 kg/m^2) and obese (≥30 kg/m^2)
Dehydration indicators		
Water intake	Derived from the question: *"How many glasses of water do you drink each day?"*	None, 1 – 5 cups/day, 6 – 10 cups/day, ≥10 cups/day
Whole body water mass	Calculated from impedance measurements at baseline assessment	Quartiles
Urea-creatinine ratio	Calculated from serum urea and serum creatinine, measured using a Beckman Coulter AU5800 at baseline assessment	Below normal (<40 mmol/L), normal (40 – 100 mmol/L), above normal (>100 mmol/L)
Other lifestyle factors		
Smoking	Derived from the following questions: *"Do you smoke tobacco now?"; "In the past, how often have you smoked tobacco?"; "In your lifetime, have you smoked a total of at least 100 time?"; "How old were you when you first started smoking on most days?"; "What type of tobacco do you mainly smoke?"; "About how many cigarettes did you smoke on average each day?"; "How old were you when you last smoked on most days?"; "In the time that you smoked, did you ever stop for more than 6 months?"; "Why did you stop smoking?"; "How many times did you try to give up smoking before you were successful?"; "Do you think you may start smoking again?"; "Does anyone in your household smoke?"; "At home, about how many hours per week are you exposed to other people's tobacco smoke?"; "Outside of your home, about how many hours per week are you exposed to other people's tobacco smoke?"*	Non-smokers, ex-smokers, current

Alcohol intake frequency	Derived from the question: *"About how often do you drink alcohol?"*	Non-drinkers, special occasions only, 1 – 3 times/month, 1 – 2 times/week, 3 – 4 times/week, daily or almost daily
Intensity of physical activity	Derived from the following questions: *"In a typical week, on how many days did you walk for at least 10mins at a time?"; "How many mins did you usually spend walking on a typical day?"; "In a typical week, on how many days did you do 10mins or more of moderate physical activities like carrying light loads, cycling at a normal pace (do not include walking)?"; "How many mins did you usually spend doing moderate activities on a typical day?"; "In a typical week, how many days did you do 10mins or more of vigorous physical activity (these are activities that make you sweat or breathe hard such as fast cycling, aerobic, heavy lifting)?"; "How many mins did you usually spend doing vigorous activities on a typical day?"*	None, light/moderate, strenuous
Tea consumption	Derived from the question: "How many cups of tea do you drink each day (include black and green tea)?"	<1 cup/day, 1 – 2 cups/day, 3 – 4 cups/day, >4 cups/day
Stressful events within the past 2 years	Derived from the question: *"In the last 2yrs have you experienced any of the following?"*	None, serious illness/injury to self, death/serious illness/injury to a close relative, marital separation/divorce, financial difficulties
Processed meat consumption	Derived from the question: *"How often do you eat processed meats (such as bacon, ham, sausages, meat pies, kebabs, burgers, chicken nuggets)?"*	Never, less than once per week, once a week, >2 times per week
Daily fresh fruit consumption	Derived from the question: *"About how many pieces of fresh fruit would you eat per day (count one apple, one banana, 10 grapes etc. as one piece)?"*	<1-piece, 1 piece, 2 pieces, 3 pieces, ≥4 pieces

Source: Supplemental data included online and directly sourced from (Pham et al., 2021)

Appendix B

Baseline Coffee Consumption, Total Brain Volume, and Incidence of Dementia and Stroke

	%, *n*	Coffee Drinker (%)	>6 Cups/ Day (%)	TBV** Median (IQR)	Incident Dementia (%, *n*)	Incident Stroke (%, *n*)
Sex						
Male	45.7 (182,370)	68.4	2.9	1488.8 (1441.0, 1536.0)	8.8 (2,447)	15.0 (3,595)
Female	54.3 (216,276)	59.3	1.8	1514.8 (1464.4, 1564.7)	5.7 (1,886)	8.9 (2,586)
P		$< 1 \times 10^{-300}$		3.5×10^{-130}	3.0×10^{-32}	1.4×10^{-74}
Age						
39 – 49 y	87,573 (22.0)	61.9	2.9	1555.1 (1512.7, 1595.6)	1.1 (158)	3.7 (493)
50 – 59 y	131,944 (33.1)	63.3	2.5	1505.2 (1463.6, 1548.8)	3.3 (652)	7.7 (1,459)
60 – 73 y	179,129 (44.9)	64.4	1.9	1457.1 (1416.3, 1500.4)	13.8 (3,523)	17.7 (4,229)
P		1.2×10^{-30}		$< 1 \times 10^{-300}$	1.31×10^{-271}	1.2×10^{-257}
BMI						
Underweight <18.5	1,987 (0.5)	58.8	2.7	1525.8 (1468.2, 1556.2)	9.5 (31)	13.6 (37)
Normal 18.5 – 25	129,989 (32.6)	63.0	1.9	1511.0 (1458.4, 1561.6)	6.6 (1,211)	9.5 (1,644)
Overweight 25 – 30	169,951 (42.6)	64.4	2.3	1496.3 (1448.3, 1547.0)	7.3 (1,766)	11.7 (2,609)
Obese ≥ 30	95,534 (24.0)	62.5	2.8	1497.6 (1448.5, 1543.0)	8.8 (1,232)	14.4 (1,826)
Missing	1,185 (0.3)	58.0	2.4	1491.2 (1429.8, 1554.1)	28.3 (91)	29.1 (65)
P		9.0×10^{-9}		5.2×10^{-11}	0.010	8.4×10^{-11}
Education						
None	17.4 (69,128)	58.1	2.9	1482.1 (1434.7, 1526.3)	15.0 (1,539)	18.4 (1,672)
Intermediate	35.8 (142,597)	62.2	2.5	1482.1 (1434.7, 1526.3)	6.4 (1,278)	10.8 (2,026)
High	46.0 (183,641)	66.6	2.0	1501.3 (1451.3, 1551.2)	5.3 (1,395)	9.8 (2,723)
Missing	0.8 (3,280)	57.5	4.4	1485.5 (1442.1, 1541.5)	19.0 (121)	13.3 (102)
P		$< 1 \times 10^{-300}$		0.004	5.8×10^{-45}	5.8×10^{-45}
Stressful Life Events						
None	56.3 (224,381)	64.2	2.0	1498.1 (1448.1, 1548.3)	7.3 (2,258)	11.4 (3,361)
Serious illness/injury	8.8 (35,024)	61.0	2.9	1501.2 (1447.0, 1553.9)	13.8 (752)	18.0 (865)

Family death or illness	26.7 (106,567)	62.9	2.2	1506.3 (1456.6, 1556.2)	5.9 (910)	10.2 (1,458)
Divorce or separation	1.9 (7,434)	63.6	3.4	1520.6 (1474.7, 1564.9)	5.7 (76)	8.6 (94)
Financial difficulties	5.8 (23,313)	63.1	3.9	1518.9 (1468.7, 1564.8)	6.6 (250)	12.1 (398)
Missing	0.5 (1,927)	61.5	2.0	1495.8 (1458.5, 1546.5)	17.6 (87)	15.4 (57)
P		6.7×10^{-21}		0.10	1.3×10^{-10}	1.3×10^{-8}
History of Depression						
Yes	94.3 (376,132)	63.7	2.2	1502.0 (1451.6, 1551.8)	7.2 (3,899)	11.6 (5,800)
No	5.7 (22,514)	59.3	3.4	1504.1 (1457.5, 1556.2)	12.8 (434)	12.8 (381)
P		1.1×10^{-18}		0.005	3.0×10^{-37}	1.9×10^{-5}
Chronic Illness						
Yes	66.6 (265,333)	64.9	2.1	1505.2 (1454.7, 1555.1)	4.5 (1,619)	8.9 (3,088)
No	31.2 (124,426)	60.5	2.7	1491.4 (1443.8, 1542.4)	13.4 (2,518)	17.5 (2,902)
Missing	2.2 (8,887)	62.6	2.6	1500.8 (1445.8, 1557.4)	13.7 (196)	14.8 (191)
P		7.3×10^{-204}		1.6×10^{-5}	3.3×10^{-131}	4.5×10^{-71}

** TBV – Total Brain Volume

According to Phan et al. (2021) "*P* values were from log-likelihood ratio tests using logistic regression (for coffee drinking), linear regression (for brain volume) or logistic regression (for disease risk), adjusting for age, sex, and assessment center..." (p. 6)

Appendix C

Association between Coffee Consumption and Brain Volume (Phan et al., 2021)

Outcome	Models	Beta	LCI **	UCI **	*P*
Total brain volume (N = 17,702)	Adjusted for basic covariates	-1.865	-2.310	-1.421	2.2×10^{-16}
	Adjusted for all covariates	-1.416	-1.893	-0.938	7.4×10^{-9}
Gray matter volumes (N = 17,702)	Adjusted for basic covariates	-1.294	-1.565	-1.024	7.4×10^{-21}
	Adjusted for all covariates	-0.910	-1.196	-0.624	7.4×10^{-10}
White matter volume (N = 17,702)	Adjusted for basic covariates	-0.571	-0.867	-0.275	1.5×10^{-4}
	Adjusted for all covariates	-0.506	-0.825	-0.186	0.0020
Total hippocampal volume (N = 17,689)	Adjusted for basic covariates	-0.015	-0.022	-0.007	8.2×10^{-5}
	Adjusted for all covariates	-0.011	-0.018	-0.003	0.0092
Left hippocampal volume (N = 17,689)	Adjusted for basic covariates	-0.007	-0.011	-0.003	0.0016
	Adjusted for all covariates	-0.005	-0.009	-0.0004	0.031
Right hippocampal volume (N = 17,689)	Adjusted for basic covariates	-0.008	-0.012	-0.004	1.2×10^{-4}
	Adjusted for all covariates	-0.006	-0.010	-0.001	0.015
White matter hyperintensities volume (N = 16,730)	Adjusted for basic covariates	0.040	-0.014	0.093	0.15
	Adjusted for all covariates	-0.011	-0.068	0.046	0.71

Note: (p. 7) See Appendix A for a list of covariates identified in this study.

**Upper and Lower Confidence Intervals (UCI and LCI) assume 95% confidence

Appendix D

Association Between Very High Coffee Consumption and Brain Volume (Phan et al., 2021)

Outcome	Models	Beta	LCI	UCI	*P*
Total brain volumes (N = 17,702)	Adjusted for basic covariates	-1.865	-2.310	-1.421	2.2×10^{-16}
	Adjusted for socioeconomic status	-1.848	-2.293	-1.402	7.7×10^{-16}
	Adjusted for diseases status	-1.867	-2.312	-1.423	2.3×10^{-16}
	Adjusted for anthropometric measures	-1.655	-2.097	-1.212	2.4×10^{-13}
	Adjusted for dehydration indicator	-1.643	-2.087	-1.198	4.9×10^{-13}
	Adjusted for lifestyle factors	-1.549	-2.025	-1.072	1.9×10^{-10}
	Adjusted for all covariates	-1.416__	-1.893	-0.938	7.4×10^{-9}
Grey matter volumes (N = 17,702)	Adjusted for basic covariates	-1.294	-1.565	-1.024	7.4×10^{-21}
	Adjusted for socioeconomic status	-1.266	-1.537	-0.996	3.4×10^{-19}
	Adjusted for diseases status	-1.281	-1.550	-1.012	1.6×10^{-20}
	Adjusted for anthropometric measures	-1.092	-1.358	-0.826	1.0×10^{-15}
	Adjusted for dehydration indicator	-1.099	-1.367	-0.832	1.1×10^{-15}
	Adjusted for lifestyle factors	-1.043	-1.332	-0.754	1.5×10^{-12}
	Adjusted for all covariates	-0.910	-1.196	-0.624	7.4×10^{-10}
White matter volumes (N = 17,702)	Adjusted for basic covariates	-0.571	-0.867	-0.275	1.5×10^{-4}
	Adjusted for socioeconomic status	-0.581	-0.878	-0.285	1.3×10^{-4}
	Adjusted for diseases status	-0.587	-0.883	-0.290	1.1×10^{-4}
	Adjusted for anthropometric measures	-0.563	-0.859	-0.266	2.0×10^{-4}
	Adjusted for dehydration indicator	-0.543	-0.841	-0.246	3.5×10^{-4}
	Adjusted for lifestyle factors	-0.505	-0.821	-0.189	0.0017
	Adjusted for all covariates	-0.506	-0.825	-0.186	0.0020
Total hippocampal volumes (N = 17,689)	Adjusted for basic covariates	-0.015	-0.022	-0.007	8.2×10^{-5}
	Adjusted for socioeconomic status	-0.015	-0.022	-0.007	9.6×10^{-5}
	Adjusted for diseases status	-0.015	-0.022	-0.008	6.3×10^{-5}
	Adjusted for anthropometric measures	-0.012	-0.019	-0.004	0.0018
	Adjusted for dehydration indicator	-0.012	-0.019	-0.004	0.0019
	Adjusted for lifestyle factors	-0.012	-0.020	-0.004	0.0030
	Adjusted for all covariates	-0.011	-0.018	-0.003	0.0092
Left hippocampal volumes (N = 17,689)	Adjusted for basic covariates	-0.007	-0.011	-0.003	0.0016
	Adjusted for socioeconomic status	-0.007	-0.011	-0.003	0.0016
	Adjusted for diseases status	-0.007	-0.011	-0.003	0.0013
	Adjusted for anthropometric measures	-0.005	-0.009	-0.001	0.019
	Adjusted for dehydration indicator	-0.005	-0.009	-0.001	0.019
	Adjusted for lifestyle factors	-0.006	-0.010	-0.001	0.013
	Adjusted for all covariates	-0.005	-0.009	-0.0004	0.031
Right hippocampal volumes (N = 17,689)	Adjusted for basic covariates	-0.008	-0.012	-0.004	1.2×10^{-4}
	Adjusted for socioeconomic status	-0.008	-0.012	-0.004	1.6×10^{-4}
	Adjusted for diseases status	-0.008	-0.012	-0.004	1.1×10^{-4}
	Adjusted for anthropometric measures	-0.007	-0.011	-0.003	0.0016
	Adjusted for dehydration indicator	-0.007	-0.011	-0.003	0.0016
	Adjusted for lifestyle factors	-0.006	-0.011	-0.002	0.0060
	Adjusted for all covariates	-0.006	-0.010	-0.001	0.015
White matter hyperintensities volumes (N = 16,730)	Adjusted for basic covariates	0.040	-0.014	0.093	0.15
	Adjusted for socioeconomic status	0.043	-0.011	0.097	0.12
	Adjusted for diseases status	0.034	-0.019	0.087	0.21
	Adjusted for anthropometric measures	0.022	-0.031	0.076	0.41

Adjusted for dehydration indicator	0.032	-0.022	0.086	0.24
Adjusted for lifestyle factors	-0.010	-0.067	0.047	0.72
Adjusted for all covariates	-0.011	-0.068	0.046	0.71

Note: All measured regions reflected significant inverse linear relationships with coffee consumption, except for white matter hypertrophy volume. Data obtained from Phan et al. (2021).

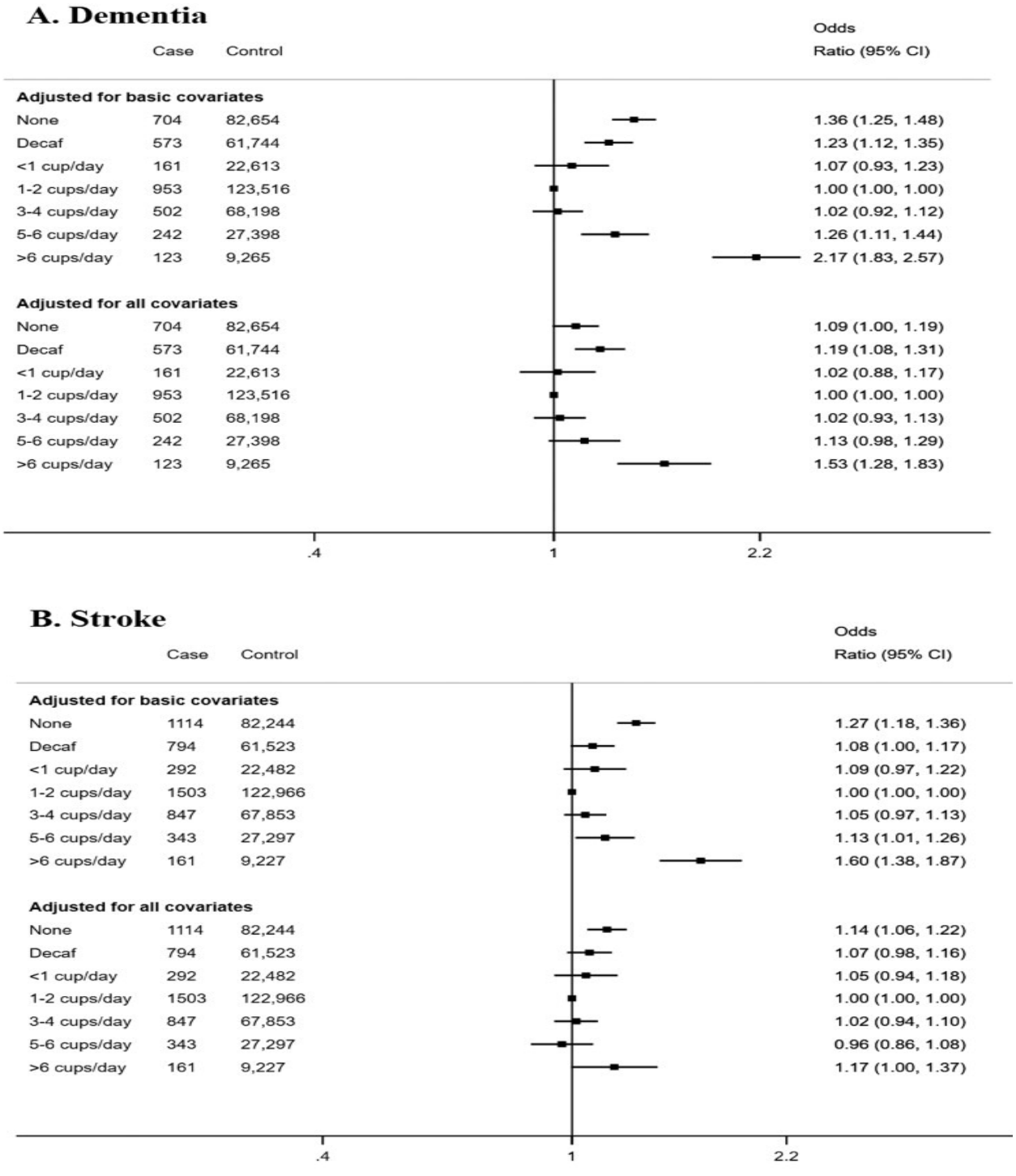
Appendix E

Association Between Decaf Coffee Consumption and Brain Volume (Phan et al., 2021)

Outcome	Models	Beta	LCI	UCI	P
Total brain volumes (N = 6,250)	Adjusted for basic covariates	-0.776	-1.606	0.055	0.07
	Adjusted for socioeconomic status	-0.818	-1.647	0.010	0.05
	Adjusted for diseases status	-0.767	-1.598	0.065	0.07
	Adjusted for anthropometric measures	-0.637	-1.460	0.186	0.13
	Adjusted for dehydration indicators	-0.682	-1.517	0.153	0.11
	Adjusted for lifestyle factors	-0.863	-1.770	0.044	0.06
	Adjusted for all covariates	-0.982	-1.901	-0.063	0.04
Grey matter volumes (N = 6,250)	Adjusted for basic covariates	-0.621	-1.105	-0.137	0.01
	Adjusted for socioeconomic status	-0.659	-1.141	-0.177	0.01
	Adjusted for diseases status	-0.619	-1.102	-0.136	0.01
	Adjusted for anthropometric measures	-0.462	-0.938	0.014	0.06
	Adjusted for dehydration indicators	-0.519	-1.003	-0.035	0.04
	Adjusted for lifestyle factors	-0.689	-1.215	-0.164	0.01
	Adjusted for all covariates	-0.747	-1.275	-0.219	0.01
White matter volumes (N = 6,250)	Adjusted for basic covariates	-0.155	-0.685	0.375	0.57
	Adjusted for socioeconomic status	-0.159	-0.689	0.370	0.56
	Adjusted for diseases status	-0.148	-0.678	0.383	0.59
	Adjusted for anthropometric measures	-0.174	-0.703	0.355	0.52
	Adjusted for dehydration indicators	-0.163	-0.697	0.370	0.55
	Adjusted for lifestyle factors	-0.174	-0.750	0.402	0.55
	Adjusted for all covariates	-0.235	-0.825	0.356	0.44
Total hippocampal volumes (N = 6,246)	Adjusted for basic covariates	-0.011	-0.024	0.003	0.11
	Adjusted for socioeconomic status	-0.011	-0.024	0.003	0.11
	Adjusted for diseases status	-0.011	-0.025	0.002	0.09
	Adjusted for anthropometric measures	-0.009	-0.022	0.005	0.21
	Adjusted for dehydration indicators	-0.009	-0.023	0.004	0.18
	Adjusted for lifestyle factors	-0.007	-0.021	0.008	0.37
	Adjusted for all covariates	-0.007	-0.022	0.008	0.35
Left hippocampal volumes (N = 6,246)	Adjusted for basic covariates	-0.007	-0.014	0.001	0.07
	Adjusted for socioeconomic status	-0.007	-0.014	0.0004	0.06
	Adjusted for diseases status	-0.007	-0.015	0.0002	0.06
	Adjusted for anthropometric measures	-0.006	-0.013	0.002	0.14
	Adjusted for dehydration indicators	-0.006	-0.014	0.001	0.10
	Adjusted for lifestyle factors	-0.005	-0.013	0.003	0.21
	Adjusted for all covariates	-0.006	-0.015	0.002	0.14
Right hippocampal volumes (N = 6,246)	Adjusted for basic covariates	-0.004	-0.011	0.004	0.31
	Adjusted for socioeconomic status	-0.004	-0.011	0.004	0.33
	Adjusted for diseases status	-0.004	-0.012	0.003	0.28
	Adjusted for anthropometric measures	-0.003	-0.010	0.005	0.44
	Adjusted for dehydration indicators	-0.003	-0.010	0.005	0.46
	Adjusted for lifestyle factors	-0.001	-0.009	0.007	0.73
	Adjusted for all covariates	-0.001	-0.009	0.007	0.84
White matter hyper intensities (N = 5,905)	Adjusted for basic covariates	0.014	-0.081	0.108	0.78
	Adjusted for socioeconomic status	0.018	-0.076	0.112	0.70
	Adjusted for diseases status	0.018	-0.076	0.112	0.71
	Adjusted for anthropometric measures	-0.001	-0.095	0.092	0.98
	Adjusted for dehydration indicators	0.009	-0.084	0.102	0.85
	Adjusted for lifestyle factors	-0.017	-0.121	0.086	0.75
	Adjusted for all covariates	-0.014	-0.118	0.089	0.79

Appendix F

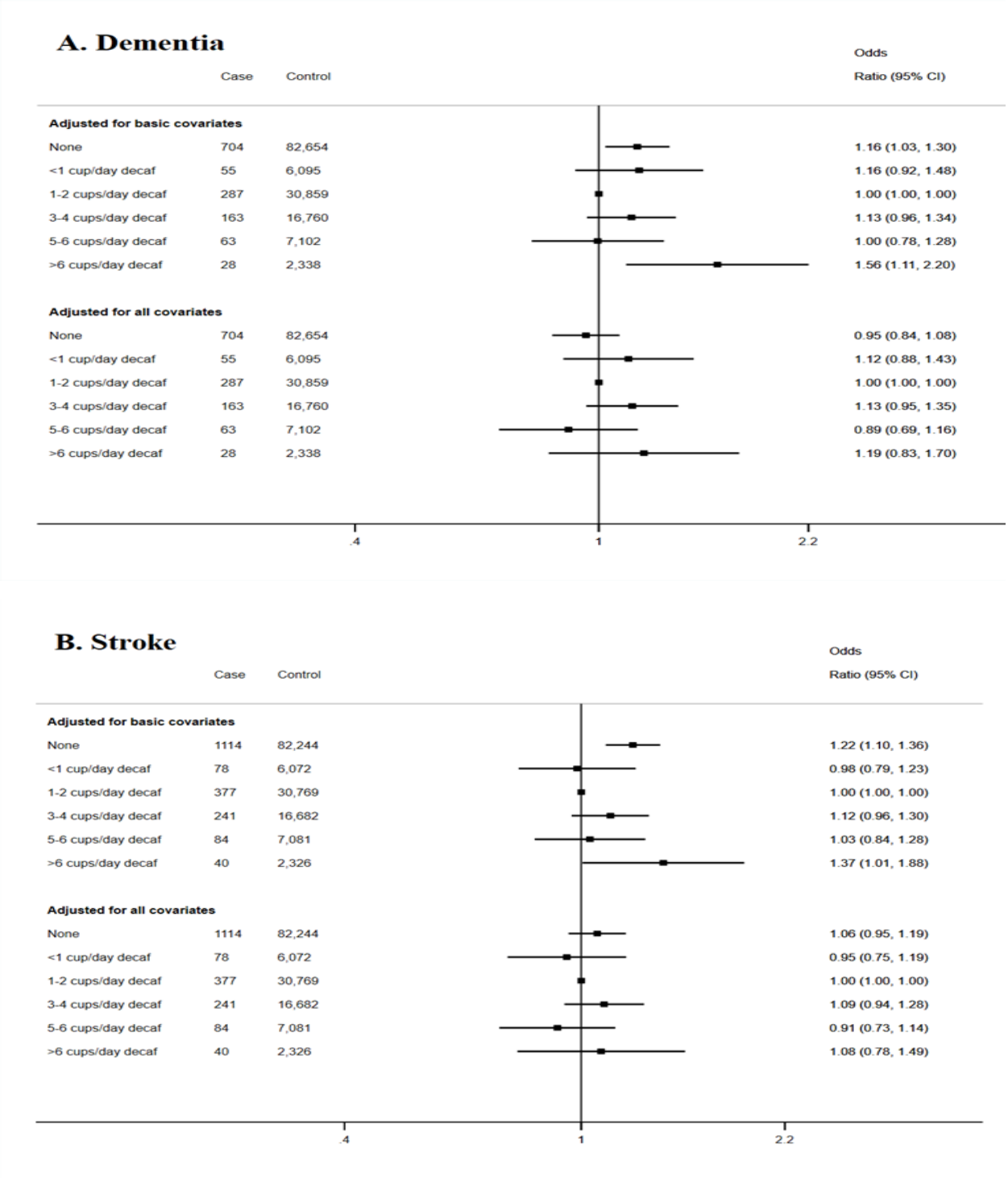
Association Between Coffee Consumption and Incidence of Dementia (a) and Stroke (b)



Note: Images obtained from Phan et al. (2021, p. 8)

Appendix G

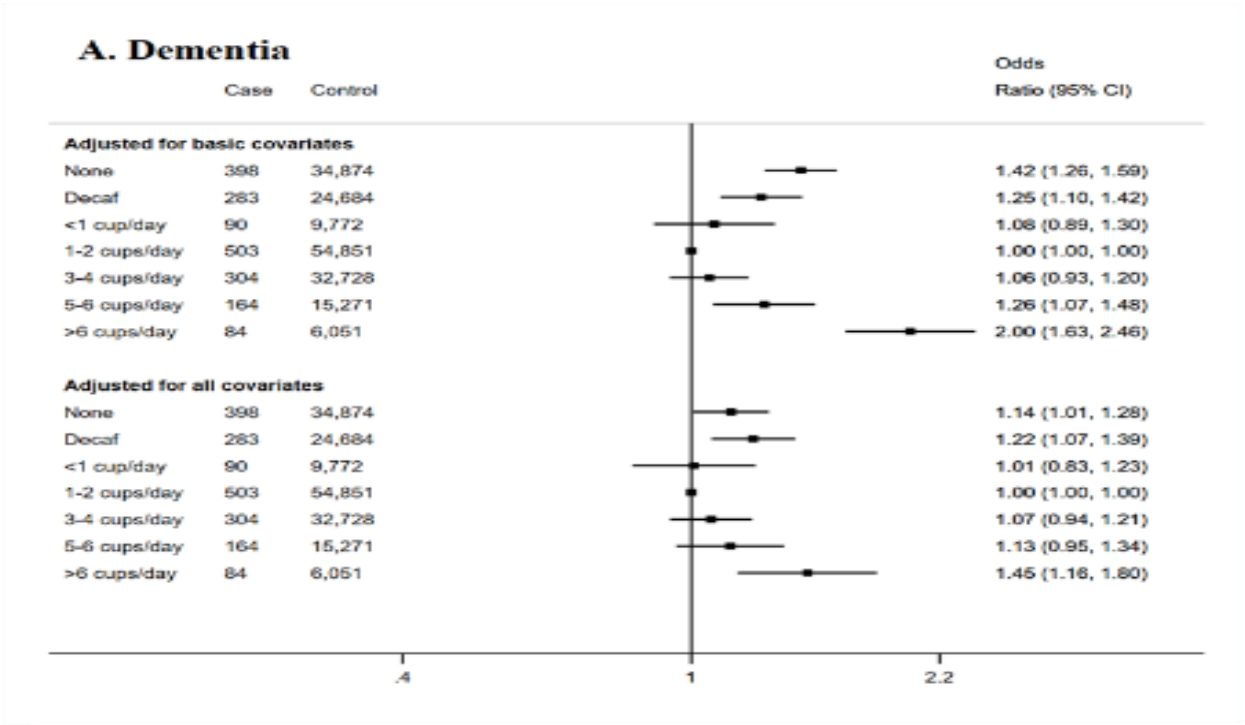
Association of Decaf Coffee Consumption with Incidence of Dementia (a) and Stroke (b)

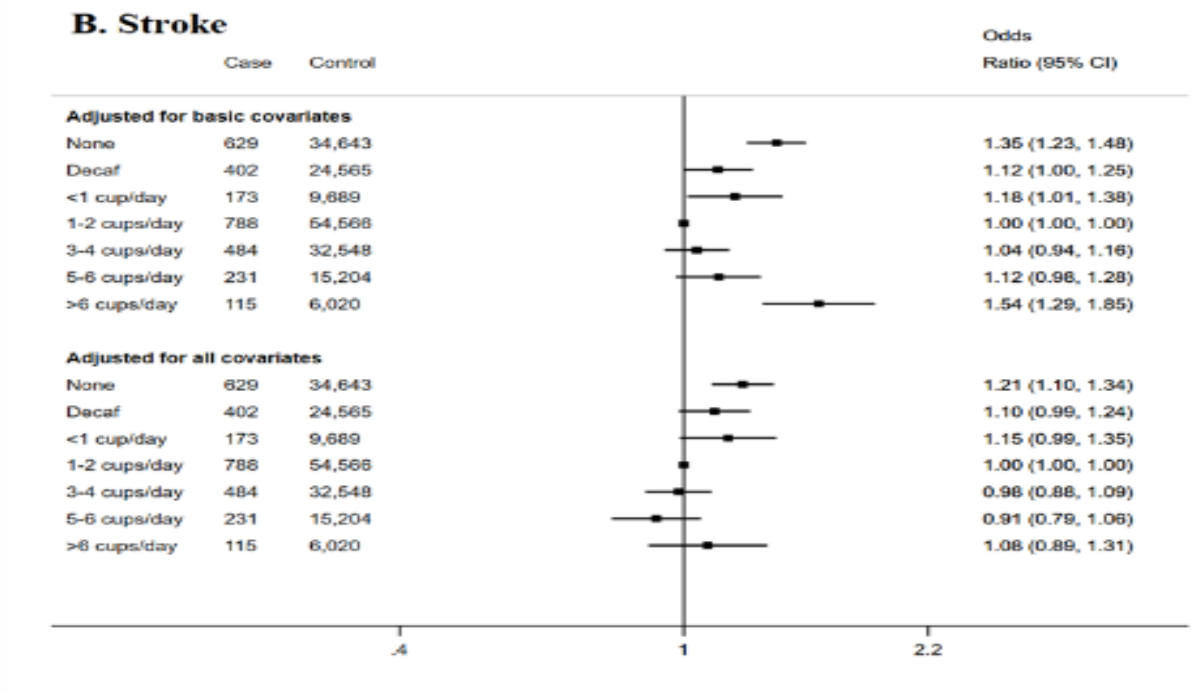


Note: Images were obtained from Phan et al. (2021)

Appendix H

Association of Coffee Consumption with Incidence of Dementia (a) and Stroke (b) in Participants 60 years Old and Older.

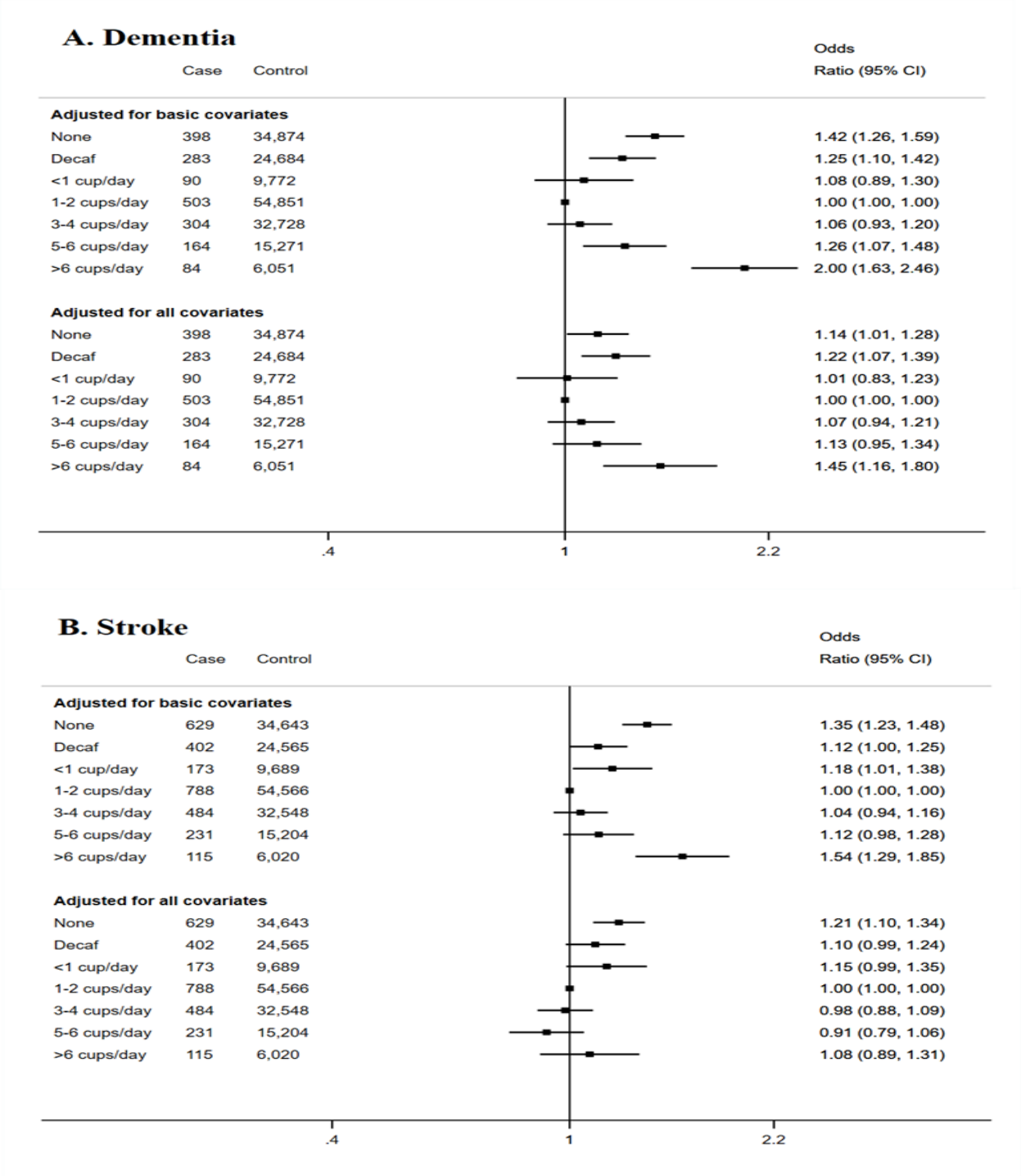




Note: images obtained from Phan et al. (2021).

Appendix I

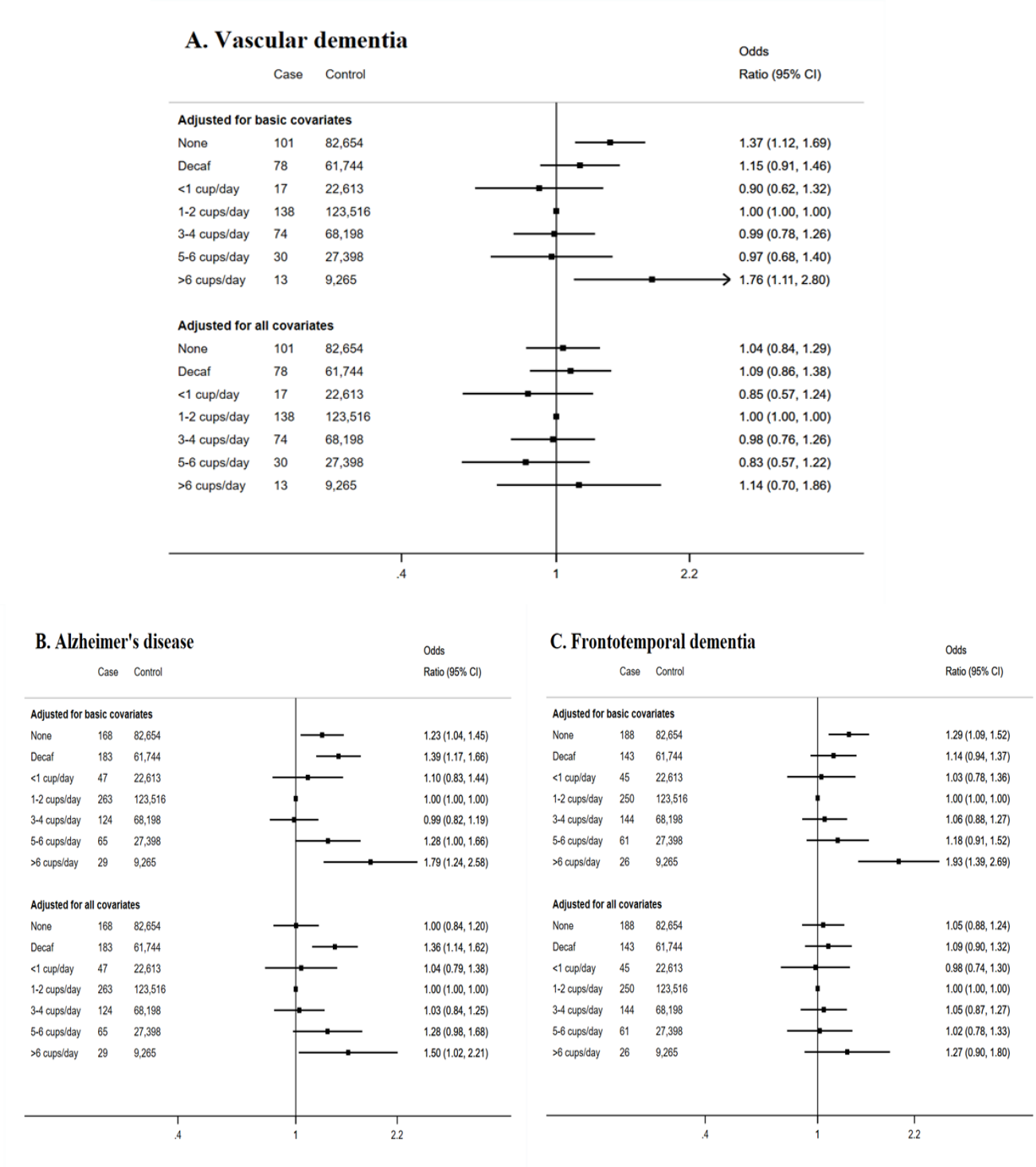
Association of Coffee Consumption with Incidence of Dementia (a) and Stroke (b) in Non-Smoking Participants



Note: images obtained from Phan et al. (2021).

Appendix J

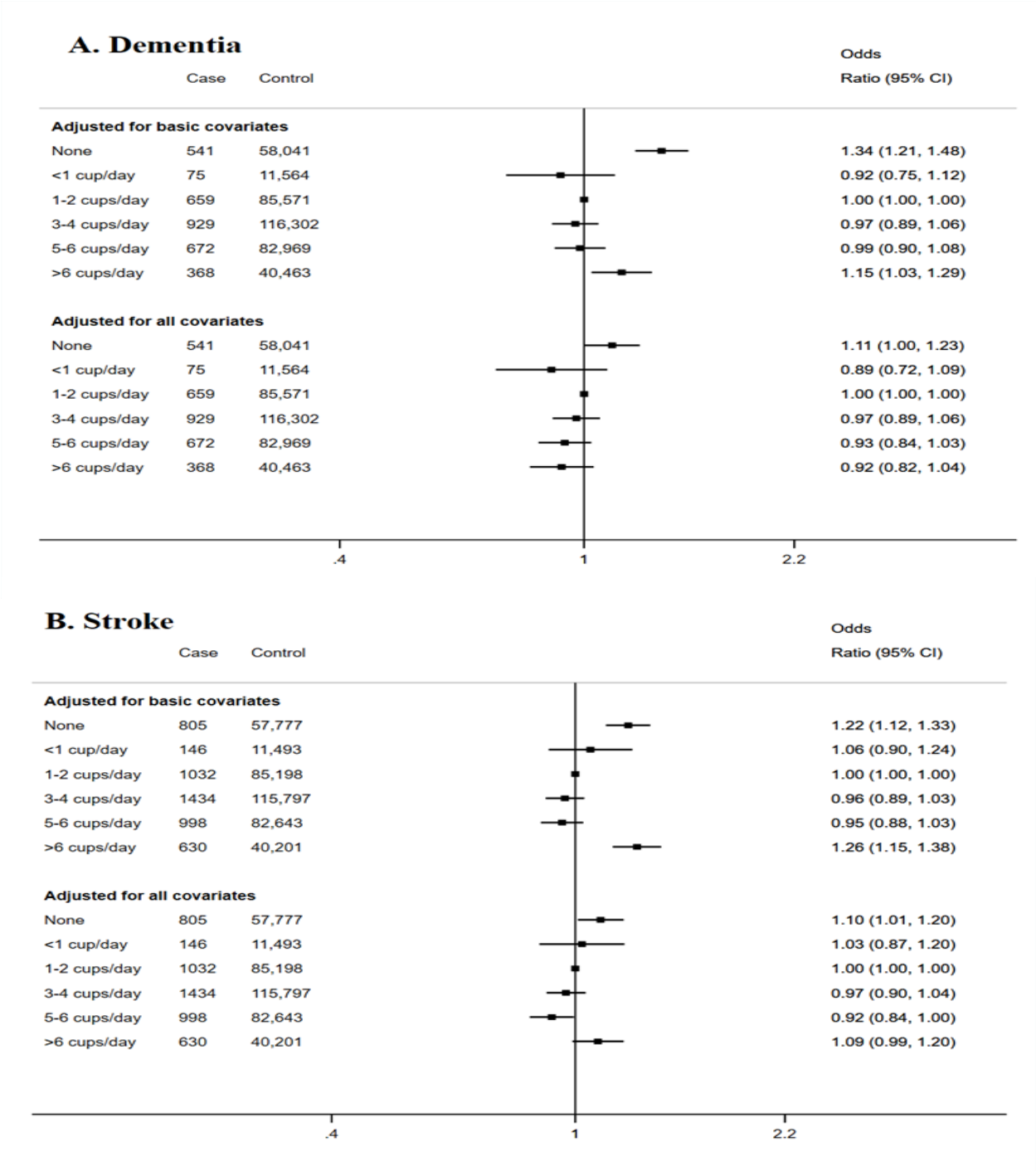
Association between Coffee Consumption and Dementia Subtypes



Note: Images obtained from Phan et al. (2021). Coffee consumption is associated with an increased incidence of Alzheimer's Disease, but not other subtypes of dementia.

Appendix K

Model to Relate Tea Consumption with Incidence of Dementia or and Stroke



*Note:*images were obtained from Phan et al. (2021). Tea consumption does not reflect the same U-shaped pattern found in the coffee-containing analyses, above.