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Supplementary Data

High Blood Caffeine Levels in MCI Linked to Lack of Progression to Dementia

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AD TRANSGENIC MOUSE STUDY METHODS (from Cao C, Wang L, Lin X, Mamcarz M, Zhang C, Bai G, Nong J, Sussman S, Arendash GW (2011) Caffeine synergizes with another coffee component to increase plasma GCSF: Linkage to cognitive benefits in Alzheimer's mice. *J Alzheimers Dis* **25**, 323-335.)

At 6–8 months of age, AβPPsw+PS1 transgenic mice were injected intraperitoneally with 200 μl of one of the following: caffeinated coffee, decaffeinated coffee, caffeine, or saline solution (6-7 mice per group). A post-treatment blood sample (0.2 cc) was taken 3 h thereafter, with plasma separated and stored at −80°C for later analysis of cytokine levels. Commercial drip ground coffee (Maxwell House, Kraft Foods, etc.) was utilized to make both caffeinated and decaffeinated (filtered) coffee. For both caffeinated and decaffeinated

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coffee, concentration was done prior to storage at −20°C. On the day of treatment, concentrated coffee and decaffeinated coffee aliquots were reconstituted, keeping all non-caffeinergic components of coffee at the same concentration for both of these treatments. For the treatment solutions containing caffeine, the amount of caffeine administered for the acute i.p. treatment was: caffeinated coffee (1.5 mg), decaffeinated coffee (0.06 mg), and caffeine solution (1.5 mg). Prior to administration, the pH of each solution was measured and adjusted to pH 5.3 (the pH of coffee). The amount of caffeine administered for the caffeine and caffeinated coffee treatment (1.5 mg) was equivalent to a human intake of 500 mg caffeine (e.g., five 8-oz cups of drip coffee).

For determination of each cytokine response to the various coffee/caffeine treatments, the mean plasma cytokine value for each of these three treatment groups was divided by the mean plasma cytokine value for the saline (control) treatment group. Thus a percent difference was attained for each of the coffee/caffeine treatments versus saline control. To compare these percent differences in AD mouse to those from MCI patients, the mean plasma cytokine levels for the MCI→MCI (stable) group were divided by the respective mean plasma cytokine levels for the MCI→AD (conversion) group, serving as a control. Though not directly comparable, the resulting percent differences in plasma cytokine levels for "high caffeine intake" MCI patients and those for AD mice given various acute caffeine/coffee treatments are meaningful in that they are both in reference to appropriate controls.