APPENDIX

eMethods

Imputation of missing covariates with BART

BART was first used to impute the missing covariates in the FRS score, assumed to be missing at random [1]. Note, only single covariate items were imputed in this step, and not cases where the full set of covariates in the FRS were missing. For example, FRS after dropout was not imputed and instead considered when calculating the cardiovascular risk trajectory groups. The approach involves factoring the covariates with missingness into a set of univariate sequential conditional distributions and applying BART for continuous or binary outcomes [2] to model each of these conditional models separately. We specify the variables from enrollment to the fifth timepoint in time order, and within the same timepoint, the variables with less missingness are specified before those with more missingness. The BART models are used for making predictions given the observed data, and the missing data are further imputed by sampling from these predictive distributions. A detailed description of the procedure can be found elsewhere [3].

Analysis of cross-sectional FRS values

For comparison with the longitudinal FRS trajectories, the predictive accuracy of cross-sectional FRS values was also assessed with BART for the incidence of AD dementia, VaD, and death. For these analyses, we assigned participants into one of three groups based on the suggested cutoff values from the original FRS study (low risk: 0-6%, medium risk: 6-20%, high risk: 20%+ [4]). As there were no participants who had an FRS value under 6% at their final recorded timepoint, analyses concerning the final level of risk only featured the medium and high risk groups. As alternative measures, tertile and quartile splits of the FRS distributions were performed (low risk: 1st quartile / tertile, medium: 2nd and 3rd quartile / 2nd tertile, high risk: 4th quartile / 3rd tertile), in accordance with previous research [5,6].

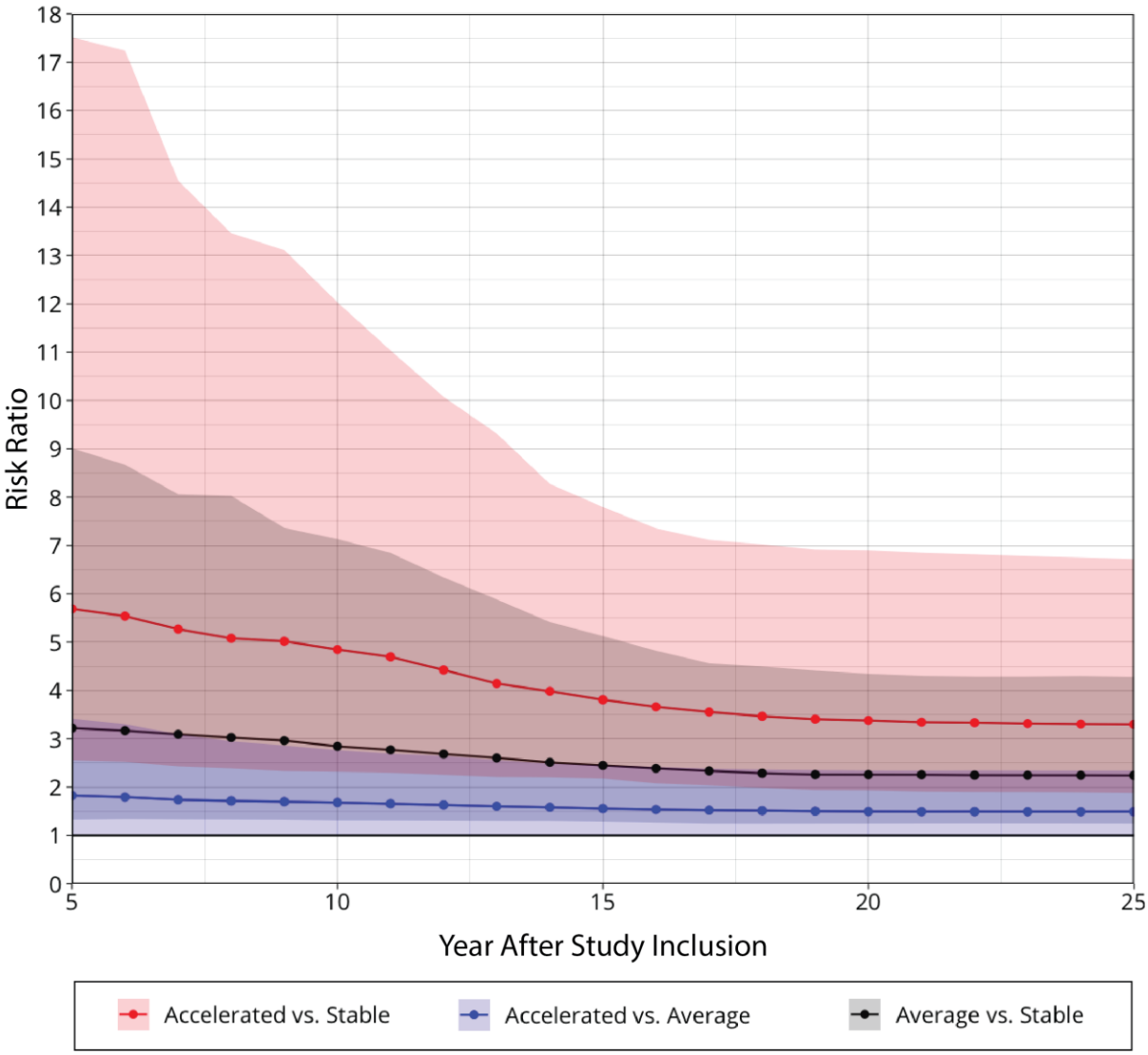
Prediction of EM decline with BART

Furthermore, BART was used to predict EM values which were then used as a benchmark for decline. Predictive models were constructed for each timepoint, incorporating age, gender, and education as covariates. Each timepoint prediction model utilized the data available in all prior timepoints (i.e. predictions for T2 used data from T1, predictions for T3 used data from T1 and T2, etc.). EM decline was assumed to have occurred for participants who subsequently scored below 0.05% of the variance predicted by the model at each relevant timepoint.

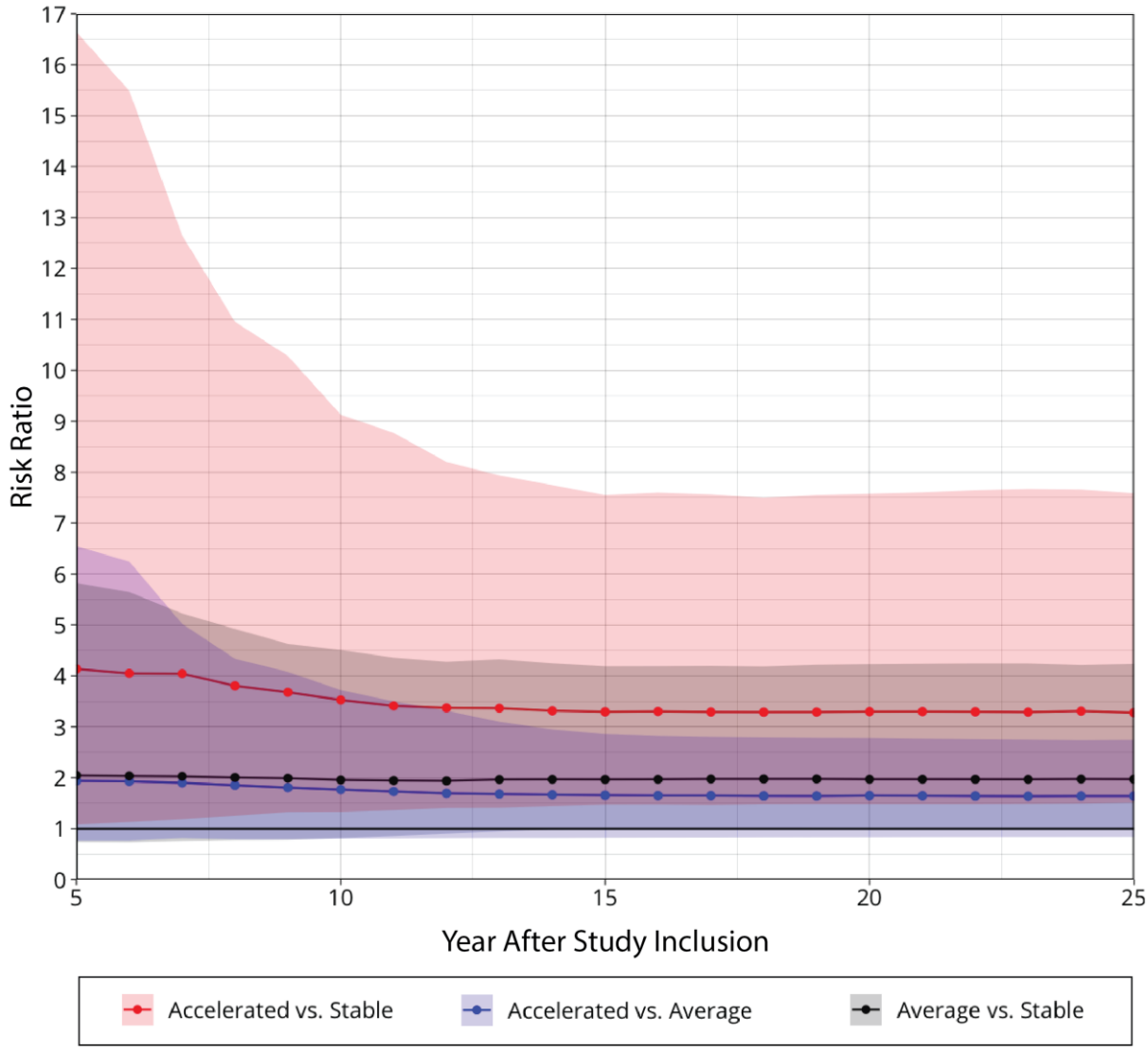
References

1. Rubin DB. Inference and Missing Data. *Biometrika.* 1976;63(3):581-590.
2. Chipman HA, George EI, McCulloch RE. Bart: Bayesian Additive Regression Trees. *Ann Appl Stat.* 2010;4(1):266-298.
3. Xu D, Daniels MJ, Winterstein AG. Sequential BART for imputation of missing covariates. *Biostatistics.* 2016;17(3):589-602.
4. D'Agostino RB, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care - The Framingham Heart Study. *Circulation.* 2008;117(6):743-753.
5. Rabin JS, Schultz AP, Hedden T, et al. Interactive Associations of Vascular Risk and beta-Amyloid Burden With Cognitive Decline in Clinically Normal Elderly Individuals Findings From the Harvard Aging Brain Study. *Jama Neurology.* 2018;75(9):1124-1131.
6. Song RX, Xu H, Dintica CS, et al. Associations Between Cardiovascular Risk, Structural Brain Changes, and Cognitive Decline. *J Am Coll Cardiol.* 2020;75(20):2525-2534.

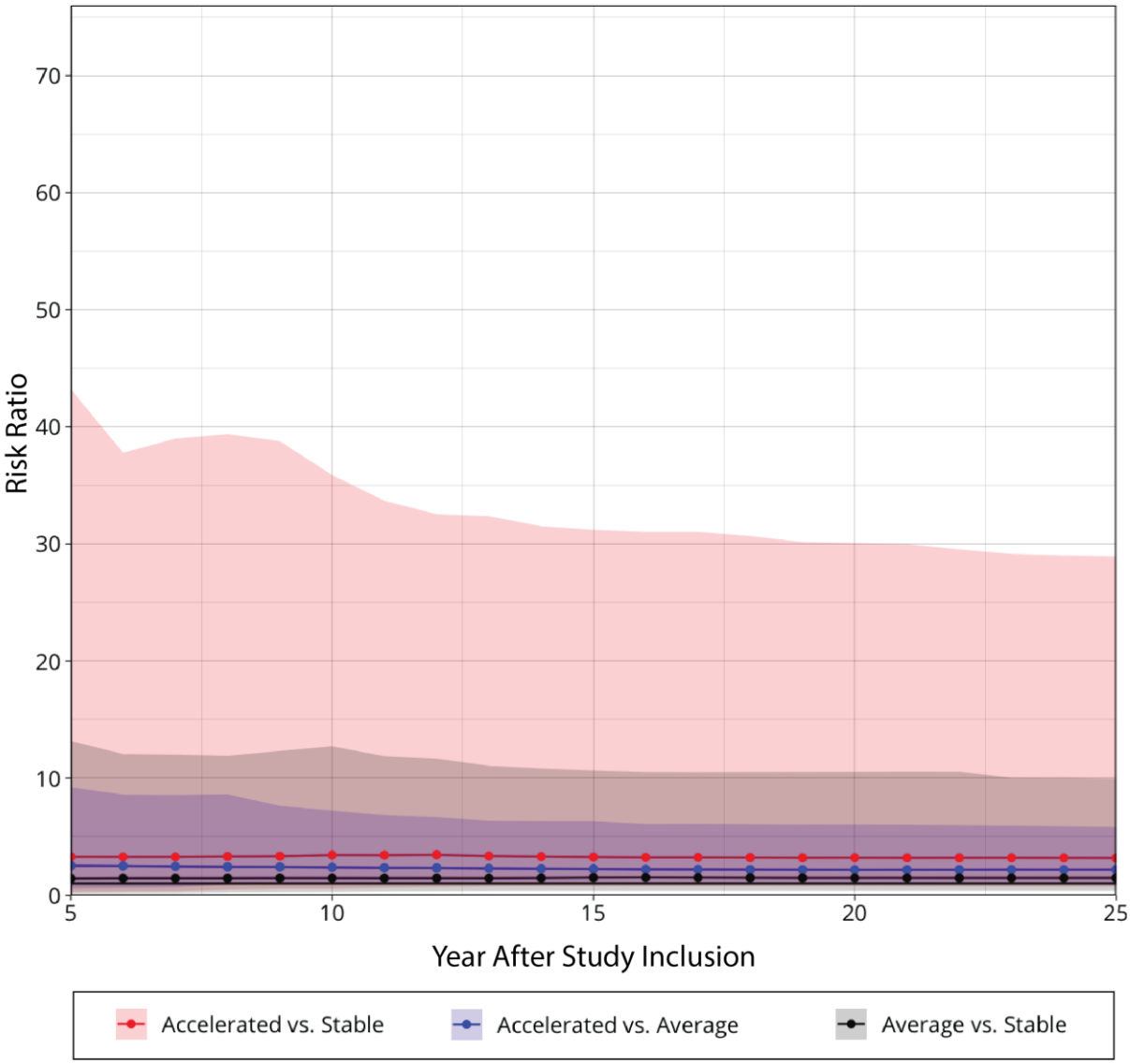
eFigure 1.
Risk ratio graph for cumulative incidence of Alzheimer's disease in old (70+) participants, split by Framingham Risk Score trajectory groups.
The risk ratio of the comparisons accelerated vs. stable, and average vs. stable, show an elevated risk of Alzheimer's disease. Other comparisons (accelerated vs. average, average vs. accelerated) did not show an elevated level of risk. Shaded areas represent 95% credible intervals (CI). The accelerated risk group shows the highest relative level of risk when compared to the stable risk group, from 5.7 at T2, to 3.3 at T5 (95% CI 2.6–17.5 at T2, 1.9-6.7 at T5). The average risk group as compared to the stable risk group showed a risk ratio of 3.1 to 2.2 across the study timespan (95% CI 1.3–8.9 at T2, 1.2-4.4 at T5). The accelerated risk group relative to the average risk group showed a risk ratio of 1.8 at T2, to 1.5 at T5 (95% CI 1–3.4 at T2, 0.97-2.3 at T5).



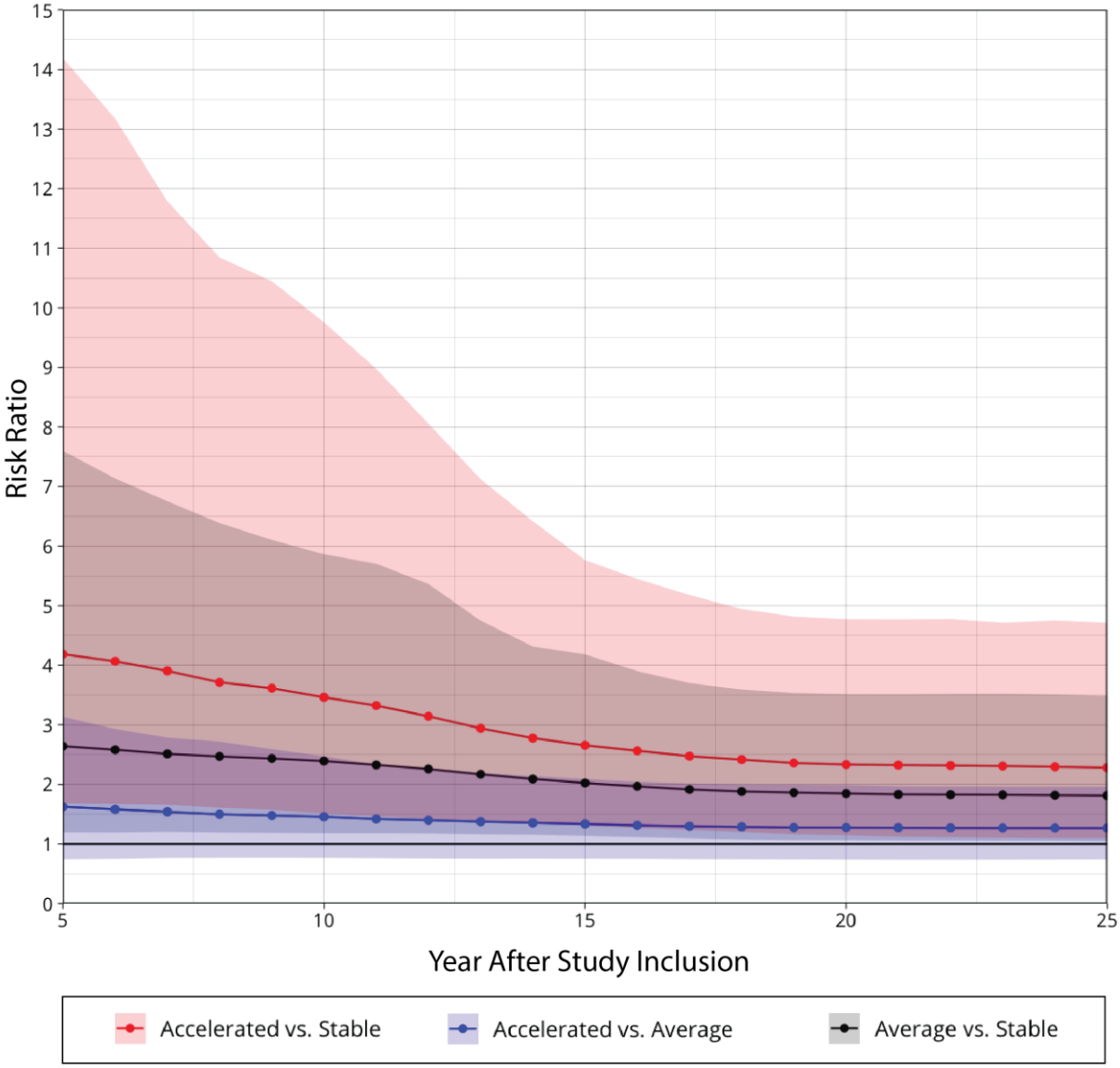
eFigure 2.
Risk ratio graph for cumulative incidence of vascular dementia in old (70+) participants, split by Framingham Risk Score trajectory groups.
The accelerated risk group as compared to the stable risk group showed a consistently elevated level of risk of vascular dementia. Other comparisons (accelerated vs. average, average vs stable, and vice versa) did not show an elevated level of risk. Shaded areas represent 95% credible intervals (CI). The accelerated risk group shows the highest relative level of risk when compared to the stable risk group, from 4.1 at T2, to 3.3 at T5 (95% CI 1.1–16.6 at T2, 1.5-7.6 at T5). The average risk group as compared to the stable risk group remained relatively constant with a risk ratio of 2.1 to 2 across the study timespan), although the credible intervals were not consistently elevated above 1 (95% CI 0.7–5.8 at T2, 1-4.2 at T5). The accelerated risk group relative to the average risk group showed a risk ratio of 1.9 at T2, to 1.6 at T5 (95% CI 0.76–6.5 at T2, 0.83-2.7 at T5).



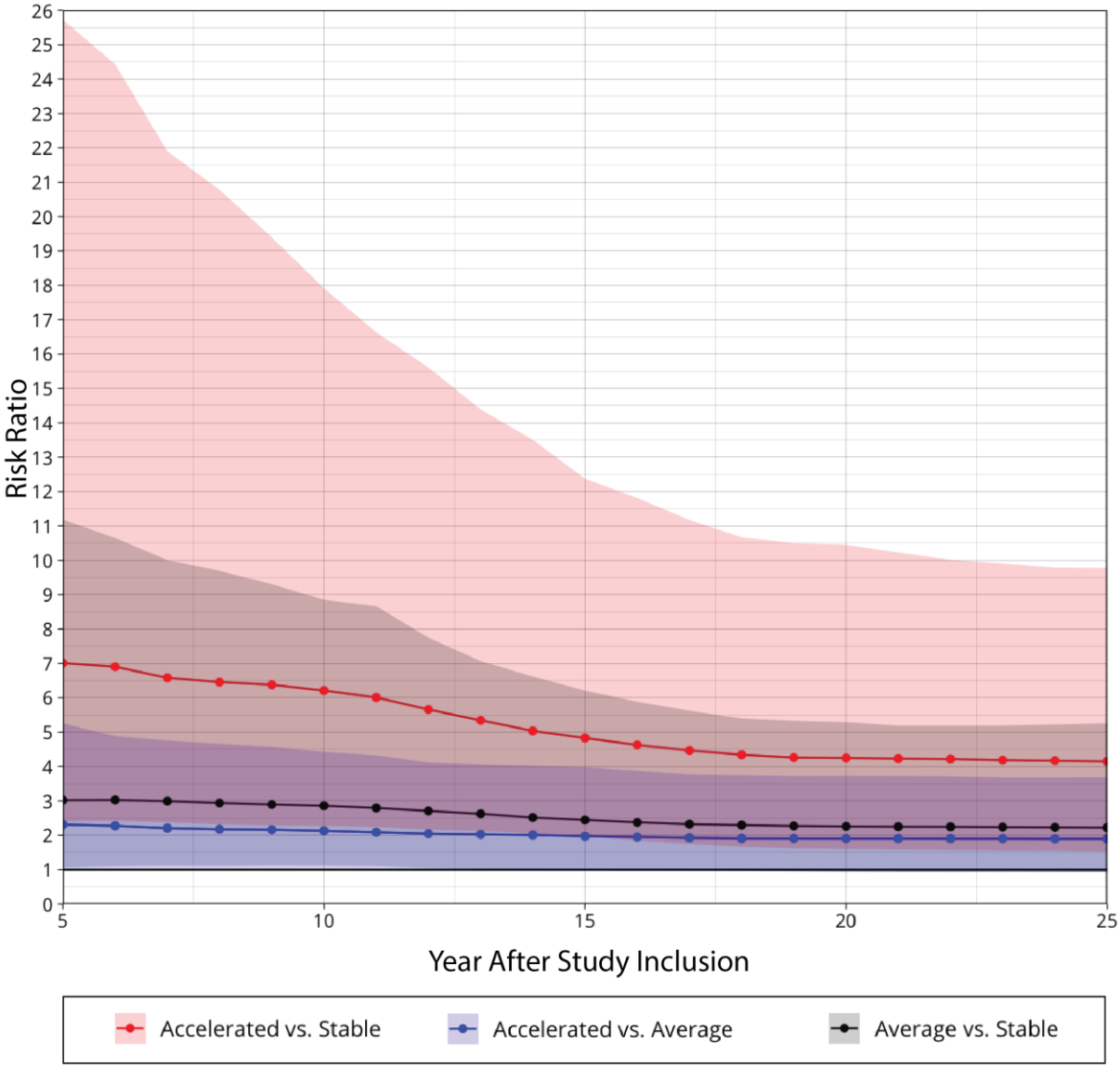
eFigure 3.
Risk ratio graph for incidence of vascular dementia in old (70+) participants, split by baseline Framingham Risk Score cutoffs.
Groups were derived from thresholds for participants' Framingham risk score at study inclusion (i.e. baseline), where: Low <6%, Medium 6-20%, and High: >20%. Shaded areas represent 95% credible intervals (CI). Only the high vs. medium group showed an elevated risk of vascular dementia across the study timespan, however only from T3, with a risk ratio of 2.4-2.2 from T3 to T5, respectively (95% CI 1-7.2 at T3, 1-5.8 at T5). The high vs. low groupings showed a risk ratio of 3.3-3.2 from T2 to T5 (95% CI 0.3-43.2 at T2, 0.7-28.9 at T5), while the medium vs. low ratio ranged from 1.4-1.5 across the study timespan (95% CI 0.2-13.2 at T2, 0.4-9.9 at T5). Other comparisons (medium vs. high, and low vs. medium) did not show a consistently elevated level of risk.



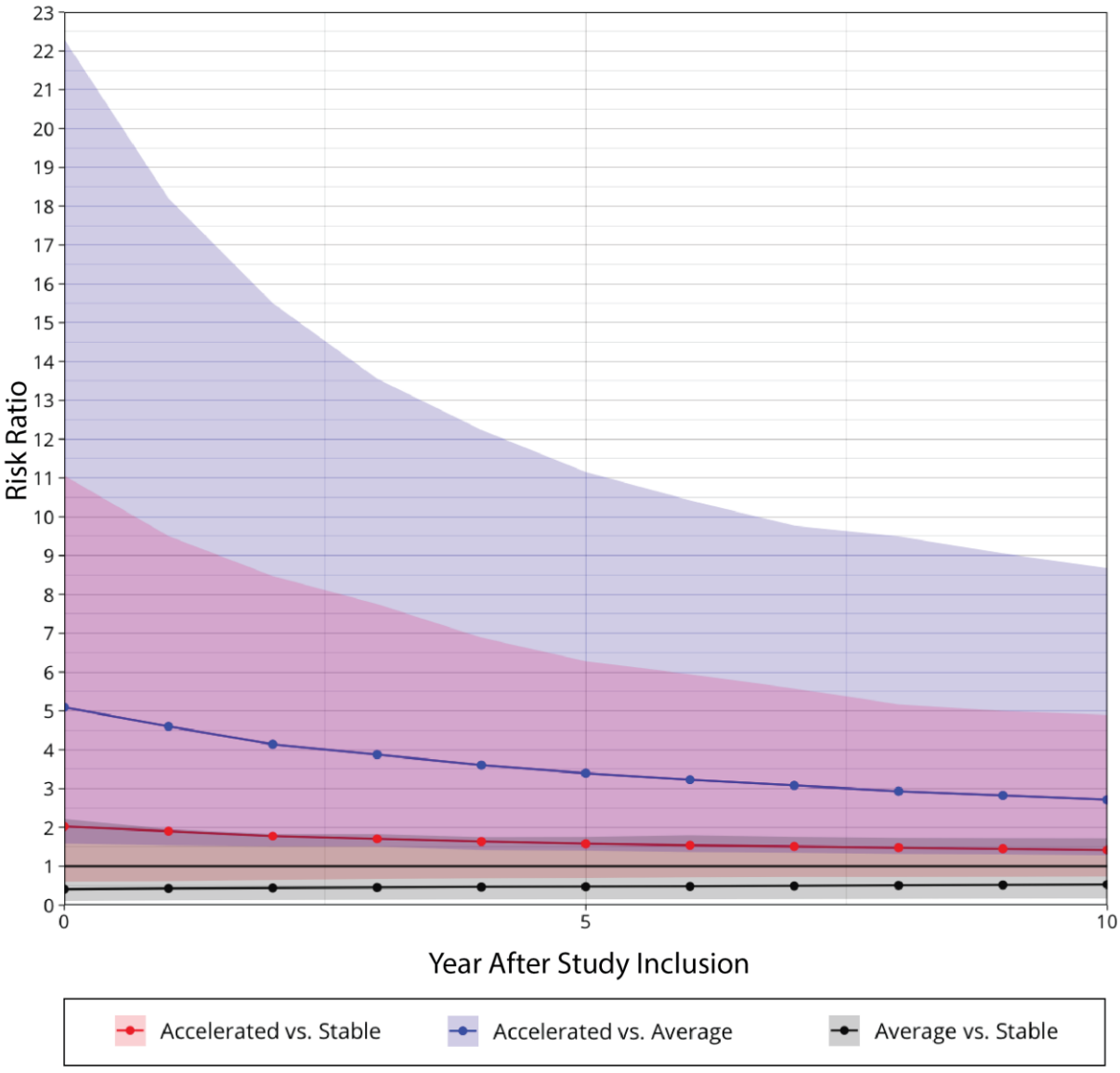
eFigure 4.
Risk ratio graph for incidence of Alzheimer's disease in APOE4+ participants, split by Framingham Risk Score trajectory groups.
Both the accelerated risk group and the average risk group, as compared to the stable risk group, showed a consistently elevated level of risk of Alzheimer's disease. The comparison of accelerated vs. average did not show an elevated level of risk. Shaded areas represent 95% credible intervals (CI). The accelerated risk group shows the highest level of risk when compared to the stable risk group, from 4.2 at T2, to 2.3 at T5 (95% CI 1.7–14.2 at T2, 1.1-4.7 at T5). The average risk group as compared to the stable risk group showed a risk ratio of 2.6 to 1.8 across the study timespan (95% CI 1.2–7.6 at T2, 1-3.5 at T5). The accelerated risk group relative to the average risk group showed a risk ratio of 1.6 at T2, to 1.3 at T5 (95% CI 0.7–3.1 at T2, 0.7-2 at T5).



eFigure 5.
Risk ratio graph for incidence of Alzheimer's disease in APOE4- participants, split by Framingham Risk Score trajectory groups.
The accelerated risk group, as compared to the stable risk group, showed a consistently elevated level of risk of Alzheimer's disease. The comparison of accelerated vs. average, and average vs. stable did not show a consistently elevated level of risk. Shaded areas represent 95% credible intervals (CI). The accelerated risk group, when compared to the stable risk group, shows a risk ratio of 7 at T2, to 4.1 at T5 (95% CI 2.4–25.7 at T2, 1.5-9.8 at T5). The average risk group as compared to the stable risk group showed a risk ratio of 3 to 3.3 across the study timespan (95% CI 1.1–11.2 at T2, 0.9-5.3 at T5). The accelerated risk group relative to the average risk group showed a risk ratio of 2.3 at T2, to 1.9 at T5 (95% CI 0.99–5.3 at T2, 0.9-3.7 at T5).



eFigure 6.
Risk ratio graph for survival following vascular dementia diagnosis, split by Framingham Risk Score trajectory groups.
Participants in the accelerated, relative to the average FRS trajectory groups showed an elevated risk of death following vascular dementia diagnosis. None of the other comparisons (accelerated vs. stable, average vs. stable, and vice versa) showed a consistently elevated risk of death. As the timescale is bound to measurements available following diagnosis, the timespan was restricted. Shaded areas represent 95% credible intervals (CI). The accelerated risk group, when compared to the stable risk group, showed a risk ratio from 2 at the first available timepoint following diagnosis, to 1.4 at the last timepoint (95% CI 0.6–11.1 at year 0, 0.7-4.9 at year 10). The average risk group as compared to the stable risk group showed a risk ratio of 0.4 to 0.5 across the available timepoints (95% CI 0.1–2.2 at year 0, 0.2-1.7 at year 10). The accelerated risk group relative to the average risk group showed a risk ratio of 5.1 to 2.7 across the available timepoints (95% CI 1.6–22.3 at year 0, 1.3-8.7 at year 12).



eFigure 7.
Risk ratio graph for episodic memory decline, split by Framingham Risk Score trajectory groups.
The accelerated risk group as compared to the stable risk group showed a consistently elevated level of risk of episodic memory decline. Other comparisons (accelerated vs. average, and average vs stable and vice versa) did not show an elevated level of risk. Shaded areas represent 95% credible intervals (CI). The accelerated risk group shows a risk ratio of 1.4 at T2, to 1.2 at T5 (95% CI 1–1.9 at T2, 1-1.5 at T5). The average risk group as compared to the stable risk group had a risk ratio of 1.2 to 1.1 across the study timespan (95% CI 0.99–1.4 at T2, 1-1.3 at T5). The accelerated risk group relative to the average risk group showed a risk ratio of 1.2 at T2, to 1.1 at T5 (95% CI 0.8–1.4 at T2, 0.8-1.2 at T5).