# Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

**eTable 1.** Participants' demographics and study information for the DIAN, ADNI, and HABS baseline data for the highest FHS-CVD tertile group. Mean (Standard deviation) or number (percentage) are reported.

| | DIAN (N=81) | ADNI (N=159) | HABS (N=93) |
|---|---|---|---|
| **Age (years)** | 48.5 (8.6) | 77.4 (6.5) | 77.0 (6.4) |
| **Estimated year to symptom onset (years)** | -.5 (8.5) | NA | NA |
| **APOE e4 (yes)** | 26 (32%) | 80 (50%) | 22 (24%) |
| **Sex (Female)** | 24 (30%) | 18 (11%) | 21 (23%) |
| **Education (years)** | 14 (3) | 16 (3) | 15 (3) |
| **Cerebral microbleed (yes)** | 17 (21) | 19 (12%) | 31 (34%) |
| **CDR (>=1)** | 48 (60%) | 110 (69%) | 0 (0%) |
| **Diagnostic group (dementia)** | 33 (41%) | 28 (18%) | 0 (0%) |
| **Amyloid group (high)** | NA | 87 (60%) | 43 (46%) |
| **WMH volume** (normalized to ICV=1300cm$^3$) | 3.2 (8) | 12 (10) | 8 (9) |
| **GM volume** (normalized to ICV=1300cm$^3$) | 504 (41) | 350 (26) | 490 (29) |
| **Follow-up time (years)** | 2 (1.9) | 2.8 (2.3) | 5.1 (3.7) |
| **FHS-CVD score** | 10.4 (5.6) | 65 (13) | 51 (11) |
| **Hypertension (yes)** | 9 (11%) | 111 (70%) | 61 (66%) |
| **Hypercholestromia (yes)** | 17 (21%) | 91 (57%) | 48 (52%) |
| **Diabetes (yes)** | 2 (2.5%) | 29 (18%) | 22 (24%) |

**eTable 2.** Sensitivity analyses using cross-sectional (baseline) DIAN data.

| White matter hyperintensities volume ~ | Primary model (r2=.32) | Sensitivity analysis 1 (r2=.32) | Sensitivity analysis 2 (r2=.32) | Sensitivity analysis 3 (r2=.46) |
|---|---|---|---|---|
| **Age** | **.35 (.21, .5), t=4.7, p<.001*** | **.36 (.21, .51), t=4.8, p<.001*** | **.29 (.1, .49), t=3.0, p=.003*** | **.39 (.11, .67), t=2.8, p=.007*** |
| **Cerebral microbleed (yes)** | **.48 (.04, .93), t=2.1, p=0.03*** | NA | .4 (-.06, .86), t=1.7, p=.09 | -.01 (-.57, .55), t=-.03, p=.9 |
| **One CMB (Possible CAA)** | NA | .28 (-.3, .85), t=1.0, p=.3 | NA | NA |
| **≥2 CMBs (Probable CAA)** | NA | **.72 (.08, 1.36), t=2.2, p=0.02*** | NA | NA |
| **Gray matter volume** | **-.17 (-.32, -.03), t=-2.3, p=0.02*** | **-.17 (-.31, -.02), t=-2.2, p=0.02*** | **-.17 (-.32, -.02), t=-2.3, p=.02*** | **-.45 (-.71, -.19), t=-3.4, p=.001*** |
| **Amyloid burden** | .08 (-.05, .21), t=1.1, p=.2 | .08 (-.05, .21), t=1.2, p=.2 | .08 (-.05, .21), t=1.2, p=.2 | -.01 (-.23, .22), t=.05, p=.9 |
| **Framingham Heart Study Cardiovascular Disease risk score** | NA | NA | .08 (-.09, .26), t=.9, p=.3 | -.08 (-.34, .17), t=-.6, p=.5 |

*Standardized beta values are shown. Positive beta values indicate positive associations.*

*Sensitivity analysis 1: primary model with pseudo-ordinal CMB burden (1 CMB/≥2 CMBs: 12/12)*

*Sensitivity analysis 2: adding FHS-CVD*

*Sensitivity analysis 3: the same model of sensitivity analysis 1 in the highest tertile of FHS-CVD*

**eTable 3.** Sensitivity analyses using longitudinal DIAN data.

| white matter hyperintensities volume rate of change ~ | Primary model (r2=.5) | Sensitivity analysis 1 (r2=.5) | Sensitivity analysis 2 (r2=.5) | Sensitivity analysis 3 (r2=.49) |
|---|---|---|---|---|
| Age | .47 (.33, .6), t=6.8, p<0.001* | .49 (.34, .63), t=6.8, p<0.001* | .42 (.24, .61), t=4.5, p<0.001* | .55 (.23, .86), t=3.5, p=0.001* |
| Cerebral microbleed | .65 (.25, 1.1), t=3.2, p=0.001* | NA | .58 (.17, 1.0), t=2.8, p=0.006* | .12 (-.42,.66), t=.4, p=.6 |
| One CMB (possible CAA) | NA | -.09 (-.81,.64), t=.2, p=.8 | NA | NA |
| ≥2 CMBs (Probable CAA) | NA | .9 (.45, 1.35), t=3.9, p<0.001* | NA | NA |
| gray matter volume rate of change | -.21 (-.34, -.07), t=-3.1, p=0.002* | -.18 (-.32, -.05), t=-2.7, p=0.008* | -.2 (-.34, -.07), t=-2.9, p=0.003* | -.37 (-.63, -.1), t=-2.8, p=0.008* |
| amyloid burden | .07 (-.06,.2), t=1.1, p=.3 | .06 (-.07,.19), t=.9, p=.3 | .08 (-.05,.21), t=1.2, p=.2 | .06 (-.19,.31), t=.5, p=.6 |
| Framingham Heart Study Cardiovascular Disease risk score | NA | NA | .06 (-.11,.24), t=.7, p=.4 | -.21 (-.52,.1), t=-1.3, p=.2 |

*Standardized beta values are shown. Positive beta values indicate positive associations.*

*Sensitivity analysis 1: primary model with pseudo-ordinal CMB burden (1 CMB/≥2 CMBs: 8/15)*

*Sensitivity analysis 2: adding FHS-CVD*

*Sensitivity analysis 3: the same model of sensitivity analysis 1 in the highest tertile of FHS-CVD*

**eTable 4.** Sensitivity analyses using cross-sectional (baseline) ADNI data.

| White matter hyperintensities volume ~ | Primary model (r2=0.34) | Sensitivity analysis 1 (r2=0.35) | Sensitivity analysis 2 (r2=0.36) | Sensitivity analysis 3 (r2=0.28) |
|---|---|---|---|---|
| Age | .4 (.32, .47), t=10.5, p<.001* | .4 (.32, .47), t=10.5, p<.001* | .38 (.29, .47), t=8.2, p<.001* | .41 (.25, .56), t=5.1, p<.001* |
| Cerebral microbleed | .32 (.04, .6), t=2.3, p=.02* | NA | .23 (-.06, .5), t=1.6, p=.1 | .1 (-.4, .58), t=.4, p=.6 |
| One CMB (possible CAA) | NA | .07 (-.37, .5), t=.3, p=.7 | NA | NA |
| ≥2 CMBs (Probable CAA) | NA | .46 (.12, .79), t=2.7, p=.007* | NA | NA |
| Gray matter volume | -.26 (-.33, -.18), t=-6.8, p<.001* | -.25 (-.33, -.18), t=-6.6, p<.001* | -.25 (-.34, -.17), t=-6.1, p<.001* | -.17 (-.33, -.01), t=-2.1, p=.03* |
| Amyloid burden (high) | .16 (.01, .3), t=2.2, p=.03* | .16 (.01, .3), t=2.2, p=.03* | .15 (-.01, .3), t=1.9, p=.06 | .25 (-.06, .56), t=1.6, p=.1 |
| Framingham Heart Study Cardiovascular Disease risk score | NA | NA | .07 (-.02, .16), t=1.6, p=.1 | .01 (-.14, .16), t=0.12, p=.9 |

*Standardized beta values are shown. Positive beta values indicate positive associations.*

*Sensitivity analysis 1: primary model with pseudo-ordinal CMB burden (1 CMB/≥2 CMBs: 15/29)*

*Sensitivity analysis 2: adding FHS-CVD*

*Sensitivity analysis 3: the same model of sensitivity analysis 1 in the highest tertile of FHS-CVD*

**eTable 5.** Sensitivity analyses using longitudinal ADNI data.

| white matter hyperintensities volume rate of change ~ | Primary model (r2=.27) | Sensitivity analysis 1 (r2=.28) | Sensitivity analysis 2 (r2=.28) | Sensitivity analysis 3 (r2=.24) |
|---|---|---|---|---|
| Age | .35 (.28, .43), t=9.1, p<0.001* | .35 (.27, .43), t=9.0, p<0.001* | .34 (.25, .44), t=7.0, p<0.001* | .34 (.18, .5), t=4.2, p<0.001* |
| Cerebral microbleed | .24 (.06, .41), t=2.7, p=0.008* | NA | .23 (.04, .42), t=2.3, p=0.02* | .46 (.11, .82), t=2.6, p=0.01* |
| One CMB (possible CAA) | NA | .12 (-.12, .35), t=1.0, p=.3 | NA | NA |
| ≥2 CMBs (Probable CAA) | NA | .35 (.12, .58), t=3.0, p=0.003* | NA | NA |
| gray matter volume rate of change | -.23 (-.31, -.15), t=-5.6, p<0.001* | -.23 (-.31, -.15), t=-5.6, p<0.001* | -.23 (-.32, -.14), t=-5.0, p<0.001* | -.31 (-.48, -.14), t=-3.6, p<0.001* |
| amyloid burden (high) | .19 (.02, .35), t=2.3, p=.02* | .17 (.01, .33), t=2.1, p=.03* | .16 (-.02, .34), t=1.8, p=.07 | -.1 (-.47, .26), t=-.5, p=.5 |
| Framingham Heart Study Cardiovascular Disease risk score | NA | NA | .03 (-.06, .12), t=0.6, p=.5 | -.09 (-.25, .07), t=-1.1, p=.2 |

*Standardized beta values are shown. Positive beta values indicate positive associations.*

*Sensitivity analysis 1: primary model with pseudo-ordinal CMB burden (1 CMB/≥2 CMBs: 66/78)*

*Sensitivity analysis 2: adding FHS-CVD*

*Sensitivity analysis 3: the same model of sensitivity analysis 1 in the highest tertile of FHS-CVD*

**eTable 6.** Sensitivity analyses using cross-sectional (baseline) HABS data.

| White matter hyperintensities volume ~ | Primary model (r2=0.21) | Sensitivity analysis 1 (r2=0.22) | Sensitivity analysis 2 (r2=0.24) | Sensitivity analysis 3 (r2=0.3) |
|---|---|---|---|---|
| Age | .34 (.22, .46), t=5.4, p<.001* | .35 (.23, .47), t=5.6, p<.001* | .34 (.21, .48), t=5.0, p<.001* | .46 (.27, .66), t=4.7, p<.001* |
| Cerebral microbleed | 0.28 (.03,.53), t=2.2, p=.02* | NA | 0.16 (-.1,.4), t=1.2, p=.2 | .06 (-.3, .5), t= .3, p=.8 |
| One CMB (possible CAA) | NA | 0.13 (-.16,.43), t=.9, p=.3 | NA | NA |
| ≥2 CMBs (Probable CAA) | NA | 0.53 (.16,.89), t=2.8, p=.005* | NA | NA |
| Gray matter volume*amyloid burden [high] | -.23 (-.45, -.01), t=-2.1, p=.04* | -.23 (-.45, -.01), t=-2.1, p=.04* | -.27 (-.5, -.04), t=-2.4, p=.01* | -.2 (-.6, .1), t=-1.3, p=.2 |
| Framingham Heart Study Cardiovascular Disease risk score | NA | NA | 0.1 (-.02,.23), t=1.6, p=.1 | .03 (-.2,.2), t= .3, p=.8 |

*Standardized beta values are shown. Positive beta values indicate positive associations.*

*Sensitivity analysis 1: primary model with pseudo-ordinal CMB burden (1 CMB/≥2 CMBs: 47/27)*

*Sensitivity analysis 2: adding FHS-CVD*

*Sensitivity analysis 3: the same model of sensitivity analysis 1 in the highest tertile of FHS-CVD*

*As a significant gray matter volume by amyloid group interaction was observed in HABS analyses, this term was retained in statistical models.*

eTable 7. Sensitivity analyses using longitudinal HABS data.

| White matter hyperintensities volume rate of change~ | Primary model (r2=0.18) | Sensitivity analysis 1 (r2=0.19) | Sensitivity analysis 2 (r2=0.23) |
|---|---|---|---|
| Age | .34 (.21, .46), t=5.4, p<.001* | .26 (.11, .4), t=3.4, p=.001* | .32 (.1, .55), t=2.8, p=.006* |
| Gray matter volume rate of change*amyloid burden[high] | -.27 (-.51, -.03), t=-2.2, p=.03* | -.30 (-.55, -.04), t=-2.3, p=.02* | -.13 (-.6, .3), t=-.6, p=.5 |
| Framingham Heart Study Cardiovascular Disease risk score | NA | 0.13 (-.01,.27), t=1.8, p=.06 | .02 (-.2,.23), t= .2, p=.8 |

*Standardized beta values are shown. Positive beta values indicate positive associations.*

*Sensitivity analysis 1: adding FHS-CVD*

*Sensitivity analysis 2: the same model of sensitivity analysis 1 in the highest tertile of FHS-CVD*
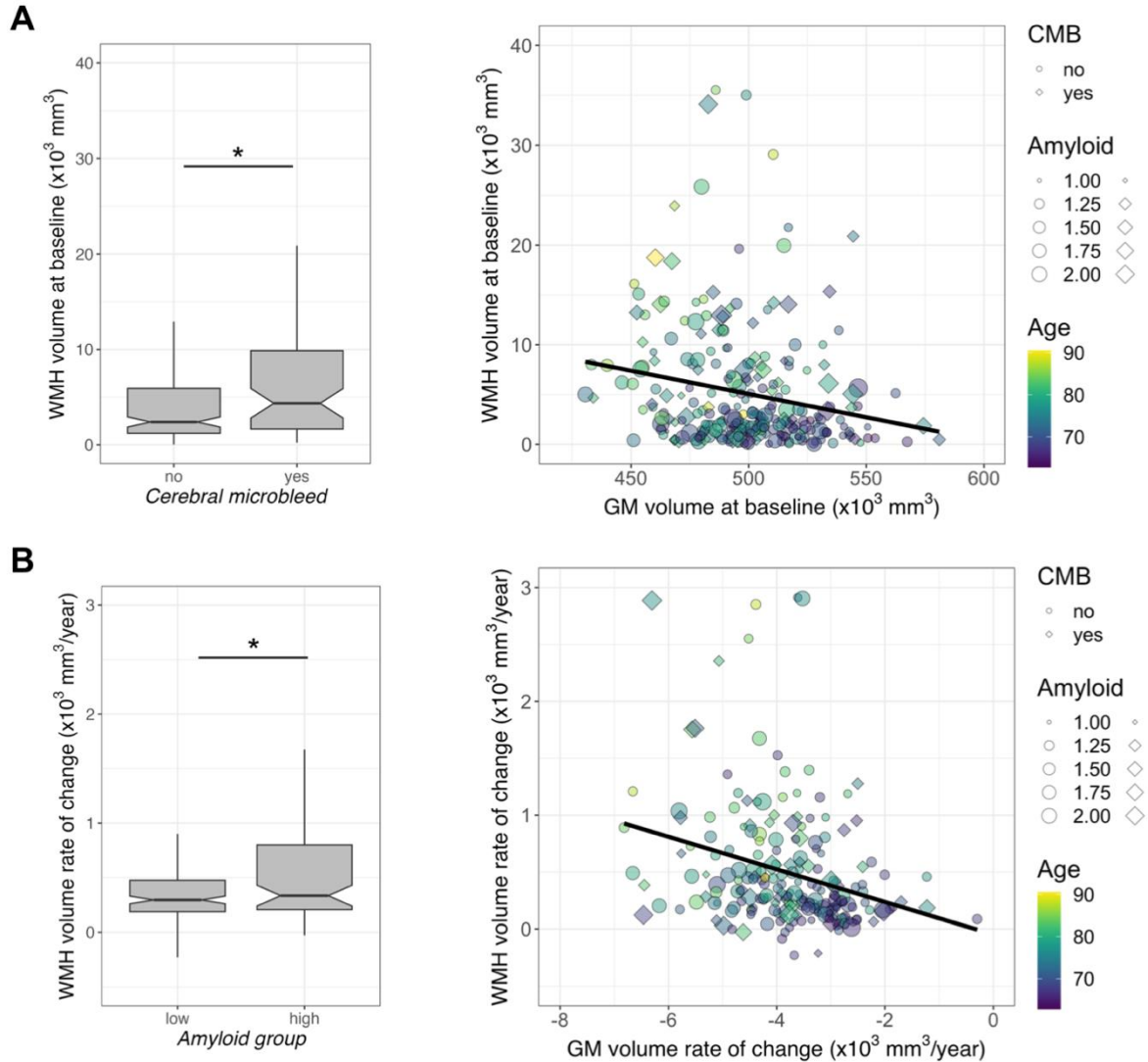
*As a significant gray matter volume by amyloid group interaction was observed in HABS analyses, this term was retained in statistical models. Longitudinal CMB data was not available in HABS participants.*

**eTable 8.** Sample characteristics for ADNI Participants without baseline CMB.

| | CMB emergent (n=100) | CMB negative (n=427) |
|---|---|---|
| **Age (years)** | 73.3 (7.0) | 72.2 (7.2) |
| **Sex (Female)** | 49 (49%) | 210 (49%) |
| **APOE e4 (yes)** | 52 (52%) | 192 (45%) |
| **Education (years)** | 16 (3) | 16 (3) |
| **WMH volume** | 10 (10) | 8 (8) |
| **GM volume** | 364 (26) | 359 (31) |
| **Diagnostic group (dementia)** | 8 (8%) | 57 (13%) |
| **Amyloid group** | 49 (49%) | 192 (47%) |
| **Framingham Heart Study Cardiovascular Disease risk score** | 38 (22) | 37 (22) |
| **Clinical dementia rating (1+)** | 59 (59%) | 238 (56%) |
| **Follow-up time (years)** | 4.8 (2.8) | 3.5 (2.7) |
| **Number of sessions** | 3.6 (1.3) | 3.5 (1.3) |

**eTable 9.** Sensitivity analysis for hazard ratios

| Factors | Hazard ratio | 95% CI | p-value |
|---|---|---|---|
| **FHS-CVD group** | | | |
| Medium (compared to Low) | 0.76 | 0.46-1.27 | 0.3 |
| High (compared to Low) | 1.19 | 0.69-2.04 | 0.5 |
| **Amyloid group** | 1.54 | 0.99-2.39 | 0.05 |
| High (compared to Low) | | | |
| **WMH volume** | **2.58\*** | **1.56-4.28** | **0.001** |
| High (compared to Low) | | | |
| **Age** | 0.97 | 0.94-1.01 | 0.11 |
| **GM volume** | 1.0 | 0.99-1.01 | >0.9 |

**eFigure.** Cerebral microbleeds (CMB) and gray matter (GM) volume are associated with WMH volume in older adults from HABS at baseline. Older adults with CMB were observed to have greater WMH volume at baseline (top left). In addition, baseline WMH volume was negatively associated with GM volume in HABS participants (top right). Using longitudinal MRI data from HABS, we observed WMH volume growth was greater in the high amyloid group than the lower amyloid group (bottom left) and was also related to the rate of GM volume decline (bottom right).

*: p<0.05