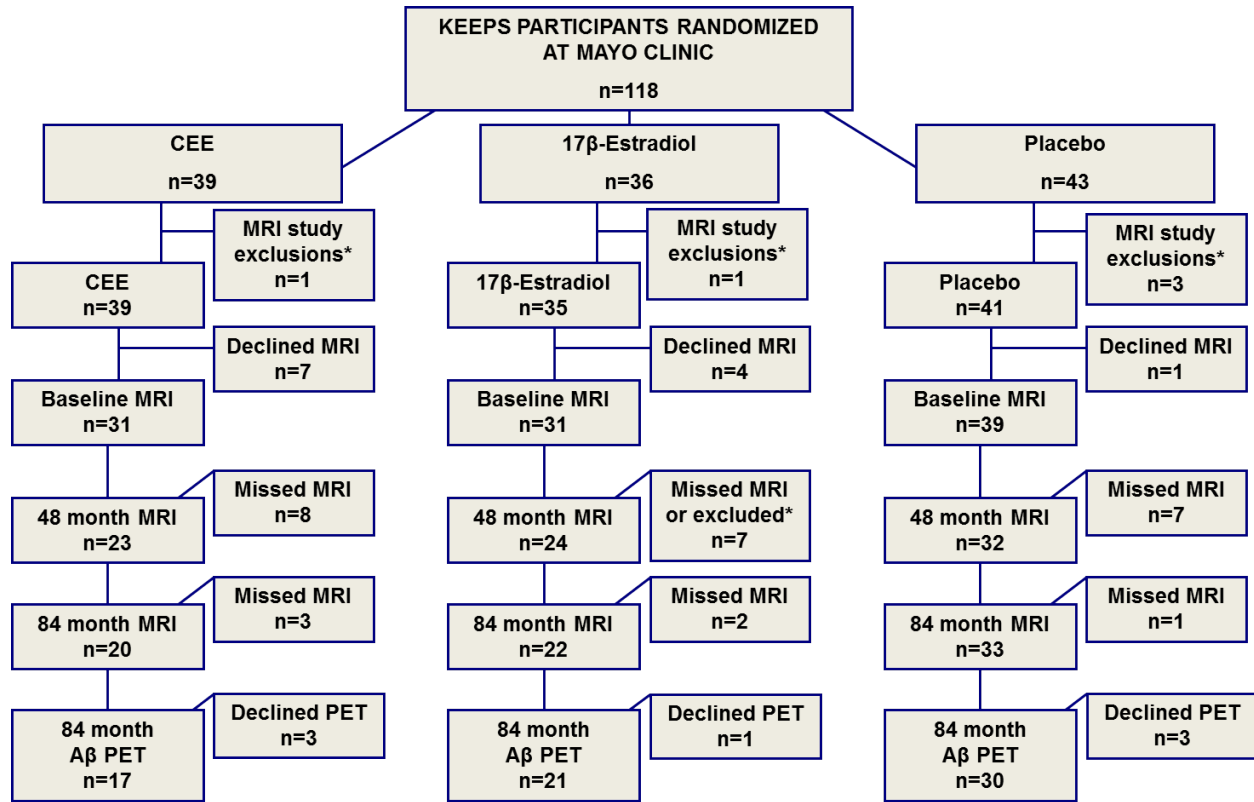**Figure e-1:** Participation flowchart

* There were five exclusions at baseline MRI: MRI incompatible implant (n=1); posterior fossa developmental abnormality and hydrocephalus (n=1); multiple sclerosis (n=2); benign brain tumor (n=1). A participant from the 17β-estradiol group developed breast cancer after completing the baseline MRI scan and underwent chemotherapy. Her structural MRI data at month 48 and 84 was excluded from the analysis due to the potential adverse effects of chemotherapy on brain structure. One of the baseline FLAIR scans failed quality control therefore and had to be excluded from the analysis.

Figure e-2: Area under the receiver characteristic curve (AUROC) estimates (black circles) and 95% confidence intervals (CI; lines) in discriminating oral conjugated equine estrogen (CEE) and transdermal 17β-estradiol groups from placebo are displayed for each of the 21 regions of interest. The ranked AUROC values >0.5 indicate that the cortical volumes declined less in the oral CEE or the transdermal 17β-estradiol groups compared to placebo. The ranked AUROC values <0.5 indicate that the cortical volumes declined more in the oral CEE or the transdermal 17β-estradiol groups compared to placebo over the 84 months (7 years) of follow-up. The p-values are corrected for multiple comparisons using false discovery rate (FDR) correction. Statistically significant findings were present only in the superior and middle frontal gyri cortical volume change, which was less in the 17β-estradiol group compared to placebo (p=0.04; FDR corrected for multiple comparisons).