GRAM Model Documentation

# Model Set Up and Parameters

## Individual Attributes

|  |  |  |
| --- | --- | --- |
| **Attribute Name** | **Attribute Label** | **Attribute Value** |
| ALIVE | Alive status | 0 = Dead  1 = Alive |
| AGE | Age | Numeric between  50 . . . 100 |
| SEX | Sex | 1 = Male  2 = Female |
| EDU | Highest level of education | 1 = College degree or more  2 = High school or GED  3 = Less than high school |
| RACEETH | Ethnicity | 0 = Not Hispanic or Black  1 = Hispanic or Black |
| INCOME | Annual income level | 0 = Low income (<$9,000)  1 = Medium income ($9,000-$36,000)  2 = High income (>$36,000) |
| MEDBUR | Medical burden sum score | Integer between  0 . . . 15 |
| APOE4 | APOE4 allele carrier status | 0 = Not a carrier  1 = Carrier (homozygous or heterozygous) |
| AB | Amyloid beta status (determined by ???) | 0 = No amyloid beta accumulation  1 = Amyloid beta accumulation |
| TX | Treatment status | 0 = Treatment on/provided  1 = Treatment off/stopped |
| SYN | Unobserved (true) cognitive syndrome status | 0 = Cognitively intact  1 = Cognitively impaired |
| CDR | Unobserved cognitive assessment based on the CDR-SB | Numeric between  0 . . . 18  At increments of 0.5 |
| SEV | Unobserved severity of cognitive impairment | 0 = Mild cognitive impairment  1 = Mild dementia  2 = Moderate dementia  3 = Severe dementia |
| BHA | Observed cognitive assessment based on the BHA | 0 = Cognitively intact (or normal aging)  1 = Cognitively impaired (or pathological aging) |
| CDR\_obs | Observed cognitive assessment based on the CDR-SB | Numeric between  0 . . . 18  At increments of 0.5 |
| SEV\_obs | Observed severity of cognitive impairment | 0 = Mild cognitive impairment  1 = Mild dementia  2 = Moderate dementia  3 = Severe dementia |
| FUN | Functional assessment based on the FAQ |  |
| QALY | Quality-adjusted life years | Numeric |
| COST | Costs incurred | Numeric (USD) |

## Model Settings

Stored as elements of list `l.inputs`.

|  |  |  |
| --- | --- | --- |
| **Setting Name** | **Description** | **Default Value** |
| scenario | Name of the scenario | “GRAM natural course of disease” |
| n.ind | Number of individuals to simulate | 3000 |
| n.cycle | Number of cycles (time steps) to simulate | 50 |
| seed\_stochastic | Seed for generating random values for stochastic parameters | 20240202 |
| strategy | Filled in during model run | NA |
| strategy\_strat1 | Strategy being compared | “control” |
| strategy\_strat2 | Strategy being compared | “intervention\_dmt” |
| Tx | Filled in during model run | 0 |
| Tx\_strat1 | Treatment strategy | 0 |
| Tx\_strat2 | Treatment strategy | 1 |
| seed\_pa | Seed for generating random values that drive probabilistic analysis | 20241022 |
| n.psa | Number of PSA iterations | 10 |
| r.discount\_QALY | Discount rate for QALYs | 0.03 |
| r.discount\_COST | Discount rate for costs | 0.03 |

## Model Inputs

|  |  |  |  |
| --- | --- | --- | --- |
| **Input Name** | **Input Description** | **Input Value** | **Source** |
| **Starting Population** | | | |
| AGE\_start\_mean | Mean age at time = 0 | 50 | Assumed. |
| AGE\_start\_sd | Standard deviation of starting age | 0 | Assumed. |
| p.SEX\_start\_male | Probability of being male | 0.5 | Assumed. |
| p.SEX\_start\_female | Probability of being female | 0.5 | Assumed. |
| p.EDU\_start | Vector of probabilities for education level | College = 0.4  High school = 0.5  Less than high school = 0.1 | PLACEHOLDER |
| p.RACEETH\_start | Vector of probabilities for race/ethnicity | Not Hispanic/Black = 0.65  Hispanic/Black = 0.35 | PLACEHOLDER |
| p.INCOME\_start | Vector of probabilities for income level | Low income = 0.35  Medium income = 0.55  High income = 0.10 | PLACEHOLDER |
| p.APOE4\_start | Vector of probabilities for APOE4 status | Non-carrier = 0.7  Carrier = 0.3 | PLACEHOLDER |
| **Mortality** | | | |
| hr.mort\_mci | Hazard rate for death for MCI compared to cognitively normal | 1.82 |  |
| hr.mort\_mil | Hazard rate for death for mild dementia compared to cognitively normal | 2.92 |  |
| hr.mort\_mod | Hazard rate for death for moderate dementia compared to cognitively normal | 3.85 |  |
| hr.mort\_sev | Hazard rate for death for severe dementia compared to cognitively normal | 9.52 |  |
| m.lifetable | Table with probability of dying by age | 51x1 table | Social security actuarial life table |
| **Onset of cognitive impairment** | | | |
| m.hr\_mci | Table with incidence rate of MCI by age | 51x1 table | [Gillis 2019](https://pmc.ncbi.nlm.nih.gov/articles/PMC6416157/) and authors’ calculation |
| log\_EDU | Log-transformed hazard function parameter for education | log(0.95) | [Angevaare 2021](https://www.neurology.org/doi/10.1212/WNL.0000000000013017) |
| log\_APOE4 | Log-transformed hazard function parameter for APOE4 carrier status | log(1.18) | [Angevaare 2021](https://www.neurology.org/doi/10.1212/WNL.0000000000013017) |
| log\_MEDBUR | Log-transformed hazard function parameter for medical burden | log(1.09) | [Angevaare 2021](https://www.neurology.org/doi/10.1212/WNL.0000000000013017) |
| log\_INCOMEmed | Log-transformed hazard function parameter for medium income (reference: low) | log(0.80) | [Angevaare 2021](https://www.neurology.org/doi/10.1212/WNL.0000000000013017) |
| log\_INCOMEhi | Log-transformed hazard function parameter for high income (reference: low) | log(0.73) | [Angevaare 2021](https://www.neurology.org/doi/10.1212/WNL.0000000000013017) |
| sens\_BHA | Sensitivity of the BHA to detect impairment | 0.72 during MCI  0.99 during dementia | Possin 2018 |
| spec\_BHA | Specificity of the BHA | 0.85 | Possin 2018 |
| **Progression of cognitive impairment** | | | |
| cutoff\_CDR | Keys for CDR-SB cutoff points | Min = 0  MCI = 0.5  Mild dementia = 4.5  Moderate dementia = 9.5  Severe dementia = 16.5  Max = 18.0 | O’Bryant 2012 |
| r.CDRfast\_mean | Mean annual rate of change in CDR-SB score for fast progressors | 1.5 | [Williams 2014](https://pmc.ncbi.nlm.nih.gov/articles/PMC3660405/#:~:text=in%20all%20analyses.-,The%20annual%20rate%20of%20change%20in%20CDR%2DSB%20scores%20was,in%20the%20CDR%201%20sample.), calibrated |
| r.CDRfast\_sd1 | Standard deviation for CDR-SB annual rate of change for fast progressors | 1.26 | [Williams 2014](https://pmc.ncbi.nlm.nih.gov/articles/PMC3660405/#:~:text=in%20all%20analyses.-,The%20annual%20rate%20of%20change%20in%20CDR%2DSB%20scores%20was,in%20the%20CDR%201%20sample.), calibrated |
| r.CDRslow\_mean | Mean annual rate of change in CDR-SB score for fast progressors | 0.5 | [Williams 2014](https://pmc.ncbi.nlm.nih.gov/articles/PMC3660405/#:~:text=in%20all%20analyses.-,The%20annual%20rate%20of%20change%20in%20CDR%2DSB%20scores%20was,in%20the%20CDR%201%20sample.), calibrated |
| r.CDRslow\_sd1 | Standard deviation for CDR-SB annual rate of change for fast progressors | 1.07 | [Williams 2014](https://pmc.ncbi.nlm.nih.gov/articles/PMC3660405/#:~:text=in%20all%20analyses.-,The%20annual%20rate%20of%20change%20in%20CDR%2DSB%20scores%20was,in%20the%20CDR%201%20sample.), calibrated |
| r.CDR\_sd2 | Standard deviation for individual year-to-year variation in CDR-SB progression rate | 0 | Assumed. |
| r.CDR\_sd3 | Standard deviation in CDR-SB progression rate due to rater reliability | 0 | PLACEHOLDER |
| **Health State Utilities** | | | |
| u.healthy | Health state utility for cognitively normal | 0.85 | PLACEHOLDER |
| u.mci | Health state utility for MCI | 0.73 | PLACEHOLDER |
| u.mil | Health state utility for mild dementia | 0.69 | PLACEHOLDER |
| u.mod | Health state utility for moderate dementia | 0.53 | PLACEHOLDER |
| u.sev | Health state utility for severe dementia | 0.38 | PLACEHOLDER |
| **Costs** |  |  |  |
| c.healthy | Annual medical costs for healthy | 0 | PLACEHOLDER |
| c.mci | Annual medical costs for MCI | 13364 | PLACEHOLDER |
| c.mil | Annual medical costs for mild dementia | 26727 | PLACEHOLDER |
| c.mod | Annual medical costs for moderate dementia | 31644 | PLACEHOLDER |
| c.sev | Annual medical costs for severe dementia | 40645 | PLACEHOLDER |
| **Treatments** | | | |
| c.Tx | Annual cost of treatment | 5000 | PLACEHOLDER |
| rr.TX\_mci | Risk ratio for conversion to dementia while on treatment | 0.8 | PLACEHOLDER |
| Tx\_t\_max | Maximum duration treatment is provided (years) | 5 | PLACEHOLDER |

# Model Functions

## Updating Attributes

#### TIME

Each cycle represents one year. At the beginning of each cycle, TIME is increased by 1.

#### ALIVE

Mortality rates are applied based on age. Individual probabilities for death are calculated by adjusting life table probabilities (CITE) for the increased mortality rate for MCI and dementia (including differing severity). These probabilities are then compared to the random number generated for each individual at each cycle to determine outcome.

#### AGE

For those who remain alive, AGE is updated by 1 year. Others are assigned NA.

#### SEX

For those who remain alive, SEX is iterated to the next cycle. Others are assigned NA.

#### RACE/ETHNICITY

For those who remain alive, RACEETH is iterated to the next cycle. Others are assigned NA.

#### INCOME

For those who remain alive, INCOME is iterated to the next cycle. Others are assigned NA.

#### EDUCATION

For those who remain alive, EDU is iterated to the next cycle. Others are assigned NA.

#### MEDICAL BURDEN

For those who remain alive, MEDBUR is iterated to the next cycle. Others are assigned NA.

#### APOE4 STATUS

For those who remain alive, APOE4 is iterated to the next cycle. Others are assigned NA.

#### COGNITIVE IMPAIRMENT STATUS (SYNDROME)

For those who remain alive, the probability of each individual developing MCI during the next cycle is calculated based on age-specific incidence rate (extrapolated from Gillis et al) and a Cox proportional hazards model to account for individual-level predictors (Angevaare et al). Others are assigned NA.

The age-specific hazard is estimated as equal to the age-specific incidence rate. This is used as the baseline hazard in the hazard function, which estimates the hazard in the next cycle depending on education level, APOE4 carrier status, medical burden, and income level. The hazard is then transformed into a probability, which is conditionally applied to individuals who were not cognitively impaired in the previous cycle.

Those who were already cognitively impaired in the previous cycle remain cognitively impaired in the next cycle. Backwards transitions (i.e., improvements) are not possible.

Update cognitive status score: Cognition is measured and monitored with the Clinical Demenita Rating – sum of boxes score. This scale incorporates both cognitive and functional status and ranges between 0-18 in increments of 0.5. *Healthy individuals* are assigned a score of 0. *Individuals who newly transition in MCI* (in the current cycle) get assigned a random CDR-SB score between 0.5 and 4.0. These values are drawn from a right-skewed beta distribution to allow more people to have lower CDR-SB scores at diagnosis. Individuals who remain in MCI (but did not newly transition) incur an increase of 1.67 point (on average, allowing for random variability across individuals). Individuals who newly transition into dementia are first assigned a severity (mild/moderate/severe) based on pre-defined landing probabilities for dementia severity. They are then assigned a CDR-SB score between 4.5-9.0, 9.5-15.5, 16.0-18.0 from a uniform distribution, for mild/moderate/severe dementia respectively (CITE O’BRYANT). Individuals who maintain their dementia syndrome attribute from the prior cycle incur an increase in CDR-SB score by 2 points on average, allowing for random variability across individuals. People who are no longer alive do not have a CDR-SB score.

Update dementia severity: Dementia severity is reassessed for those with dementia, using the same CDR-SB cutoff scores described above. People who are no longer alive or do not have dementia (i.e., are cognitively intact or have mild cognitive impairment) are not assigned a severity.

Update functional status: A post-hoc FAQ score is calculated for those who are alive. This is based on the correspondence of CDR-SB and FAQ scales. An explicit FAQ progression is not depicted.

Update treatment status: ???