SUPPLEMENTAL MATERIAL

Marijuana Use and the Risk of Early Ischemic Stroke: The Stroke Prevention in Young Adults Study.

This study was conducted with the consent of all study participants and was approved by the University of Maryland at Baltimore Institutional Review Board.

Supplementary Methods:
Recruitment paths for cases (survivors, agree) and controls (search, recruit, approve) are outlined to provide further insight into study subject ascertainment and potential participation biases.

Study population.
The Stroke Prevention in Young Adults (SPYA) Study is a population-based, case-control study designed to identify risk factors associated with early-onset ischemic stroke. Participants were recruited from the greater Baltimore-Washington area in three different periods: Stroke Prevention in Young Women-1 (SPYW-1) conducted from 1992 to 1996, Stroke Prevention in Young Women-2 (SPYW-2) conducted from 2001 to 2003, and Stroke Prevention in Young Men (SPYM) conducted from 2003 to 2007. In the initial study period, only women were recruited, the upper age limit was 44 years, and controls were in a 2:1 ratio to cases and were frequency-matched to cases by age, sex, region of residence. Women were recruited in the second study period and men in the third study period. In the last two study periods, the upper age limit was 49 years, and controls were in a 1:1 ratio to cases and were additionally matched for race.

Definitions of cases and controls.
"*Case participants*" were hospitalized with a first cerebral infarction identified by discharge surveillance from one of the 59 hospitals in the greater Baltimore-Washington area and direct referral from regional neurologists. IS with the following characteristics were excluded from participation: stroke occurring as an immediate consequence of trauma; stroke within 48 hours after a hospital procedure, stroke within 60 days after the onset of a nontraumatic subarachnoid hemorrhage, and cerebral venous thrombosis. All cases had neuroimaging that was consistent with cerebral infarction, although neuroimaging was not used for case ascertainment. The abstracted hospital records of cases were reviewed and adjudicated by a pair of neurologists according to previously published procedures [28,29], with any disagreements resolved by a third neurologist. All cases had age of first stroke between 15 and 49 years and were recruited within three years of stroke.

"*Control participants*" without a history of stroke were identified by random-digit-dialing (RDD). Controls were balanced to cases by age and region of residence (by Maryland County) in each study and were additionally balanced for race in SPYW-2 and SPYM. Traditional stroke risk factors and other study variables, including age, race/ethnicity, history of hypertension, diabetes mellitus, myocardial infarction (MI), and current smoking status (defined as use within one month prior to event for cases and at a comparable reference time for controls), were also collected during a standardized interview.

Recruitment Results.
Unlike other countries (e.g. Sweden) that maintain individually identifiable databases on all persons that can be evaluated for research purposes, in the United States there is no ideal method for generating a random sample of the population. As outlined in above, in the present study, identified case subjects were matched with control subjects sought on the basis of gender, age,

race and geographical location (i.e. Maryland County) using RDD. The most conservative formula for the calculation of the control response rate is as follows:

$$\frac{\text{Final \# Enrolled}}{\text{[Final \# Enrolled + non-responses to RDD + non-responses to study center]}} \times \frac{\text{\# of successfully screened number's}}{\text{\# of phone number's released}}$$

Using the above formula, the overall response rate for all recruitment phases combined was 65.59%. This calculation of the response rates includes those telephone numbers that we were unable to successfully screen. Often groups utilizing random-digit-dialing to identify controls adjust for those telephone numbers that were never determined. In other words, of the telephone numbers where no determination was made, a certain percentage were assumed to be households, others to be business, and other non-working numbers. In our very conservative calculation of the response rate we did not make these assumptions, and all numbers not reached were counted against the success rate. The response rate based on numbers successfully screened was 87.1%.

In the initial phase of the study, during the recruitment of women only, we obtained information on vascular risk factors from 38 control refusals as well as 392 control participants. There were no significant differences by Fisher's Exact Test in the distribution of smoking history, hypertension history, diabetes history, current oral contraceptive use, age, race, and education.

Power.

A power calculation for the primary risk exposure analysis was performed using the online power calculator at http://sampsize.sourceforge.net/iface/s3.html#ccp This calculator indicates the current study has an 80% Power to detect an Odds Ratio = 1.33, assuming exposed controls = 40% (as consistent with MJ uses among controls in the current study), an alpha risk level of 5%, a case/control ratio = 1, and a sample size of 782 cases and 782 controls (mean of total sample size of 1564; number of cases (n=751) and controls (n=813)).