**Supplementary Material**

**Potential Factors Associated with Cognitive Improvement of Individuals Diagnosed with Mild Cognitive Impairment or Dementia in Longitudinal Studies**

**Supplementary Material A: Additional details on the statistical model**

A GLMM with fixed effects of *m* variables and a random intercept term takes the general form

where is the probability of participant transitioning backwards at observation . is the mean intercept and is the log odds ratio associated with a one unit increase in variable . represents a specific deviance from for individual *i* which accounts for the variability in the likelihood of transitioning between individuals. represents the random error which accounts for the variability within individuals. Hence, parameters and represent the variance between and within individuals, respectively.

The model parameters were estimated using Markov chain Monte Carlo (MCMC) methods, implemented within the runMLwiN function from the R2MLwiN package. The MCMC engine uses Gibbs sampling, and it was assumed that all parameters had improper uniform prior distributions. Convergence of the MCMC algorithms was assessed visually from the traces of each parameter.

**Supplementary Material B: Cases of back-transitions**

**Table B1.** Number of AzY BA back-transitions in ADNI and NACC where individuals after transitioning from state A to state B, remained at state B for z years (zY) before they transition back to state A. In brackets we present the total number of AzY BC transitions, where CCN, MCI, D

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|  | | **No of transitions** | |
| **ADNI** | **NACC** |
| **CNzY MCICN** | CN1Y MCICN | 10 (63) | 191 (656) |
| CN2Y MCICN | 0 (31) | 33 (239) |
| CN3Y MCICN | 0 (17) | 7 (79) |
| CN4Y MCICN | 0 (3) | 1 (29) |
| CN5Y MCICN | 0 (2) | 0 (16) |
| CN6Y MCICN | 0 (0) | 0 (8) |
| CN7Y MCICN | 0 (0) | 0 (4) |
| CN8Y MCICN | 0 (0) | 0 (1) |
| CN9Y MCICN | 0 (0) | 0 (0) |
| **MCIzY DMCI** | MCI1Y DMCI | 9 (221) | 42 (733) |
| MCI2Y DMCI | 1 (126) | 8 (386) |
| MCI3Y DMCI | 0 (74) | 3 (198) |
| MCI4Y DMCI | 1 (39) | 2 (98) |
| MCI5Y DMCI | 0 (19) | 1 (42) |
| MCI6Y DMCI | 0 (11) | 0 (19) |
| MCI7Y DMCI | 0 (3) | 0 (6) |
| MCI8Y DMCI | 0 (1) | 0 (2) |
| MCI9Y DMCI | 0 (0) | 0 (0) |

**Table B2.** Number of zY BA back-transitions in ADNI and NACC where individuals remained at state B for z years (zY) since the first diagnosis at baseline before they transition back to state A. In brackets we present the total number of zY BC transitions, where CCN, MCI, D. Note that the time since the transition to MCI and D diagnosed at baseline is unknown

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|  | | **No of transitions** | |
| **ADNI** | **NACC** |
| **zY MCICN** | 1Y MCICN | 25 (791) | 204 (1,770) |
| 2Y MCICN | 14 (572) | 79 (997) |
| 3YMCICN | 11 (378) | 30 (450) |
| 4Y MCICN | 9 (220) | 12 (186) |
| 5Y MCICN | 2 (80) | 5 (77) |
| 6Y MCICN | 0 (33) | 0 (32) |
| 7Y MCICN | 0 (27) | 0 (14) |
| 8Y MCICN | 0 (22) | 0 (8) |
| 9Y MCICN | 0 (14) | 0 (2) |
| 10Y MCICN | 1 (2) | 0 (0) |
| **zY DMCI** | 1Y DMCI | 2 (270) | 51 (2,721) |
| 2Y DMCI | 1 (164) | 13 (2,313) |
| 3Y DMCI | 0 (12) | 6 (1,299) |
| 4Y DMCI | 1 (3) | 4 (712) |
| 5Y DMCI | 0 (0) | 0 (370) |
| 6Y DMCI | 0 (0) | 0 (171) |
| 7Y DMCI | 0 (0) | 1 (77) |
| 8Y DMCI | 0 (0) | 1 (26) |
| 9Y DMCI | 0 (0) | 0 (3) |
| 10Y DMCI | 0 (0) | 0 (0) |

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| **A**  H:\Back-transitions\NumberOfBackTransitionersInEachGroup\Updated_ForPaper_18-09-17\BackTrans_Histograms\BackTransitioners_Times\Updated_ForPaper_AllDem_31-03-18\BackTransitioners_Times_ADNI.tif | **B**  H:\Back-transitions\NumberOfBackTransitionersInEachGroup\Updated_ForPaper_18-09-17\BackTrans_Histograms\BackTransitioners_Times\Updated_ForPaper_AllDem_31-03-18\BackTransitioners_Times_NACC.tif |

**Figure B1.** Number of times that back-transitioners have moved from MCI to CN, and from D to CN and MCI in A) ADNI and B) NACC. It is observed that some individuals have moved even three times from MCI to CN, which means that they have transitioned at least 5 times between the CN and MCI states.

**Supplementary Material C: Results in Model 2a, Model 2b and Model 3**

**Table C1.** Potential factors associated with MCICN transitions in Model 2a where the association between the MMSE scores at the previous visit and back-transitions was considered. represents the number of assessments used to develop the GLMMs, i.e., the number of MCI cases that had the chance to transition to a previous clinical state in a subsequent assessment. CI: credible interval, SD: standard deviation, ICC: intraclass correlation coefficient, : -value, \*: 0.05, \*\*: 0.01, \*\*\*: 0.001

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| **Model 2a**  **MCICN** | **ADNI**  **( 3,451)** | | | **NACC**  **( 5,108)** | | |
| **Fixed effects** | **Odds Ratio** | **(95% CI)** |  | **Odds Ratio** | **(95% CI)** |  |
| **Age at visit** | 0.95 | (0.90, 0.99) | \* | 0.97 | (0.96, 0.99) | \*\*\* |
| **Gender (male**+**)** | 1.11 | (0.57, 2.14) |  | 1.14 | (0.87, 1.48) |  |
| **Education (12 years**+**)** | 3.75 | (1.03, 13.7) | \* | 0.77 | (0.56, 1.06) |  |
| **ApoE ε4, 1 allele**  **(absence of ApoE ε4**+**)** | 0.89 | (0.45, 1.77) |  | 0.52 | (0.39, 0.70) | \*\*\* |
| **ApoE ε4, 2 alleles**  **(absence of ApoE ε4**+**)** | 0.25 | (0.05, 1.23) |  | 0.19 | (0.09, 0.38) | \*\*\* |
| **Time between visits** | 2.53 | (1.28, 5.00) | \*\* | 1.38 | (1.13, 1.68) | \*\* |
| **Intercept** | 3.3E-07 | (2.2E-09, 4.7E-05) | \*\*\* | 4.2E-06 | (4.6E-07, 3.8E-05) | \*\*\* |
| **MMSE at previous visit** | 1.44 | (1.23, 1.69) | \*\*\* | 1.49 | (1.38, 1.61) | \*\*\* |
| **Random effects** | **Variance** | **SD** | **ICC** | **Variance** | **SD** | **ICC** |
| **Roster ID (Intercept)** | 3.87 | 1.97 | 0.54 | 2.92 | 1.71 | 0.47 |
| +Reference category. | | | | | | |

**Table C2.** Potential factors associated with transitions from D to less severe states in Model 2a where the association between the MMSE scores at the previous visit and back-transitions was considered. represents the number of assessments used to develop the GLMMs, i.e., the number of dementia cases that had the chance to transition to a previous clinical state in a subsequent assessment. CI: credible interval, SD: standard deviation, ICC: intraclass correlation coefficient, : -value, \*: 0.05, \*\*: 0.01, \*\*\*: 0.001

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| **Model 2a**  **DCN/MCI** | **ADNI**  **(1,425)** | | | **NACC**  **( 8,068)** | | |
| **Fixed effects** | **Odds Ratio** | **(95% CI)** |  | **Odds Ratio** | **(95% CI)** |  |
| **Age at visit** | 0.95 | (0.90, 1.01) |  | 1.00 | (0.97, 1.03) |  |
| **Gender (male**+**)** | 0.43 | (0.16, 1.21) |  | 0.79 | (0.47, 1.35) |  |
| **Education (12 years**+**)** | 1.36 | (0.33, 5.66) |  | 0.45 | (0.26, 0.79) | \*\* |
| **ApoE ε4, 1 allele**  **(absence of ApoE ε4**+**)** | 1.25 | (0.49, 3.18) |  | 0.60 | (0.35, 1.03) |  |
| **ApoE ε4, 2 alleles**  **(absence of ApoE ε4**+**)** | 0.10 | (0.01, 1.39) |  | 0.30 | (0.11, 0.83) | \* |
| **Time between visits** | 2.30 | (0.69, 7.64) |  | 1.61 | (1.02, 2.54) | \* |
| **Intercept** | 3.8E-06 | (1.6E-08, 8.9E-04) | \*\*\* | 8.2E-08 | (4.4E-09, 1.8E-06) | \*\*\* |
| **MMSE at previous visit** | 1.50 | (1.24, 1.81) | \*\*\* | 1.60 | (1.46, 1.75) | \*\*\* |
| **Random effects** | **Variance** | **SD** | **ICC** | **Variance** | **SD** | **ICC** |
| **Roster ID (Intercept)** | 0.00016 | 0.013 | 0.01 | 6.56 | 2.56 | 0.43 |
| +Reference category. | | | | | | |

**Table C3.** Potential factors associated with MCICN transitions in Model 2b where the association between the ADAS-Cog 11 scores at the previous visit and back-transitions was considered. represents the number of assessments used to develop the GLMMs, i.e., the number of MCI cases that had the chance to transition to a previous clinical state in a subsequent assessment. CI: credible interval, SD: standard deviation, ICC: intraclass correlation coefficient, : -value, \*: 0.05, \*\*: 0.01, \*\*\*: 0.001

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| **Model 2b**  **MCICN** | **ADNI**  **(3,450)** | | |
| **Fixed effects** | **Odds Ratio** | **(95% CI)** |  |
| **Age at visit** | 0.97 | (0.93, 1.01) |  |
| **Gender (male**+**)** | 0.98 | (0.51, 1.86) |  |
| **Education (12 years**+**)** | 3.19 | (0.91, 11.2) |  |
| **ApoE ε4, 1 allele**  **(absence of ApoE ε4**+**)** | 1.04 | (0.52, 2.08) |  |
| **ApoE ε4, 2 alleles**  **(absence of ApoE ε4**+**)** | 0.34 | (0.07, 1.67) |  |
| **Time between visits** | 1.91 | (0.95, 3.84) |  |
| **Intercept** | 0.05 | (0.01, 0.32) | \*\* |
| **ADAS-Cog 11 at previous visit** | 0.77 | (0.70, 0.85) | \*\*\* |
| **Random effects** | **Variance** | **SD** | **ICC** |
| **Roster ID (Intercept)** | 3.45 | 1.86 | 0.51 |
| +Reference category. | | | |

**Table C4.** Potential factors associated with transitions from D to less severe states in Model 2b where the association between the ADAS-Cog 11 scores at the previous visit and back-transitions was considered. represents the number of assessments used to develop the GLMMs, i.e., the number of dementia cases that had the chance to transition to a previous clinical state in a subsequent assessment. CI: credible interval, SD: standard deviation, ICC: intraclass correlation coefficient, : -value, \*: 0.05, \*\*: 0.01, \*\*\*: 0.001

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| **Model 2b**  **DCN/MCI** | **ADNI**  **( 1,419)** | | |
| **Fixed effects** | **Odds Ratio** | **(95% CI)** |  |
| **Age at visit** | 0.96 | (0.90, 1.01) |  |
| **Gender (male**+**)** | 0.52 | (0.20, 1.37) |  |
| **Education (12 years**+**)** | 1.89 | (0.51, 7.00) |  |
| **ApoE ε4, 1 allele**  **(absence of ApoE ε4**+**)** | 1.22 | (0.49, 3.01) |  |
| **ApoE ε4, 2 alleles**  **(absence of ApoE ε4**+**)** | 0.09 | (0.01, 1.23) |  |
| **Time between visits** | 3.14 | (0.98, 10.1) |  |
| **Intercept** | 1.05 | (0.10, 11.1) |  |
| **ADAS-Cog 11 at previous visit** | 0.83 | (0.76, 0.90) | \*\*\* |
| **Random effects** | **Variance** | **SD** | **ICC** |
| **Roster ID (Intercept)** | 0.00940 | 0.097 | 0.01 |
| +Reference category. | | | |

**Table C5.** Potential factors associated with MCICN transitions in Model 3 where the association between the GDS scores relative to the previous visit and back-transitions was considered. represents the number of assessments used to develop the GLMMs, i.e., the number of MCI cases that had the chance to transition to a previous clinical state in a subsequent assessment. CI: credible interval, SD: standard deviation, ICC: intraclass correlation coefficient, : -value, \*: 0.05, \*\*: 0.01, \*\*\*: 0.001

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| **Model 3**  **MCICN** | **ADNI**  **( 1,814)** | | | **NACC**  **( 5,292)** | | |
| **Fixed effects** | **Odds Ratio** | **(95% CI)** |  | **Odds Ratio** | **(95% CI)** |  |
| **Age at visit** | 0.94 | (0.91, 0.98) | \*\* | 0.96 | (0.94, 0.97) | \*\*\* |
| **Gender (male**+**)** | 1.05 | (0.62, 1.80) |  | 1.28 | (0.97, 1.67) |  |
| **Education (12 years**+**)** | 3.32 | (0.94, 11.7) |  | 1.21 | (0.88, 1.65) |  |
| **ApoE ε4, 1 allele**  **(absence of ApoE ε4**+**)** | 0.91 | (0.52, 1.57) |  | 0.44 | (0.32, 0.60) | \*\*\* |
| **ApoE ε4, 2 alleles**  **(absence of ApoE ε4**+**)** | 0.24 | (0.05, 1.16) |  | 0.11 | (0.05, 0.22) | \*\*\* |
| **Time between visits** | 1.07 | (0.51, 2.23) |  | 1.36 | (1.12, 1.66) | \*\* |
| **Intercept** | 0.05 | (0.01, 0.23) | \*\*\* | 0.25 | (0.15, 0.44) | \*\*\* |
| **Change in GDS** | 0.97 | (0.83, 1.14) |  | 0.95 | (0.91, 1.00) |  |
| **Random effects** | **Variance** | **SD** | **ICC** | **Variance** | **SD** | **ICC** |
| **Roster ID (Intercept)** | 0.00165 | 0.041 | 0.01 | 3.78 | 1.94 | 0.53 |
| +Reference category. | | | | | | |

**Table C6.** Potential factors associated with transitions from D to less severe states in Model 3 where the association between the GDS scores relative to the previous visit and back-transitions was considered. represents the number of assessments used to develop the GLMMs, i.e., the number of dementia cases that had the chance to transition to a previous clinical state in a subsequent assessment. CI: credible interval, SD: standard deviation, ICC: intraclass correlation coefficient, : -value, \*: 0.05, \*\*: 0.01, \*\*\*: 0.001

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| **Model 3**  **DCN/MCI** | **ADNI**  **( 750)** | | | **NACC**  **( 7,078)** | | |
| **Fixed effects** | **Odds Ratio** | **(95% CI)** |  | **Odds Ratio** | **(95% CI)** |  |
| **Age at visit** | 0.96 | (0.91, 1.02) |  | 0.98 | (0.95, 1.00) |  |
| **Gender (male**+**)** | 0.54 | (0.19, 1.53) |  | 0.71 | (0.41, 1.24) |  |
| **Education (12 years**+**)** | 2.37 | (0.46, 12.2) |  | 0.96 | (0.53, 1.73) |  |
| **ApoE ε4, 1 allele**  **(absence of ApoE ε4**+**)** | 0.66 | (0.25, 1.73) |  | 0.40 | (0.22, 0.73) | \*\* |
| **ApoE ε4, 2 alleles**  **(absence of ApoE ε4**+**)** | 0.08 | (0.01, 1.08) |  | 0.08 | (0.02, 0.26) | \*\*\* |
| **Time between visits** | 0.88 | (0.17, 4.51) |  | 1.72 | (1.04, 2.84) | \* |
| **Intercept** | 0.06 | (0.00, 0.63) | \* | 3.9E-03 | (1.2E-03, 1.3E-02) | \*\*\* |
| **Change in GDS** | 0.99 | (0.79, 1.24) |  | 0.93 | (0.85, 1.03) |  |
| **Random effects** | **Variance** | **SD** | **ICC** | **Variance** | **SD** | **ICC** |
| **Roster ID (Intercept)** | 0.001 | 0.001 | 0.01 | 10.68 | 3.27 | 0.76 |
| +Reference category. | | | | | | |