Supplemental Material

Effects of simvastatin on white matter integrity in healthy middle-aged adults: a secondary analysis of a randomized controlled trial

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Supplemental Table 1. Baseline participant characteristics for full study population (n=88)

| Characteristic                        | Placebo (n=44) | Simvastatin (n=44) | P Value |
|---------------------------------------|----------------|--------------------|---------|
| Age, mean (SD), y                     | 54.8 (7.8)     | 56.2 (6.5)         | 0.36    |
| Female sex                            | 32 (74.4)      | 31 (70.5)          | >0.99   |
| White/Caucasian race                  | 43 (97.7)      | 44 (100)           | >0.99   |
| APOE-ε4 positive                      | 17 (38.6)      | 17 (38.6)          | >0.99   |
| ASCVD 10-y risk score, median [IQR]   | 2.2 [1.0-3.8]  | 2.9 [1.4-4.4]      | 0.24    |
| BMI, mean (SD)                        | 27.6 (5.6)     | 27.2 (5.6)         | 0.75    |
| Blood pressure                        |                |                    |         |
| Systolic, mean (SD), mm Hg            | 124 (17)       | 125 (16)           | 0.69    |
| Diastolic, mean (SD), mm Hg           | 73 (11)        | 72 (9.9)           | 0.85    |
| Serum lipid profile (fasting)         |                |                    |         |
| Total cholesterol, mean (SD), mg/dL   | 207 (34)       | 207 (36)           | 0.94    |
| Triglycerides, mean (SD), mg/dL       | 102 (40)       | 112 (58)           | 0.32    |
| HDL-C, mean (SD), mg/dL               | 63 (17)        | 63 (21)            | 0.82    |
| LDL-C, mean (SD), mg/dL               | 123 (28)       | 122 (28)           | 0.93    |

Abbreviations: APOE, apolipoprotein E; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol

*aOne American Indian/Native American participant in placebo group
### Supplemental Table 2. Summary of ANCOVA models for effect of simvastatin treatment on diffusion tensor imaging measures

| Variable                  | 6 months β coefficient (SE) | 12 months β coefficient (SE) | 18 months β coefficient (SE) |
|---------------------------|-----------------------------|------------------------------|------------------------------|
|                           | FA  | MD  | RD  | AD  | FA  | MD  | RD  | AD  | FA  | MD  | RD  | AD  |
| Treatment – simvastatin   | -0.02 | 0.44 | 0.47 | 0.42 | 0.07 | 0.0005 | -0.002 | 0.008 | 0.88** | -0.79 | -1.10* | -0.48 |
|                           | (0.28) | (0.48) | (0.54) | (0.43) | (0.37) | (0.50) | (0.59) | (0.43) | (0.31) | (0.44) | (0.52) | (0.39) |
| Age                       | -0.03 | 0.06 | 0.07 | 0.05 | 0.002 | 0.01 | 0.01 | 0.01 | 0.02 | 0.05 | 0.04 | 0.05 |
|                           | (0.02) | (0.03) | (0.04) | (0.03) | (0.03) | (0.04) | (0.04) | (0.03) | (0.02) | (0.03) | (0.04) | (0.03) |
| Sex – Male                | 0.24 | -0.43 | -0.50 | -0.35 | -0.19 | -0.007 | 0.10 | -0.10 | -0.81* | 0.24 | 0.55 | -0.07 |
|                           | (0.32) | (0.54) | (0.61) | (0.49) | (0.42) | (0.56) | (0.67) | (0.48) | (0.35) | (0.50) | (0.59) | (0.44) |
| APOE-ε4 – positive         | -0.07 | 0.17 | 0.19 | 0.15 | -0.18 | 0.66 | 0.72 | 0.59 | 0.67* | 0.09 | -0.19 | 0.37 |
|                           | (0.29) | (0.50) | (0.56) | (0.45) | (0.39) | (0.52) | (0.62) | (0.45) | (0.32) | (0.46) | (0.54) | (0.40) |

Abbreviations: APOE, apolipoprotein E; FA, fractional anisotropy; MD, mean diffusivity; RD, radial diffusivity; AD, axial diffusivity; SE, standard error

* P < 0.05, ** P < 0.01
**Supplemental Figure 1.** Region of interest (ROI) analysis showing 18-month percent change in WM DTI measures. Points represent mean (± SEM) for each ROI (averaged bilaterally, except for forceps major and forceps minor). *P < 0.05 (uncorrected); ANCOVA models controlling for age, sex, APOE-ε4 genotype. Abbreviations: ATR, Anterior thalamic radiation; CST, corticospinal tract; CCG, cingulum cingulate gyrus; CHB, cingulum hippocampal bundle; IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; SLF, superior longitudinal fasciculus; UF, uncinate fasciculus; SLFT, superior longitudinal fasciculus (temporal part); Fmaj, forceps major; Fmin, forceps minor.

**Supplemental Figure 2.** Exploratory voxel-based morphometry (VBM) analyses of 12- and 18-month percent change in WM volume (Simvastatin > Placebo, \(P_{\text{uncorr}} < 0.01\), n =10,000 permutations followed by threshold-free cluster enhancement).
Supplemental Figure 3. 18-month percent change in total cholesterol vs. 18-month change in DTI neuroimaging measures. Abbreviations: FA, fractional anisotropy; MD, mean diffusivity; RD, radial diffusivity.